2026

CRETE GREECE

THE 14TH BIENNIAL INTERNATIONAL 22q11.2 SCIENTIFIC MEETING

hosted by the 22q11.2 Society

ZEUS ELEVA MIRABELLO BAY RESORT

CRETE, GREECE | JULY 13 - JULY 17, 2026

EDUCATION AND COLLABORATION ON THE JEWEL OF GREECE

The 22q11.2 Society *warmly welcomes* Attendees to the 2026 International 22q11.2 Scientific Meeting

13th Biennial International 22q11.2 Conference, Óbidos, Portugal, July 16-18, 2024

Inaugural 22q11.2 Deletion Conference, Strasburg, France, September 5-6, 1998

THE 14TH BIENNIAL INTERNATIONAL 22q11.2 SOCIETY CONFERENCE

Dear Conference Attendees,

It is with pure joy that the 22q11.2 Society Trustees and Advisors welcome you to the 14th Biennial International 22q11.2 Scientific Meeting, celebrating 28 years of sharing knowledge while fostering collaboration and camaraderie as a unique community, all on the beautiful island of Crete - the jewel of Greece.

Beginning with the inaugural meeting in Strasbourg, France in 1998, this assembly is imagined as a scientific retreat where attendees, currently hailing from more than twenty countries across five continents, will become immersed in everything 22q over the course of four days. While enjoying ample opportunities for discussion and discovery, no doubt participants will also appreciate the outstanding social program and relationships that come from spending this exceptional time together.

As is always the ambition, this 14th conference, now many years on since Strasbourg, merges the objectives of basic science discovery with interdisciplinary clinical research, with an overarching purpose of improving care for patients and families while informing our understanding of associated features in the general population. From case reports to large collaborative datasets and long-read-sequencing to the microbiome, this meeting has it all and every single contribution – short, long, or in between – will be appreciated.

This audience always wants to know more, whether from the most distinguished invited speaker to the novice junior investigator, every presenter's contribution is valued and celebrated. We are here for one another. We applaud every attendee's respective journey in bringing breakthroughs to the forefront and sharing them here in Greece. We are certain it will be worth the effort.

Enjoy the crisp sea air and breath-taking views. Enjoy the exceptional science and fabulous company. We thank you for coming and hope to see you again soon.

Yamas!

Donna M. McDonald-McGinn
22q11.2 Society Chair

Erik Boot
22q11.2 Society Trustee and 2026 Program Chair

The 22q11.2 Society

The 22q11.2 Society is an academic organization interested in advancing the study of chromosome 22q11.2 copy number variants, genes within and modifier genes outside of the 22q11.2 region, their underlying biology, and associated conditions. Members represent a broad range of backgrounds, such as: healthcare providers, clinical and basic science researchers, educators, therapists, and family advocates. To become a member, please visit **22qsociety.org**.

MISSION

The mission of the 22q11.2 Society is to promote both basic science and clinical interdisciplinary research into the biology of the 22q11.2 region, and the diagnosis, prognosis, and management of related disorders. A subsidiary goal is to exploit the knowledge so gained for the benefit of populations of individuals with more common conditions.

As such, we endeavor to:

- Promote collaborative and international partnerships in understanding features associated with chromosome 22q11.2 differences
- Support the provision of guidance in best practice care
- Facilitate research surrounding causes, clinical features, and treatment
- Encourage collaboration and communication between clinicians and researchers in studying these conditions
- Raise awareness and promote education throughout a broad range of clinical communities and the general public
- Strive for the highest ethical standards in research and clinical practice involving children and adults affected by these conditions

VISION

The vision of the 22q11.2 Society is to be the international leader in promoting research related to the chromosome 22q11.2 region.

Executive Trustees

Donna McDonald-McGinn, *Chair*

Director of the 22q and You Center, Chief of the Section of Genetic Counseling, and Senior Principal Scientist at the Children's Hospital of Philadelphia and Professor of Clinical Pediatrics at the Perelman School of Medicine of the University of Pennsylvania, Philadelphia, USA

Anne Bassett, *Treasurer*

Dalglish Family Chair in 22q11.2 Deletion Syndrome (22q11.2DS) and the Director of the Dalglish Family 22q Clinic at Toronto General Hospital, Toronto, Ontario, Canada

Peter Scambler, *Vice-Treasurer*

Emeritus Professor of Molecular Medicine at the Institute of Child Health, London, UK

Ann Swillen, *Secretary*

Professor in the Department of Human Genetics and the Department of Rehabilitation Sciences at KU, Leuven, Leuven, Belgium

Trustees

Bernice Morrow

Professor in the Departments of Genetics, Obstetrics & Gynecology and Women's Health, and Pediatrics at the Albert Einstein College of Medicine, New York, USA

Sólveig Óskarsdóttir

Specialist in pediatrics, immunology, and 22q11.2 DS at Sahlgrenska University Hospital, Gothenburg, Sweden

Beata Nowakowska

Associate Professor and Head of the Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland

Erik Boot

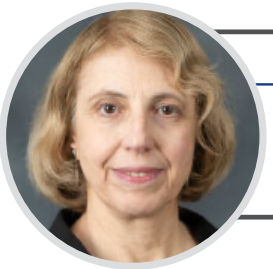
Physician specialized in intellectual disability medicine at the multidisciplinary 22q11.2 clinics for adults at Heeren Loo, Maastricht, Netherlands

Hanadys Ale

Director of the 22q Network of the America's, Medical Director of the 22q Multidisciplinary Clinic at Joe DiMaggio Children's Hospital, Hollywood, FL, USA

Jill Arganbright

Associate Professor of Surgery and Clinical Assistant Professor of Otorhinolaryngology at the University of Missouri Kansas City School of medicine and specialized in velopharyngeal insufficiency (VPD) at Children's Mercy Hospital in Kansas City, USA



Natalie Blagowidow

Director, Harvey Institute of Human Genetics, Greater Baltimore Medical Center, Baltimore, MD, USA

Ania Fiksinski

Psychologist (PhD) and Researcher at Maastricht University and the Wilhelmina Children's Hospital / University Medical Center, Utrecht, Netherlands

Emily Gallagher

Craniofacial Pediatrician at Seattle Children's Hospital, Associate Professor in the Department of Pediatrics at the University of Washington School of Medicine, Director of the Seattle Children's 22q Program, Seattle, USA

Doron Gothelf

Professor of Psychiatry at Sackler Faculty of Medicine, Tel Aviv University, the pioneer, Director of the Behavioral Neurogenetics Center and Director of Child Psychiatry Division at Sheba Medical Center, Tel Aviv, Israel

Loydie Jerome-Majewska

Associate Professor in the Department of Pediatrics at McGill University, Montreal, Canada

Sulgana Saitta

Director of Reproductive Genetics, Clinical Professor of Pediatrics, and geneticist at the David Geffen School of Medicine at UCLA, Los Angeles, USA

Maude Schneider

Assistant Professor at the Faculty of Psychology and Educational Sciences of the University of Geneva, head of the Clinical Psychology Unit for Intellectual and Developmental Disabilities, Geneva, Switzerland

Kathleen Sullivan

Chief of the Division of Allergy and Immunology and the Frank R. Wallace Endowed Chair in Infectious Disease at the Children's Hospital of Philadelphia, USA

Marta Unolt

Pediatric cardiologist at Bambino Gesù Pediatric Hospital, Rome, Italy

Elfi Vergaelen

Adult psychiatrist specialized in psychosomatic symptoms and intellectual disability at the University Psychiatric Center KU Leuven, Leuven, Belgium

Joris Vermeesch

Professor of Cytogenetics and Genome Research at KU Leuven, Head of the Laboratory for Cytogenetics and Genome Research, and Head of KU Leuven Genomics Core Facility at KU Leuven, Leuven, Belgium

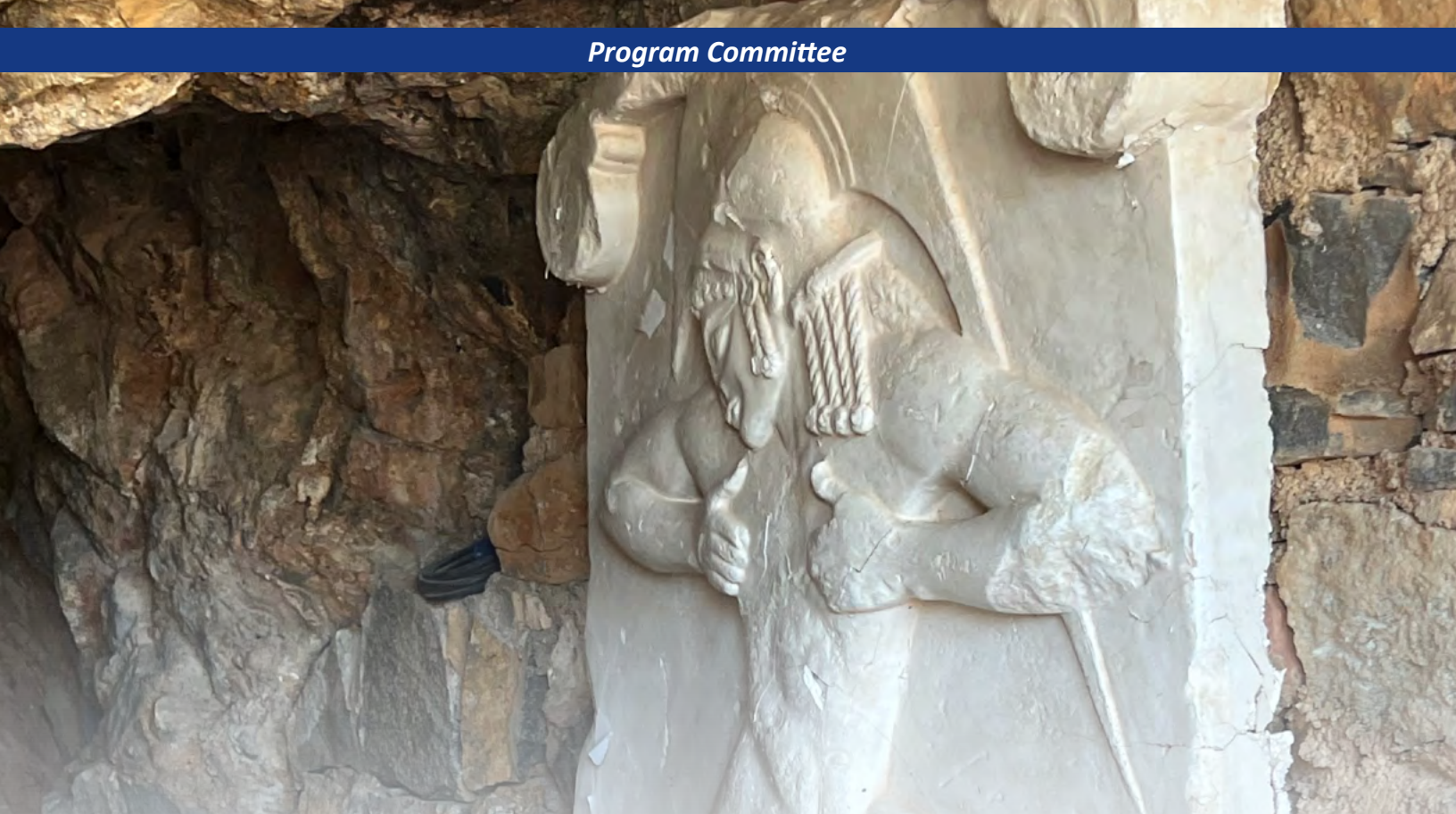
Jacob Vorstman

Associate Professor of Psychiatry at The Hospital for Sick Children and the University of Toronto, in Toronto, Canada

a parade of nations

Australia
Belgium
Brazil
Canada
China
Denmark
England
Greece
Ireland
Israel
Italy
Netherlands
Poland
Portugal
Serbia
Spain
Sweden
United States of America
Wales

Assembling in beautiful Crete, Greece summer of 2026 for the 14th Biennial International 22q11.2 Deletion Syndrome Conference



The 14th Biennial International 22q11.2 Conference Program Committee

Erik Boot
Program Chair

Anne Bassett
Associate Conference Director

Donna McDonald-McGinn
Conference Director

Hanadys Ale

Jill Arganbright

Natalie Blagowidow

Erik Boot

Ania Fiksinski

Emily Gallagher

Doron Gothelf

Loydie Jerome-Majewska

Bernice Morrow

Sólveig Óskarsdóttir

Sulagna Saitta

Peter Scambler

Maude Schneider

Kathleen Sullivan

Ann Swillen

Marta Unolt

Elfi Vergaelen

Joris Vermeesch

Jacob Vorstman

SOCIAL PROGRAM

TUESDAY, JULY 14TH * 20:00 * GRECIAN CAVE TERRACE

Welcome Reception

- All Attendees and Registered Accompanying Persons are invited to attend
- Includes our Signature 22q Cocktail, Heavy Hors d'oeuvres, and traditional Greek entertainment

WEDNESDAY, JULY 15TH * 19:00 * BAHIA MAR AND STONE THEATER

22q Olympics and Sunset Social

- All Attendees and Registered Accompanying Persons will receive the official 2026 "Olympic Vest" at registration
  - *— Please wear your 22q vest to the 22q Olympics and Sunset Social*
- All Attendees and Registered Accompanying Persons are invited to attend the PARADE OF NATIONS and participate in the 22q Olympic games
  - *— Please wear colors representing your country*
  - *— Please wear athletic clothing and footwear if participating in Olympics*
- The PARADE OF NATIONS will assemble at 18:45 at the Stone Theater
- The 22q Olympic games will follow immediately and include:
  - *— Activities appropriate for juniors, seniors, and everything in-between*
- Festivities will conclude with pizza and beverages

THURSDAY, JULY 16TH * 20:00 * ELIA TERRASSE

22q Dinner and Dancing

- All Attendees and Registered Accompanying Persons are invited to attend
- Includes dinner, dancing, and a Special Awards Presentation

FRIDAY, JULY 17TH * 13:00 * ZEUS BALLROOM AND CONFERENCE CENTER

Closing Ceremonies, Farewell Fare - Covered Terrace

- Junior Investigator Awards and Announcement of the 2028 Conference Location

Audiovisual

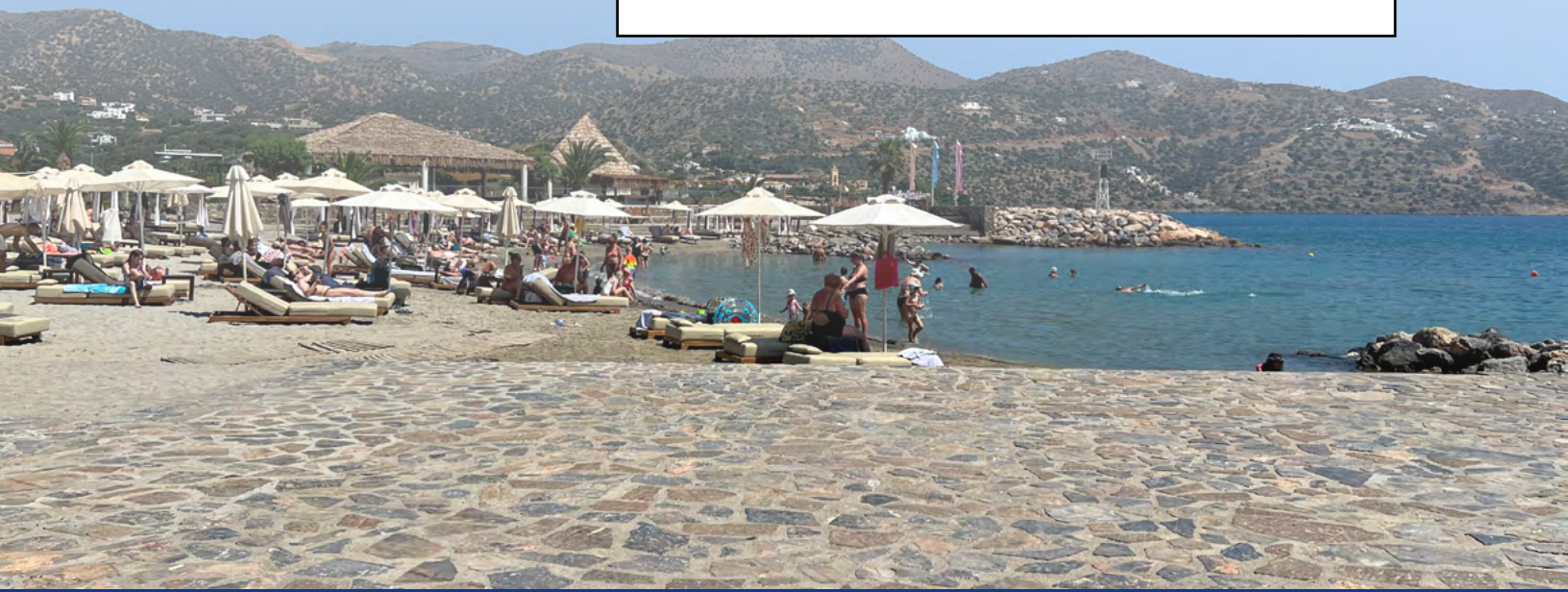
- All Power Point presentations must be uploaded to the designated Drop-Box link no later than 24 hours prior to the scheduled lecture time
  - This is mandatory
  - No changes will be accepted thereafter
  - No personal computers will be "swapped out"
  - No online presentations will be accessible
  - Berating the AV technician/assistants will immediately void the attendee's registration and the offender will be asked to leave the conference
- The Speaker Ready Room is in the Zeus Ballroom – hours of operation are posted at the registration desk
- Please ensure all slides are compatible prior to uploading
- Please keep to the allotted time as the 2026 Program is very full
- Presentations that exceed the allotted time will have the microphone silenced and slides darkened

Registration – Zeus Ballroom

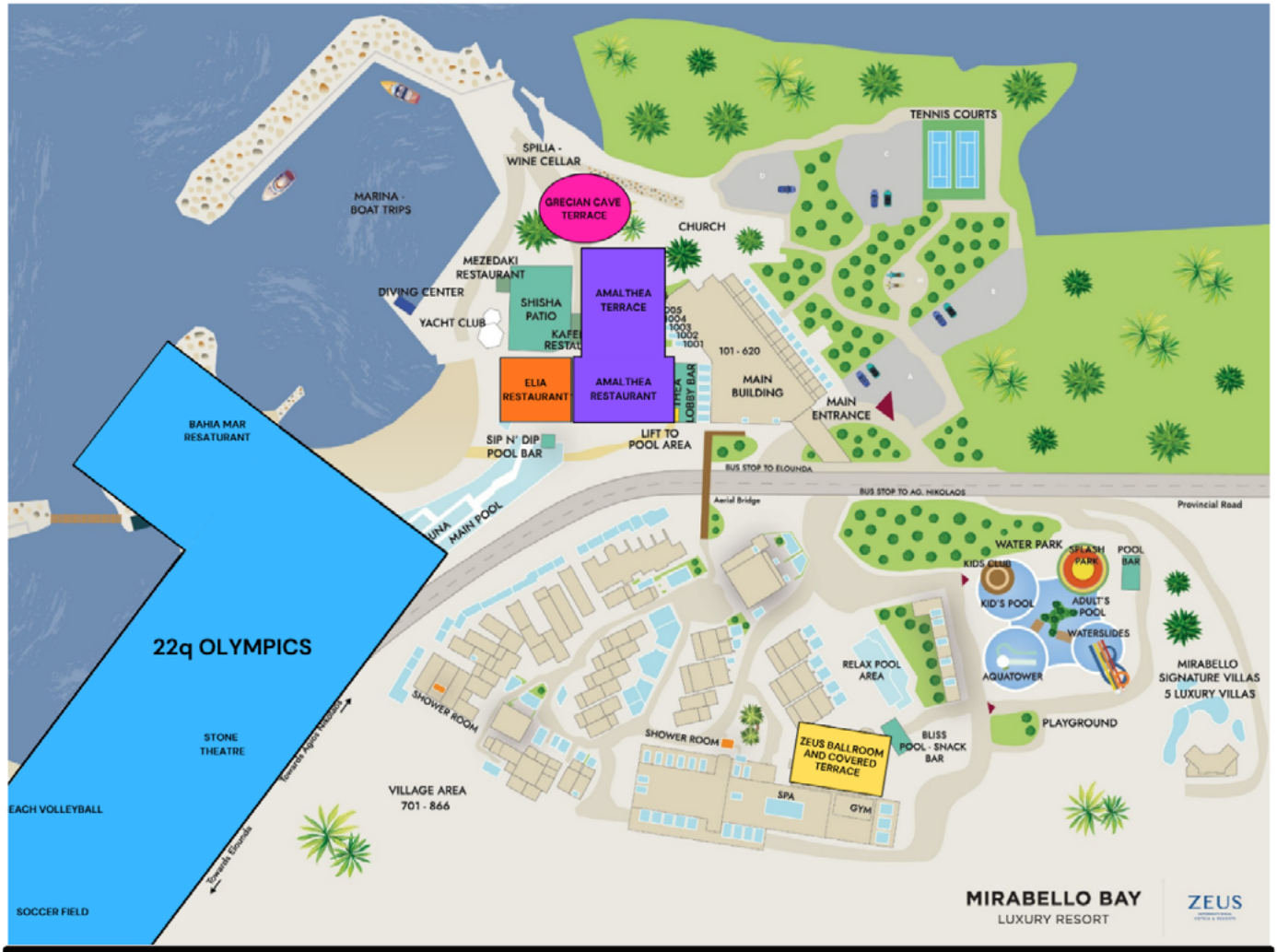
- 22q Conference Badges will be provided at Registration to all paid attendees and must be worn at all times during the Meeting and Social Program
- Registered Accompanying Person Materials will be distributed at the Registration Desk

Registration Desk Hours:

Monday, July 13th	***6:00 – 17:00***
Tuesday, July 14th	***6:00 – 17:00***
Wednesday, July 15th	***8:00 – 17:00***
Thursday, July 16th	***8:00 – 17:00***
Friday, July 17th	***8:00 – 12:00***



Zeus Eleva Mirabello Bay Resort Map



Key

- Scientific Meeting - Zeus Ballroom and Covered Terrace
- Lunch - Amalthea Restaurant
- Welcome Reception - Grecian Cave Terrace
- 22q Olympics - Stone Theatre and Bahia Mar Restaurant
- 22q Dinner and Dancing - Elia Restaurant

Angelo DiGeorge Memorial Medal of Honour

The Angelo DiGeorge Memorial Medal of Honour recognizes an outstanding contribution to our understanding and/or treatment of chromosome 22q11.2 copy number variants. The award was inaugurated in 2010 to commemorate the life and work of Dr. Angelo DiGeorge, a pioneer in describing features now known to be associated with 22q11.2 deletion syndrome.

Prospective recipients may be:

- Basic scientists working on the molecular, cellular, or developmental basis of the condition,
- Clinical scientists working on diagnosis and treatment of any aspect of the syndrome,
- Allied health professionals, educators or welfare workers who make major contributions to the wellbeing of patients and families affected, Exceptionally, organizations who fund or facilitate the above activities.

Ann Swillen presenting 2024 award to Sólveig Óskarsdóttir

The Angelo DiGeorge Memorial Medal of Honour Past Recipients:

2010 **Peter Scambler**

2012 **Donna M. McDonald-McGinn**

2014 **Anne S. Bassett**

2016 **Ann Swillen**

2018 **Bernice Morrow**

2020-2022
Nicole Sarles-Philip and Bruno Marino

2024 **Sólveig Óskarsdóttir**

2026 **To be Announced**

THE JUNIOR INVESTIGATOR AWARD

PRESENTED FOR OUTSTANDING 2026 PRESENTATIONS BY JUNIOR FACULTY MEMBERS OR TRAINEES AT THE CONCLUSION OF THE MEETING

PREVIOUS JUNIOR INVESTIGATOR AWARD RECIPIENTS:

2012 Laurie Earls

2014 Pamela Mudd

2016 Ania Fiksinksi and Wolf Demaerel

2018 Lisanne Vervoort and Tracy Hueng

2022 Daniella Miller, Daniel McGinn and Steven de Reuver

2024 Christina Blagojevic, Daniella Miller and Jente Verbesselt

2026 To be Announced

2024 Awards presented by Beata Nowakowska and Daniel McGinn

The Clodagh Murphy "UNSUNG HERO" AWARD

The Unsung Hero Award is presented at the International 22q11.2 Biennial Meeting to honor an individual having demonstrated outstanding contributions to the 22q11.2 community including:

- **COMMITMENT** *as evidenced by service to the community*
- **SELFLESS DEVOTION** *by supporting education, awareness, healthcare advances, and research*
- **COLLABORATION AND INCLUSIVITY** *with international 22q11.2 organizations, as well as the research and healthcare communities at large*
- **MAKING A NATIONAL AND INTERNATIONAL IMPACT** *on individuals with chromosome 22q11.2 differences and/or their families and caregivers*

In 2022, the 22q11.2 Society renamed the Unsung Hero Award in honour of Founding Member, Clodagh (Dot) Murphy, MD, PhD, who sadly passed in 2020.

Erik Boot presenting 2024 award to Kim Van Bekkum

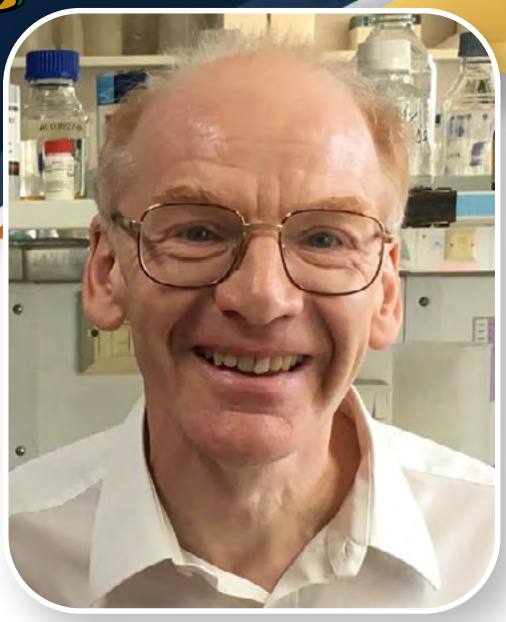
The Clodagh Murphy
"UNSUNG HERO"
AWARD

Previous Unsung Hero Award Recipients:

2012	Julie Wootton
2014	Sheila Kambin
2016	Maria Kamper
2018	Ryan Dempster
2020-2022	Ann Lawlor and Candice Hamilton-Utgyensu
2024	Kim Van Bekkum
2026	To be Announced

The Peter Scambler Invited Lecture Award

The Peter Scambler Invited Lecture, inaugurated in 2022, is a featured lecture at the Biennial International 22q11.2 Scientific Conference in honor of Founding Trustee and inaugural Chair (2013-2019), Dr. Peter Scambler. The lecture, awarded by Dr. Peter Scambler and the Trustees of the 22q11.2 Society, kicks off the scientific program at the conference.



Professor Peter Scambler, M.D.

Anne Bassett presenting 2024 award to Stephen W. Scherer

PREVIOUS PETER SCAMBLER INVITED LECTURERS:

2022	**Robert G. Kelly**
2024	**Stephen W. Scherer**
2026	**Joris R. Vermeesch**

22q11.2 Society Special Service Award

The Special Service Award, inaugurated in 2018 is periodically presented to a Program demonstrating outstanding, longstanding, exemplary, and unwavering commitment and contributions to the chromosome 22q11.2 community

PAST RECIPIENTS OF THE SPECIAL SERVICE AWARD

2018 **22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA**

2024 **The Dalglish Family 22q Clinic Toronto General Hospital, Toronto, ON, Canada**

2026 **To be announced**

2024 Recipient – The Dalglish Family 22q Clinic

Shown here: Anne Bassett, Medical Director and Clinical Team Members: Samantha D'arcy, Lisa Palmer, and Erik Boot

Sophie Astrof

Principal investigator, Head of laboratory studying cardiovascular development a nd congenital heart disease, Rutgers University, Newark, New Jersey, USA

Doron Gothelf

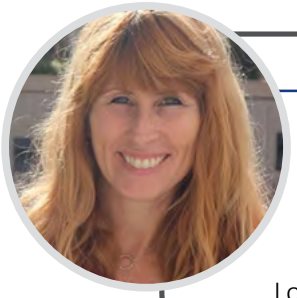
Director of the Department of Pediatric Psychiatry at The Edmond and Lily Safra Children's Hospital, Sheba Medical Center and Professor of The Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel

Anne Bassett

Director of the Dalglish Family 22q Clinic at Toronto General Hospital, and Professor Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Raquel E Gur

Professor of Psychiatry Neurology and Radiology, Director of the Neuropsychiatry Section and the Schizophrenia Research Center, and Vice Chair of Research Development in the Department of Psychiatry at the University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA



Carrie Bearden

Director, Center for the Assessment and Prevention of Prodromal States Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA

Sara R. Heras

Professor, Facultad de Farmacia, University of Granda, Granada, Spain

Ian Campbell

Assistant Professor of Pediatrics and attending physician in the Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, Pennslyvania, USA

Oksana A. Jackson

Donato D. LaRossa Endowed Chair in Plastic Surgery, Co-Director of the Cleft Lip and Palate Program, Children's Hospital of Philadelphia, Pennslyvania, USA

Donna McDonald-McGinn

Director of the 22q and You Center, Chief of the Section of Genetic Counseling, and Senior Principal Scientist at the Children's Hospital of Philadelphia and Professor of Clinical Pediatrics at the Perelman School of Medicine of the University of Pennsylvania, Philadelphia, USA

Bernice E. Morrow

Sidney L. and Miriam K. Olson Chair in Cardiology, Director of the Division of Translational Genetics, Department of Genetics, Michael F. Price Center, Albert Einstein College of Medicine, New York, USA

Beata Nowakowska

Associate Professor and Head of the Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland

Francesco Papaleo

Tenured senior researcher, Group leader of the Genetics of Cognition laboratory, Istituto Italiano di Tecnologia (IIT), Genova, Italy

Spyros Petrakis

Researcher Grade C' at the Institute of Applied Biosciences at CERTH, the Center for Research and Technology Hellas, Thessaloniki, Greece

Peter Scambler

Emeritus Professor of Molecular Medicine at the Institute of Child Health, London, UK

Cynthia B. Solot

Senior Speech and Language Pathologist, Department of Speech-Language Pathology and 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, Pennslyvania, USA

Joris Vermeesch

Professor of Cytogenetics and Genome Research at KU Leuven, Head of the Laboratory for Cytogenetics and Genome Research, and Head of KU Leuven Genomics Core Facility at KU Leuven, Leuven, Belgium

Stanislav Zakharenko

Director of the Division of Neural Circuits and Behavior, St. Jude Children's Hospital, Memphis, Tennessee, USA

THE 14TH BIENNIAL INTERNATIONAL 22q11.2 SOCIETY CONFERENCE

Zeus Eleva Mirabello Bay Hotel
Crete, Greece

TUESDAY JULY 14, 2026

6:00 ***REGISTRATION OPEN – ZEUS BALLROOM COURTYARD***

7:00 ***BREAKFAST – AMALTHEA RESTAURANT AND TERRACE***
MIRABELLO BAY RESORT GUESTS ONLY

SESSION I *OPENING CEREMONIES - ZEUS BALLROOM*

Chairs: Donna M. McDonald-McGinn and Erik Boot

8:00 **The 22q11.2 Society Welcomes a Parade of Nations to the Jewel of Greece**
Donna M. McDonald-McGinn, 22q11.2 Society Chair

Kalos Irthes stin Ellada!
Spyros Petrakis

Program Synopsis and Acknowledgements
Erik Boot, 22q11.2 Society Trustee and 2026 Program Chair

Presentation of the Angelo DiGeorge Memorial Medal of Honor
Ann Swillen, 22q11.2 Society Trustee and Secretary

Presentation of the Clodagh Murphy Memorial Unsung Hero Award
Donna McDonald-McGinn, 22q11.2 Society Chair

Opening Breath
Maria Mascarenhas, Philadelphia, PA, USA

SESSION II GENOTYPES, PHENOTYPES, AND MECHANISMS

Chairs: Peter Scambler and Joris R. Vermeesch

8:25 **001** *PETER SCAMBLER INVITED LECTURE AND OUTSTANDING ACHIEVEMENT AWARD*

Unraveling the role of segmental duplicons in predisposition and phenotypic variability of the 22q11.2 deletion syndrome

Joris R. Vermeesch, Leuven, Belgium

Award presented by Anne Bassett, 22q11.2 Society Trustee and Treasurer

8:50 **002** **Haplotype-resolved iso-seq reveals allele-specific isoform remodeling in 22q11.2 deletion patient-parent duos** *

Marta Sousa Santos, Erika Souche, David Porubsky, Natalia Olszewska, Evan E. Eichler, and Joris R.Vermeesch

8:57 **003** **Isogenic LCR22 deletions in H9 define an isoform-resolved transcript catalogue and LCR-specific regulatory programs across early development** *

Marta Sousa Santos, Erika Souche, Natalia Olszewska, and Joris R.Vermeesch

9:05 **004** **Resolving the exact breakpoints of the 22q11.2 deletion using CRISPR-Catch and long-read sequencing reveals chromosomal rearrangement mechanisms and individual variance in breakpoints**

Alexander E. Urban, Bo Zhou, Carolin Purmann, Hanmin Guo, GiWon Shin, Yiling Huang, Reenal Pattni, Qingxi Meng, Stephanie U Greer, Tanmoy Roychowdhury, Raegan N Wood, Marcus Ho, Heinrich Zu Dohna, Alexej Abyzov, Joachim F Hallmayer, Wing H Wong, and Hanlee P Ji

9:14 **005** **Optical mapping of nested 22q11.2 deletions reveals conserved structural architectures**

Steven Pastor, Oanh Tran, T. Blaine Crowley, Audrey Olson, Lydia Rockart, Daniel E. McGinn, Elaine H. Zackai, Donna M. McDonald-McGinn, and Beverly S. Emanuel

9:20 **Q&A**

9:30 **006** *INVITED PRESENTATION*

Setting the stage: The importance of deletion size, variants on the intact chromosome 22q11.2 allele, dual diagnoses, and genome-wide modifiers

Donna M. McDonald-McGinn, Philadelphia, PA, USA

9:45 **007** **Do proximal nested 22q11.2 deletions have a modified adult phenotype?**

Anne S. Bassett, Tracy Heung, Lisa Palmer, Samantha D'Arcy, Sarah Malecki, and Nikolai Reyes

9:55 **008** **Clinical phenotypes of 22q11.2 typical and atypical deletions and duplications**

Thérèse van Amelsvoort, Emma von Scheibler, Rianne van Roij, Winde Mercken, Tjitske Kleefstra, and David Linden

* *Junior Investigator*

10:02 **009** **Genotype-phenotype correlations in 22q11.2 deletion syndrome: unravelling the clinical heterogeneity**
Deepthi Jyothish, Elizabeth Brettle, Hannah Titheradge, Asma Hamad, Neha Gupta, Hakim-Moulay Debhi, and Charlotte Clarke

10:10 **010** **22q11.2-22q11.23 distal deletions and duplications: An emerging important population** *
Daniel E. McGinn, T. Blaine Crowley, Audrey Olson, Lily N. Elman, Evie Andrewes, Lydia Rockart, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, and Donna M. McDonald-McGinn

10:20 **Q&A**

10:30 ***COFFEE BREAK AND POSTER VIEWING – COVERED TERRACE***

SESSION III EXPRESSION, METHYLATION, POLYGENIC RISK SCORES, AND EXPOSOME

Chairs: Anne Bassett and Beata Nowakowska

11:10 **011** ***INVITED PRESENTATION***
Expression and methylation studies in 22q11.2 deletion syndrome
Beata A. Nowakowska, Warsaw, Poland

11:25 **012** **The 22q11.2 methylome** *
Senne Meynants, Erika Souche, Marta Sousa Santos, Nicolas Dierckxsens, Ann Swillen, Elfi Vergaelen, Jeroen Breckpot, and Joris R. Vermeesch

11:35 **013** **Impact of ancestry on prevalence of 22q11.2 deletion syndrome** *
Lydia Rockart, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Oanh Tran, Steven Pastor, Laura Schultz, Laura Almasy, Raquel Gur, Kai Wang, Ian M. Campbell, Kathleen Valverde, Elaine H. Zackai, Sulagna C. Saitta, Loydie A. Jerome-Majewska, Beverly S. Emanuel, and Donna M. McDonald-McGinn

11:45 **014** **Demographic, socioeconomic, and clinical profiles of individuals with 22q11.2 deletion and duplication syndromes: a large multi-institutional EHR study**
Hanadys Ale, Marta Telatin, Brianna Santiago, and Jennifer Keelin

11:55 **015** **An exposome-wide analysis of environmental predictors of IQ in 22q11.2 and 16p11.2 CNV carriers** *
Yelyzaveta Snihirova, Sinan Guloksuz, David EJ Linden, Ann Swillen, Marianne BM van den Bree, Raquel E Gur, Ruben C Gur, Carrie E Bearden, Jacob AS Vorstman, Jonathan Sebat, Sébastien Jacquemont, Donna McDonald-McGinn, Anne S Bassett, Mieke van Haelst, Claudia Vingerhoets, and Thérèse van Amelsvoort

* *Junior Investigator*

12:05 **016** **Characterizing environment and its relationship to psychopathology in 22q11.2 deletion syndrome**
Arielle Ered, Tyler M. Moore, Austin T. Moran, Claudine B. Van Arman, Alyssa M. Neppach, Mia Schwartzberg, R. Sean Gallagher, Simon Smerconish, Kosha Ruparel, Scott Troyan, Amy Cassidy, Lauren K. White, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Oanh Tran, Elaine H. Zackai, Beverly S. Emanuel, Ruben C. Gur, Donna M. McDonald-McGinn, and Raquel E. Gur

12:15 **017** **Combined and differential effects of polygenic, socioeconomic, and developmental markers in individuals with 22q11.2 and 16p11.2 copy number variants**
Vincent-Raphaël Bourque, Anjali Srinivasan, Samuel J R A Chawner, Laura Almasy, Laura Schultz, Ruben Gur, Marianne B M van den Bree, Donna M McDonald-McGinn, Therese van Amelsvoort, Ann Swillen, Carrie E Bearden, Raquel E Gur, Genes to Mental Health Network (G2MH), Jonathan Sebat, Jacob A S Vorstman, and Sébastien Jacquemont

12:25 **Q&A**

12:35 **018** **Investigating the non-deleted chromosome 22q11.2 allele** *
Lily N. Elman, Audrey Olsen, Evie Andrewes, Lydia Rockart, Lydia Hamilton, T. Blaine Crowley, Bekah Wang, Daniel E. McGinn, Beverly S. Emanuel, Elaine H. Zackai, Beata Nowakowska, and Donna M. McDonald-McGinn

12:42 **019** **Autosomal recessive conditions unmasked by 22q11.2 deletion: a population-level analysis using a national EHR network**
Hanadys Ale, Jessica Colon, Jorge Haddad Gomez, Emily Woolhiser, Andres Wong, Virna Kneller, and Shwetha Maharaj

12:49 **020** **Screening for *TANGO2* and other autosomal recessive conditions in individuals with 22q11.2 deletion syndrome**
Valerie J. Allegretti, Jaime C. Duncan, Laura H. Swibel Rosenthal, and Kelly E. Regan-Fendt

12:56 **021** ***TANGO2* deficiency with 22q11.21 microdeletion: metabolic and neuropsychiatric considerations**
Valerie J. Allegretti, Renee J. Wakulski, Joshua J. Baker, Laura H. Swibel Rosenthal, and Kelly E. Regan-Fendt

13:00 **022** **22q and *TANGO2* - Understanding *TANGO2* deficiency disorder via genotype-phenotype correlations in 22q11.2 deletion syndrome**
Beata A. Nowakowska, Maciej Geremek, Theresa A. Grebe, Robert Śmigiel, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Raquel Gur, Bernice Morrow, Anne Bassett, and Donna M. McDonald-McGinn

* *Junior Investigator*

13:10 **023** **Clinical consensus guidelines for acute management of *TANGO2* deficiency disorder**
Samuel J. Mackenzie, Ashton B. Ariola, Deena L. Chisholm, Jonathan Scaccia, Mike Morris, Nourhan Suleiman, Sebastian C. Tume, Svjetlana Tisma-Dupanovic, Miriam Hull, Donna M. McDonald-McGinn, Scott Ceresnak, Angela L. Hewitt, Elizabeth G. Ames, Kimberly M. Houck, Alyssa Smith, Seema R. Lalani, Megha K. Kanjia, Georgia Sarquella-Brugada, Christina Y. Miyake, Divakar S. Mithal, Kuntal Sen, Joshua K. Meisner, and Lina Ghaloul-Gonzalez

13:20 **Q&A**

13:30 **LUNCH – AMALTHEA RESTAURANT AND TERRACE**
ALL CONFERENCE ATTENDEES AND ACCOMPANYING PERSONS

SESSION IV CARDIAC DEVELOPMENT, PRENATAL DIAGNOSIS, & THE IMPORTANCE OF TBX1

Chairs: Natalie Blagowidow and Bernice Morrow

14:30 **024** ***INVITED PRESENTATION***
Multifactorial role of Tbx1 in the second heart field
Sophie Astrof, Newark, NJ, USA

14:45 **025** ***INVITED PRESENTATION***
Tbx1 acts upstream of distal enhancers in the embryonic mesoderm for cardiac outflow tract formation
Bernice E. Morrow, Bronx, NY, USA

15:00 **Q&A**

15:05 **026** **Broad phenotype of congenital heart disease in fetuses and infants with 22q11.2 deletion syndrome: an international cohort study** *
Marco Masci, Stephanie Galloway, Ronald Wapner, Alessandra Toscano, T. Blaine Crowley, Elizabeth Goldmuntz, Anne S. Bassett, Donna M. McDonald McGinn, and Lindsay R. Freud

15:15 **027** **Primary pulmonary artery anomalies in 22q11.2 deletion syndrome** *
Cristina Angellotto, T. Blaine Crowley, Daniel E. McGinn, Marta Unolt, Carolina Putotto, Elaine H. Zackai, Cristina Digilio, Paolo Versacci, Jill Savla, Robert Kelly, Bernice Morrow, Bruno Marino, and Donna M. McDonald-McGinn

15:25 **028** **Branch pulmonary artery anomalies in 22q11 deletion-diagnosis, management and medium-term outcomes – a case series**
Sanket S. Shah, Manbir Sanghera, Matthew M. Feldt, Julie Martin, Maria Kiaffas, and Nikita Raje

* ***Junior Investigator***

15:30 **Q&A**

15:40 **029** **Prenatal diagnosis of 22q11.2 deletion syndrome: What can we learn about pregnancy options from the international 22q11.2 PVPOS study?**
Natalie Blagowidow, T. Blaine Crowley, Stephanie Galloway, Daniel E. McGinn, Kimberly Gaiser, Oahn Tran, Elaine H. Zackai, Beverly S. Emanuel, Erica Schindewolf, Julie Moldenhauer, PVPOS Consortium, Qi Yan, Ron Wapner, Anne S. Bassett, Lindsay R. Freud, and Donna M. McDonald-McGinn

15:50 **030** **Prenatal diagnosis and outcomes in a large cohort of patients with 22q11.2 copy number variants** *
Daniel E. McGinn, T. Blaine Crowley, Renee Wright, Audrey Olson, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Natalie Blagowidow, Nahla Kahlek, and Donna M. McDonald-McGinn

16:00 **031** **The impact of non-invasive prenatal testing (NIPT) for 22q11.2 copy number variants**
Donna M. McDonald-McGinn, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Lydia Hamilton, Lily Elman, Evie Andrewes, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Anne Bassett, and Natalie Blagowidow

16:10 **032** **Cell-free DNA screening for the 22q11.2 microdeletion: disparities in access to testing**
Katelyn Hashimoto, Patrick Kelly, Brittany Prigmore, Kathleen D. Kueck, Thea N. Golden, and Sheetal Parmar

16:20 **Q&A**

16:30 ***AFTERNOON TEA AND POSTER VIEWING – COVERED TERRACE***

SESSION V GENOMICS, DIET, VITAMINS, AND THE MICROBIOME

Chairs: Maria Mascarenhas and Irene Zohn

17:00 **033** **Reduced dosage of *Kmt2d* modifies *Tbx1* haploinsufficiency towards phenotypes of 22q11.2DS** *
Daniella Miller, Kevyn Jackson, Timothy C. Cox, and Bernice E. Morrow

17:10 **034** **Mechanisms underlying variability in 22q11.2 deletion syndrome**
Tatiana Ferebee, Pooja Chauhan, Elias Oxman, and Irene Zohn

17:20 **035** **Nutritional implications for genetic counseling in 22q11.2 deletion syndrome: evidence from a mouse model** *
Maria Victòria Llull-Albertí, Emilia Amengual-Cladera, Angelika Merkel, Jessica Hernandez-Rodriguez, Marc Ventayol-Guirado, Juan Antonio Jimenez-Barceló, Jairo Enrique Rocha, Aina Vaquer-Picó, Víctor José Asensio-Landa, Laura Torres-Juan, Fernando Santos-Simarro, María García de Paso-Mora, Icíar Martínez-López, and Damian Heine-Suñer

* *Junior Investigator*

17:30 **036** **Studying vitamin A signaling in human heart models of 22q11.2DS**
Conchi M. Estaras, Emily Megill, Eleonora Stronati, Elizabeth Abraham, Aidan Douglas, and Mikel Zubillaga

17:40 **037** **Dietary intake patterns in children with 22q11.2 deletion syndrome: widespread micronutrient imbalances revealed following 72-hour dietary recall analysis**
Luc Santilli, Alain J. Benitez, Audrey Olson, Lydia Rockart, Robin Miccio, Lauren White, Donna McDonald-McGinn, and Maria Mascarenhas

17:50 **038** **Vitamin B12 status in adults with 22q11.2 deletion syndrome**
Samantha D'Arcy, Tracy Heung, Lisa Palmer, Nikolai Reyes, and Anne S. Bassett

18:00 **039** **First characterization of the gut microbiome in children with 22q11.2 deletion syndrome**
Alain J. Benitez, Luc Santilli, Scott G. Daniel, Audrey Olson, Lydia Rockart, Robin Miccio, Lauren White, Donna McDonald-McGinn, and Maria Mascarenhas

18:10 **040** **Microbiota–Metabolite Remodeling Links *Tbx1* Haploinsufficiency to Brain Dysfunction in 22q11.2 Deletion Syndrome**
Stefano Leo, Sabrina Bianco, Sara Cioffi, Gemma Flore, Sara Veneziano, Michele Costanzo, Marianna Caterino, Margherita Ruoppolo, Lucia Mele, Lucia Marra, Marchesa Bilio, Rosa Ferrentino, Elizabeth Illingworth, Antonio Baldini, and Gabriella Lania

18:20 **Q&A**

18:30 **Adjourn – Day 1**

20:00 ***WELCOME RECEPTION - GRECIAN CAVE TERRACE***
GROUP PHOTO, SIGNATURE COCKTAIL, AND HEAVY HORS D'OEUVRES
ALL CONFERENCE ATTENDEES AND ACCOMPANYING PERSONS

WEDNESDAY JULY 15, 2026

6:00 ***REGISTRATION OPEN – ZEUS BALLROOM COURTYARD***

7:00 ***BREAKFAST – AMALTHEA RESTAURANT AND TERRACE***
MIRABELLO BAY RESORT GUESTS ONLY

SESSION VI IMMUNE ACTIVATION, DYSREGULATION & INFLAMMATION: A NEW PARADIGM

Chairs: Hanadys Ale and Elfi Vergaelen

8:00 **041** ***INVITED PRESENTATION***
Primate-specific RNA dysregulation and innate immune activation in 22q11.2 deletion syndrome
Sara Heras, Granada, Spain

8:15 **042** **Immunologic correlates of psychotic illness in 22q11.2 deletion syndrome**
Anne S. Bassett, Katherine Beigel, Kelly Maurer, Nouf Alsaati, Raquel Gur, T. Blaine Crowley, Donna McDonald McGinn and Kathleen E. Sullivan

8:25 ***043*** **Haploinsufficiency-Driven RNA Metabolism is Associated with Immune Dysregulation and Psychosis Risk in 22q11.2 Deletion Syndrome** *
Christina Michalski, David A. Parker, Leah Cheng, Mojahidul Islam, Sidney Imes, Gabrielle Ruban, Heath Dunlop, Bruce Cuthbert, Brett Henshey, Grace Lee, Nicholas M. Massa, Opal Y. Ousley, Elaine F. Walker, David R. Goldsmith, Joseph F. Cubells, Erica Duncan, Bradley D. Pearce, Ashish A. Sharma and Zhexing Wen

8:32 **044** **Discriminating psychosis in 22q11.2 deletion syndrome using monocyte inflammation-related gene expression** *
Emma Saillart, Elfi Vergaelen, Stephan Claes, Elske Vrieze and Ann Swillen

8:39 **045** **Immune dysregulation in chromosome 22q11.2 related disorders: insights from the USIDNet registry**
Nikita Raje, Vaibhavi Vichare, Roshini Abraham, Ivan Chinn, Megan A. Cooper, Ramsay Fuleihan, Avni Y. Joshi, Monica G. Lawrence, Rebecca Marsh, Luigi Notarangelo, Jennifer M. Puck, Charlotte Cunningham Rundles, Kelly Walkovich and Kathleen Sullivan

8:46 **046** **Immune system activation following trauma in 22q11.2 deletion syndrome**
Adi Drapisz, Yana Paltavets, Shira Dar, Doron Gothelf and Michal Taler

8:50 **Q&A**

* *Junior Investigator*

9:00 **047** **Identification of whole gene deletion of *TBX1* with autoimmune cytopenias in a large pediatric cohort**
Emily M Harris, Amanda B Grimes, Yi-Lee Ting, Taylor Kim, Rachael F Grace, Kristin Shimano and Michele P. Lambert

9:08 **048** **Immune cytopenias in a large cohort of patients with 22q11.2DS: management, outcomes and unique considerations**
T. Blaine Crowley, Praharsha Konde, Samantha Gaerian, Donna McDonald-McGinn and Michele P. Lambert

9:15 **049** **Proteome wide autoantibody profiling in the 22q11.2 deletion syndrome**
Jenny Lingman Framme, Viktoria Hennings, Anna-Carin Lundell, Karolina Thörn, Christina Lundqvist, Susanne Lindgren, Vanja Lundberg, Esbjörn Telemo, Anders Fasth, Sólveig Óskarsdóttir and Olov Ekwall

9:22 **050** **Spatial multiomic studies of the thymus in individuals with 22q11.2 deletion syndrome**
Viktoria Hennings, Jenny Lingman Framme, Sólveig Óskarsdóttir and Olov Ekwall

9:28 **051** **Investigation of autoimmune alterations in 22q11.2 deletion syndrome in a single Brazilian center: preliminary results from 17 individuals** *
João Pedro Moretti and Vera Lúcia Gil-da-Silva-Lopes

9:32 **052** **Cardiac complexity predicts increased immune diagnostic burden in 22q11.2 deletion syndrome** *
Jasmyn Atalla, Blaine Crowley, Kathleen Sullivan, Jennifer Heimall Donna M. McDonald-McGinn and Timothy Buckey

9:39 **053** **Platelet function and bleeding risk in adults with 22q11.2 deletion syndrome: a cross-sectional investigational study** *
Emma N.M.M. von Scheibler, Jeltje C.C. Spapens, Magdolna Nagy, Irene M.L.W. Keularts-Körver, Floor C.J.I. Heubel-Moenen, Johan W.M. Heemskerk, Agnies M. van Eeghen, Thérèse A.M.J. van Amelsvoort and Erik Boot

9:45 **Q&A**

9:55 **054** **Immunologic outcomes following thymectomy in patients with 22q11.2 deletion syndrome**
Anne Jennings, T. Blaine Crowley, Audrey Olson, Lydia Rockart, Daniel E. McGinn, Oanh Tran, Elaine H. Zackai, Beverly S. Emanuel, J. William Gaynor, Kathleen E. Sullivan, Kathleen Valverde, and Donna M. McDonald-McGinn

10:02 **055** **TLB-101, a GMP allogeneic iPSC-derived thymic epithelial cell product for the potential treatment of congenital thymic insufficiency**
Francisco Leon, Holger A. Russ, Jessie M. Barra, Alexander S. Baker, Antonio Jimeno, J Jason Morton, Nathaniel Alzofon, Philip Ball, Lara Silverman, Paul Dunford, Christian Blount, and Yeh-Chuin Poh

* *Junior Investigator*

10:12 **056** **Therapeutic restoration of immune function through iPSC-derived human thymic epithelial cells (iTECs) - An update on bringing iTECs to the clinic**
Wenqing Wang, Abdulvasey Mohammed, Martin Arreola, Hanh Dan Nguyen, Zihao Zheng, Yujin Moon, Kelsea M. Hubka, Humza Ali Khan, Mark Krampf, Agnieszka Czechowicz, Anca Pasca, Li Li, Virginia Winn, Sean Bendall, Rosa Bacchetta, Vittorio Sebastiano, and Katja G. Weinacht

10:21 **Q&A**

10:30 ***COFFEE BREAK AND POSTER VIEWING – COVERED TERRACE***

SESSION VII HEAD, SHOULDERS, KNEES AND TOES

Chairs: Jill Arganbright and Sulagna Saitta

11:10 **057** **Postoperative hypocalcemia in children with 22q11.2 deletion syndrome: results following initiation of an institution-wide evidence-based clinical pathway**
Jill Arganbright, Meghan Tracy, Max Feldt, Nikita Raje, Janelle Noel-MacDonnell

11:20 **058** **Peri-operative pathway for hypocalcemia management in youth with 22q11.2 deletion/duplication syndrome: preliminary outcomes following palate repair** *
Douglas Villalta, Donna M. McDonald-McGinn, T. Blaine Crowley, Audrey Olsen, Daniel E. McGinn, Elaine H. Zackai, Lisa Elden, Oksana Jackson, Edna E. Mancilla, Vaneeta Bamba, Ian Campbell, and Lorraine E. Levitt Katz

11:27 **059** **Recurrent postpartum hypocalcemia in association with 22q11.2 deletion syndrome** *
Evie Andrewes, Audrey Olson, T. Blaine Crowley, Daniel E. McGinn, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Michele P. Lambert, Vaneeta Bamba, Lorraine L. Katz, Natalie Blagowidow, Lorraine Dugoff, and Donna M. McDonald-McGinn

11:31 **060** **Thyroid carcinoma and 22q11.2 deletion syndrome – A critical association**
Andrew Bauer, T. Blaine Crowley, Audrey Olson, Lily Elman, Evie Andrewes, Daniel E. McGinn, Elaine H. Zackai, Beverly Emanuel, Michele P. Lambert, Kathleen E. Sullivan, Vaneeta Bamba, Lorraine L. Katz, Julio Ricarte-Filho, Jenny Li and Donna M. McDonald-McGinn

11:41 **061** **Testosterone deficiency in males with 22q11.2 deletion syndrome: a case series**
Evana Valenzuela, Hanadys Ale, Lauren Waidner, Lauryn Bachman, and Jeremy Purrow

11:45 **062** **Delineating the incidence, accrual, and pathways to development of cardiovascular disease for 22q11.2 microdeletion using population-based and clinical data** *
Sarah L. Malecki, Tracy Heung, Samantha Morais, Refik Saskin, Drew Wilton, Therese A. Stukel, Eyal Cohen, Amol A Verma, and Anne S. Bassett

* *Junior Investigator*

11:55 **063** **Use of GLP-1 agonists and associated outcomes in adults with 22q11.2 deletion syndrome**
Samantha D'Arcy, Tracy Heung, Lisa Palmer, Nikolai Reyes, and Anne S. Bassett

12:02 **064** **Body composition and bone density in children with 22q11.2 deletion syndrome: evidence for reduced lean mass** *
Helena-Jamin Ly, Anna Svedlund, Annika Malmgren, and Solveig Oskarsdottir

12:09 **065** **Vertebral fractures in youth with 22q11.2 deletion syndrome: a case series** *
Amanda Spatz, Edna Mancilla, Donna M. McDonald-McGinn, Vaneeta Bamba, and Lorraine E. Levitt Katz

12:15 **Q&A**

12:25 **066** **Cervical spinal cord compression in association with 22q11.2 deletion syndrome** *
Jette A. Boxem, Michiel L. Houben, Malcolm L. Ecker, Gregory Heuer, Erin S. Schwartz, Tom Schlosser, Gregory Heuer, Elaine H. Zackai, T. Blaine Crowley, Donna M. McDonald-McGinn, Aebele B. Mink van der Molen, and Alexander M. Tucker

12:32 **067** **Early vertebral rotation before the adolescent growth spurt in children with 22q11.2DS: Implications for development of scoliosis** *
Annemie J. Sluijter, Peter P.G. Lafranca, René M. Castelein, Moyo C. Kruyt, Keita Ito, Michiel L. Houben, and Tom P.C. Schlösser

12:36 **068** **The role of orthopedic conditions in lower extremity pain and exercise intolerance in children with 22q11.2 deletion syndrome** *
Femke G.M. van den Helder and Michiel L. Houben

12:43 **069** **Incidental neuroradiological findings in 22q11DS: Update in an expanded sample**
J. Eric Schmitt, Simon Smerconish, David Roalf, T. Blaine Crowley, Victoria Giunta, Daniel E. McGinn, Elaine H. Zackai, Beverly S. Emanuel, Sarah Hopkins, Madeline Chadehumbe, Raquel E. Gur, Donna M. McDonald-McGinn, and Aaron Alexander-Bloch

12:53 **070** **Handgrip strength in adults with 22q11.2 deletion syndrome**
Erik Boot and Claudia Vingerhoets

13:03 **071** **The cutaneous spectrum of 22q11.2 deletion syndrome: a retrospective cohort analysis across age groups**
Hanadys Ale, Aditi Chokshi, Lucia Martinez, Victoria Rosali Gonzalez, Lucila Mesa, Victoria Griffith, Sarah Asbek, Camille Robinson, and Raul Escobar

13:13 **072** **22q through the back door** *
Lily N. Elman, Audrey Olsen, T. Blaine Crowley, Daniel E. McGinn, Evie Andrewes, Lydia Rockart, Lydia Hamilton, Oanh Tran, Jennifer Borowka, Natalie Ginn, Abraham Haimed, Michele P. Lambert, Ethan Goldberg, Beverly S. Emanuel, Elaine H. Zackai, and Donna M. McDonald-McGinn

* *Junior Investigator*

13:20 **Q&A**

13:30 **LUNCH – AMALTHEA RESTAURANT AND TERRACE**
ALL CONFERENCE ATTENDEES AND ACCOMPANYING PERSONS

SESSION VIII EYES AND EARS AND MOUTH AND NOSE

Chairs: Oksana Jackson and Emily Gallagher

14:30 **073** ***INVITED PRESENTATION***
Outcomes in patients with 22q11.2 deletion syndrome following speech surgery
Oksana A. Jackson, Philadelphia, PA, USA

14:45 **074** **Timing of surgery for velopharyngeal insufficiency in patients with 22q11.2 deletion syndrome: a retrospective chart analysis** *
Jette A Boxem, Cynthia B. Solot, Michiel L. Houben, T. Blaine Crowley, Donna M. McDonald-McGinn, Aebele B. Mink van der Molen, and Oksana A. Jackson

14:52 **075** **Bilateral buccal myomucosal flap palatoplasty for the management of velopharyngeal dysfunction in children with 22q11.2 deletion syndrome: case series of 4 patients**
Jill Arganbright, Meghan Tracy, Janelle Noel-MacDonnell, Kathryn Dent, Susan Parsons, and Nikita Raje

14:59 **076** **Presentations of congenital anterior glottic webs and laryngeal clefts in individuals with 22q11.2 deletion syndrome: patterns, outcomes, and clinical pathways**
Lisa Elden, Karen Zur, Ian Jacobs, Luv Javia, Steve Sobol, Donna McDonald-McGinn, T. Blaine Crowley, Elaine Zackai, and Ryan Ruiz

15:06 **077** **Altered Sleep Architecture and NREM Physiology in 22q11.2 Deletion Syndrome** *
Kathleen P. O'Hora, Rune Bøen, Hoki Fung, Charles Schleifer, Leila Kushan-Wells, Jennifer Xu, Natasha Reddivalam, Jared M. Saletin, and Carrie E. Bearden

15:13 **078** **Gastrointestinal symptom burden is associated with anxiety, stress, and sleep disturbance in children with 22q11.2 deletion syndrome**
Alain J. Benitez, Luc Santilli, Kush Patel, Audrey Olson, Lydia Rockart, Robin Miccio, Lauren White, Donna McDonald-McGinn, and Maria Mascarenhas

15:20 **Q&A**

15:30 **079** ***INVITED PRESENTATION***
Speech and language in 22q11.2 deletion as a window into understanding long term outcome
Cynthia Solot, Philadelphia, PA, USA

* ***Junior Investigator***

15:45 **080** **Predictors of persistent expressive language impairment in 22q11.2 deletion syndrome** *
Gracie Trulove, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Sarah Hopkins, Donna M. McDonald-McGinn, Cynthia Solot, and Samuel Alperin

15:52 **081** **Language development in 22q11.2 deletion syndrome from preschool to school-age and in adolescence: evidence from two longitudinal studies**
Tessel Boerma, Jantine Wignand, Manik Djelantik, Emma Everaert, Ania Fiksinski, Michiel Houben, Iris Selten, and Frank Wijnen

15:59 **082** **Memory, attention and vocabulary in 22q11.2 deletion syndrome: a longitudinal study** *
Jantine R. Wignand, Tessel D. Boerma, Emma Everaert, Iris S. Selten, Michiel L. Houben and Frank N.K. Wijnen

16:03 **083** **Additional diagnoses in selected patients with autism and 22q11.2 deletion syndrome: casting an even wider net**
Jennifer Rodstein, Caroline Y. Kuo, Apisadaporn Thambundit, Reina Capati and Sulagna C. Saitta

16:13 **084** **Cognitive and emotional profiles in young adults with chromosome 22q11.2 deletion syndrome**
Kathleen Angkustsiri, Andrea Schneider, Hannah Culpepper, Marwa Zafarullah, and Flora Tassone

16:20 **Q&A**

16:30 ***AFTERNOON TEA AND POSTER SESSION – COVERED TERRACE***
ALL AUTHORS PRESENT

18:00 **Adjourn – Day 2**

19:30 ***22q OLYMPICS AND SUNSET SOCIAL – BAHIA MAR AND STONE THEATER FOLLOWED BY PIZZA AND BEVERAGES***
ALL CONFERENCE ATTENDEES AND ACCOMPANYING PERSONS
PLEASE WEAR YOUR OLYMPIC VEST

* *Junior Investigator*

THURSDAY JULY 16, 2026

6:00 ***REGISTRATION OPEN – ZEUS BALLROOM COURTYARD***

7:00 ***BREAKFAST – AMALTHEA RESTAURANT AND TERRACE***
MIRABELLO BAY RESORT GUESTS ONLY

SESSION IX COGNITION AND PSYCHIATRIC ILLNESS

Chairs: Ann Swillen and Ania Fiksinski

8:00 **085** **30 years later: IQ profile among individuals with 22q11.2 deletion syndrome**
Edward M. Moss, Katherine Baum, Michael F. Woodin, T. Blaine Crowley, Elaine H. Zackai, and Donna M. McDonald-McGinn

8:10 **086** **Neurocognitive profiles of individuals with 22q11.2DS: effects of deletion size, intellectual disability, and overall psychopathology burden**
Ruben C. Gur, Donna M. McDonald-McGinn, Kosha Ruparel, Carrie Bearden, Ann Swillen, Thérèse van Amelsvoort, Jonathan Sebat, Marianne van den Bree, Sébastien Jacquemont, Anne Bassett, Jacob Vorstman, and Raquel E. Gur

8:20 **087** **Educational best practices for school-age children with 22q11.2 deletion syndrome: recommendations for educators**
Stephen R. Hooper, Edward M. Moss, Jane Summers, Katherine Baum, Ania M. Fiksinski, Maude Schneider, Cheryl Cytrynbaum, Donna M. McDonald-McGinn, Andrea Shugar, and Ann Swillen on behalf of the International Brain Behavior Consortium Study Investigators

8:30 **088** **Psychoeducation across the lifespan in 22q11.2 deletion syndrome: enhancing communication and tailored support in home, school, and work contexts**
Ann Swillen, Marie Meuris, Robin De Croon, Maxwell Szymanski, and Katrien Verbert

8:40 **089** **Interactive digital psychoeducation for 22q11.2 deletion syndrome: iterative, user-centred development of an app to support understanding of genetic complexity**
Maxwell Szymanski, Robin De Croon, Ann Swillen, Marie Meuris, and Katrien Verbert

8:47 **090** **Development and evaluation of an evidence-based group-based psychoeducation program for families affected by 22q11.2 deletion syndrome**
Ania Fiksinski, Lieke Reijn, and Michiel Houben

8:54 **091** **Rare mutations implicate CGE interneurons as a vulnerable axis of cognitive deficits across psychiatric disorders**
Stephanie A. Herrlinger, Jiayao Wang, Bovey Y Rao, Jonathan Chang, Joseph A. Gogos, Attila Losonczy and Dennis Vitkup

9:05 **Q&A**

9:15 **092** ***INVITED PRESENTATION***
22q11.2 deletion as a window into understanding the genomics of psychiatric illness
Anne Bassett, Toronto, ON, Canada

9:30 **093** **Medical burden, psychopathology and neurocognition in 22q11.2 deletion syndrome**
Raquel E. Gur, Donna M. McDonald-McGinn, Ruben C. Gur, Arielle Ered, Austin T. Moran, Claudine B. Van Arman, Alyssa M. Neppach, Mia Schwartzberg, R Sean Gallagher, Simon Smerconish, Kosha Ruparel, Scott Troyan, Tyler M. Moore, Amy Cassidy, Lauren K. White, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Oanh Tran, Elaine H. Zackai, Beverly S. Emanuel, Yana Poltavets, Ronnie Weinberger, Michal Taler, and Doron Gothelf

9:40 **094** **Developmental trajectories of irritability and associations with a psychosis-prone state in youth with 22q11.2 deletion syndrome and other neurodevelopmental copy number variants**
Jessica H. Hall, Josephine E. Haddon, Samuel J. R. A. Chawner, Jeremy Hall, Peter Holmans, Michael J. Owen and Marianne B. M. van den Bree

9:50 **095** **Exposure to trauma and post-traumatic stress disorder in 22q11.2 deletion syndrome**
Adi Drapisz, Yana Poltavets, Ronnie Weinberg, Naama De La Fonataine, Nitza Nakash-Axelrod, Michal Taller, and Doron Gothelf

10:00 **096** **Copy Number Variants in Spanish Psychiatric Care: Clinical Characteristics and Findings a Multicenter Cohort**
Damià Heine-Suñer, Maria Victoria Llull Albertí, Javier Labad, Jesús Herrera-Imbroda, Vicent Balanzá-Martínez, Amaya Hervas, Anna Maria Cueto-González, Antoni Ramos-Quiroga, Rosa Ayesa-Arriola, Iñaki Zorrilla, Ana García-Blanco, Paz García-Portilla, Edith Pomarol-Clotet, Bàrbara Arias, Covadonga Martínez, Olga Rivero, the CESPED group, and Elisabet Vilella

10:10 **097** **Association between sluggish cognitive tempo symptoms and psychiatric diagnosis in a cohort of children with 22q11.2 deletion syndrome**
Veselina Gadancheva, and Fiona McNicholas

10:16 **Q&A**

10:30 ***COFFEE BREAK – COVERED TERRACE***

SESSION X NEUROANATOMY, METABOLISM, AND CNS FUNCTION

Chairs: Jacob Vorstman and Stanislav Zakharenko

11:10 **098** ***INVITED PRESENTATION***
Emerging Discoveries on 22q11.2 and the Blood–Brain Barrier
Francesco Papaleo, Genova, Italy

11:25 **099** **Biochemical alterations in tryptophan metabolism in 22q11.2 deletion syndrome**
Cassandra J. Hatzipantelis, David E. Olson, Kathleen Angkustsiri, Andrea Schneider, and Flora Tassone

11:32 **100** **Systemic energy metabolism disruption as a biomarker of psychosis risk in 22q11.2 deletion syndrome**
Marwa Zafarullah, Hannah Culpepper, Blythe Durbin-Johnson, Andrea Schneider, Kathleen Angkustsiri, and Flora Tassone

11:40 **101** **The making and un-making of association cortico-cortical connections in 22q11DS**
Anthony -S. LaMantia, Thomas M. Maynard, Zachary D. Erwin, and Shah Rukh

11:50 **Q&A**

12:00 **102** ***INVITED PRESENTATION***
Neural circuit dysfunctions in animal and human models of schizophrenia risks
Stanislav S. Zakharenko, Memphis, TN, USA

12:15 **103** **Cerebellar regulation of top-down auditory cortical circuits and its potential role in 22q11.2 deletion syndrome**
Tae-Yeon Eom, Christopher M. Davenport, Jay Blundon, Feng Feng, Troy A. Hackett, and Stanislav S. Zakharenko

12:25 **104** **Associations between psychotic symptoms and subthalamic nuclei volumes in the 22.11.2 deletion syndrome (22q11DS) using Ultra High Field (UHF) MRI**
J. Eric Schmitt, Simon Smerconish, David Roalf, Sarah Hopkins, Aaron Alexander-Bloch, T. Blaine Crowley, R. Sean Gallagher, Daniel E. McGinn, Kosha Ruparel, Lauren K. White, Elaine H. Zackai, Anne Bassett, Ruben C. Gur, Raquel. E. Gur, Stanislav Zakharenko, and Donna M. McDonald-McGinn

12:34 **105** **Cerebellar differences in 22q11.2 duplication syndrome** *
Samuel Alperin, Madeline Chadehumbe, T. Blaine Crowley, Donna M. McDonald-McGinn, and Sarah Hopkins

12:40 **Q&A**

12:50 **106** **Neurodevelopmental perturbations in 22q11.2DS using mouse and human functional genomic approaches** *
Wenna Chen, Lijie Shi, Elisha J. Fogel, Bernice E. Morrow, and Deyou Zheng

* *Junior Investigator*

13:00 **107** **Disorganized inhibitory dynamics in hippocampal area CA1 of 22q11.2 deletion mutant mice**
Stephanie A. Herrlinger, Bovey Y Rao, Margaret E. Conde Paredes, Anna L. Tuttman, Haroon Arain, Erdem Varol, Joseph A. Gogos, and Attila Losonczy

13:10 **108** **Olfactory deficits and structural anomalies of the olfactory system in 22q11.2 deletion syndrome**
David R. Roalf, Donna M. McDonald-McGinn, Bruce I. Turetsky, Paul J. Moberg, T. Blaine Crowley, Phoebe Freedman, Monica E. Calkins, R. Sean Gallagher, Audrey Olson, Daniel E. McGinn, Lydia Rockart, Oanh Tran, Elaine H. Zackai, Beverly S. Emanuel, Kosha Ruparel, Russell T. Shinohara, Lauren White, and Raquel E. Gur

13:20 **Q&A**

13:30 **LUNCH – AMALTHEA RESTAURANT AND TERRACE**
ALL CONFERENCE ATTENDEES AND ACCOMPANYING PERSONS

SESSION XI BIOMARKERS AND MODIFIERS

Chairs: Carrie Bearden and Erik Boot

14:30 **109** ***INVITED PRESENTATION***
Impact of the 22q11.2 Deletion on Brain Structure and Function: Insights from the ENIGMA Consortium
Carrie E. Bearden, Los Angeles, CA, USA

14:45 **110** **Network-specific deviations in functional brain development in 22q11.2DS linked to psychosis**
Kaustubh Supekar, Leila Kushan, Charles Schleifer, Gabriela Repetto, Nicolas A Crossley, and Carrie Bearden

14:55 **111** **Striatal dopamine transporter binding in adults with 22q11.2 copy number variants: An [123I]FP-CIT SPECT study** *
Jeltje C.C. Spapens, Carmen F. M. van Hooijdonk, Rik Schalbroeck, Amy L. Sylvester, Erik Boot, Therese A.M.J. van Amelsvoort, Claudia Vingerhoets, and Jan Booij

15:05 **112** **Cortical myoclonus as a distinct motor phenotype of 22q11.2 deletion syndrome**
Nikolai Gil D. Reyes, Talyta Grippe, Benedetta Angeloni, Victor Lira, Connie Marras, Erik Boot, Ryan K.C. Yuen, Anthony E. Lang, Danielle M. Andrade, Robert Chen, and Anne S. Bassett

15:15 **113** **Early-onset Parkinson's disease with 22q11.2 microdeletion and pathogenic *GBA1* variant**
Nikolai Gil D. Reyes, Daniel G. Di Luca, Ivan Martinez-Valbuena, Erik Boot, Maria Corral, Ryan K.C. Yuen, Connie Marras, Anthony E. Lang, and Anne S. Bassett

* *Junior Investigator*

15:23 **114** **Assessing a polygenic risk score for Parkinson's disease in 22q11.2 deletion syndrome**
Nikolai Gil D. Reyes, Shengjie Ying, Adrian I. Espiritu, Tracy Heung, Yue Yin, Erik Boot, Anthony E. Lang, Connie Marras, Ryan K.C. Yuen, and Anne S. Bassett

15:30 **115** **Biomarkers in tear fluid: examining dopamine and p-tau in participants with 22q11.2 deletion syndrome**
Thérèse van Amelsvoort, Emma von Scheibler, Rianne van Roij, Erik Boot, Claudia Vingerhoets, David Linden, and Marlies Gijs

15:40 **116** **Dopamine-associated oxidative stress differentially compromises cortical and striatal neurons and circuits in the *LgDel* 22q11DS mouse model**
Anthony-S. LaMantia, Zachary D. Erwin, Thomas M. Maynard, Seth R. Batten, Terrence M. Lohrenz, Leonardo Barbosa, Paul Sands III, and P. Read Montague

15:50 **Q&A**

16:00 ***AFTERNOON TEA – COVERED TERRACE***

SESSION XII MODELING TOWARDS DISCOVERY

Chairs: Spyros Petrakis and Thérèse van Amelsvoort

16:30 **117** ***INVITED PRESENTATION***
Stem cell-based drug discovery for neurological disorders
Spyros Petrakis, Thessaloniki, Greece

16:45 **118** **Aberrant glutamatergic transmission and homeostatic plasticity in a human neuronal model of 22q11.2 deletion syndrome**
Weibo Niu, Jidong Guo, Ximing Ran, David Parker, Xiangru Li, Shaojun Yu, Sidney Imes, Ryan Purcell, Eric Guo, Sophia Y. Jiang, Gary J Bassell, Jennifer G Mulle, Opal Y. Ousley, Bradley Pearce, Yue Feng, Elaine F. Walker, Joseph F. Cubells, Zhaohui Qin, Erica Duncan, and Zhexing Wen

16:55 **119** **Altered neurophysiological activity of iPSC-derived neurons of 22q11.2 deletion syndrome**
Adrian J Harwood, Jeremy Hall, and Gemma Wilkinson

17:02 **120** **Mapping genes differentially expressed in 22q deletion syndrome to sub-populations of control cells defined using scRNA-seq at developmental timepoints during neuro-differentiation**
Janet C. Harwood, Karolina Dec, Jamie Wood, David Linden, Thérèse van Amelsvoort, and Adrian J. Harwood

17:09 **121** **Transcriptomic signature of iPSC-derived neural progenitor cells from 22q11.2 microduplication carriers**
Natasa Kovacevic-Grujicic, Jovana Kostic, Mina Peric, Luka Bojic, Ivana Hadzi Makuncevic, Goran Cuturilo, Adrian J. Harwood, Danijela Drakulic, Milena Stevanovic

17:16 **122** **Neural lineage-specific transcriptomic signatures of intrafamilial clinical variability in a Mother-child pair with 22q11.2 microdeletion**
Danijela Drakulic, Ivana Hadzi Makuncevic, Natasa Kovacevic-Grujicic, Mina Peric, Friederike Ehrhart, Jovana Kostic, Stefan Lazic, Goran Cuturilo, Spyros Petrakis, David E. J. Linden, Adrian J. Harwood, and Milena Stevanovic

17:23 **Q&A**

17:30 **Adjourn – Day 3**

20:00 ***DINNER AND DANCING – ELIA TERRACE***
TOP SESSION PRESENTATION AWARDS
ALL CONFERENCE ATTENDEES AND ACCOMPANYING PERSONS
PLEASE WEAR YOUR DANCING SHOES

FRIDAY JULY 17, 2026

7:00 ***BREAKFAST – AMALTHEA RESTAURANT AND TERRACE***
MIRABELLO BAY RESORT GUESTS ONLY

8:00 ***REGISTRATION OPEN – ZEUS BALLROOM COURTYARD***

SESSION XIII TREATING WHAT IS TREATABLE

Chairs: Doron Gothelf and Raquel Gur

8:30 **123** ***INVITED PRESENTATION***
The effectiveness and safety of psychopharmacotherapy in 22q11.2 deletion syndrome
Doron Gothelf, Tel Aviv, Israel

8:45 **124** **Targeting prefrontal chloride transport for cognitive remediation in 22q11.2 deletion syndrome and substance use disorders**
Arghya Mukherjee

8:55 **125** **Effects of riluzole on psychiatric symptoms, excitation-inhibition balance and functional connectivity in 22q11.2 deletion syndrome**
Claudia Vingerhoets, Amy Sylvester, Desmond Tse, Jeltje Spapens, Sophie Kappert, Nele Soons, David Linden, Dimo Ivanov, and Therese van Amelsvoort

9:05 **126** **Ten-year retrospective review of psychotropic medication use in individuals with 22q11.2 deletion syndrome** *
Samuel Alperin, Sarah Hopkins, Madeline Chadehumbe, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Oanh Tran, R. Sean Gallagher, Kosha Ruparel, Ruben Gur, Elaine H. Zackai, Beverly S. Emanuel, Raquel Gur, and Donna M. McDonald-McGinn

9:12 **127** **Exploring the relationship between ADHD medication and psychotic symptoms in 22q11.2 deletion syndrome**
Claudine B. Van Arman, Arielle Ered, Tyler M. Moore, Austin T. Moran, Alyssa M. Neppach, Mia Schwartzberg, R Sean Gallagher, Simon Smerconish, Kosha Ruparel, Scott Troyan, Amy Cassidy, Lauren K. White, T. Blaine Crowley, Daniel E. McGinn, Audrey Olson, Oanh Tran, Elaine H. Zackai, Beverly S. Emanuel, Ruben C. Gur, Donna M. McDonald-McGinn, and Raquel E. Gur

9:20 **128** **Patients with 22q11.2 deletion syndrome - Too challenging to treat?**
Anne S. Bassett

9:30 **Q&A**

* *Junior Investigator*

9:40 **129** **Resolution of dysautonomic "seizure-like" episodes following antipsychotic withdrawal in an adult with 22q11.2 deletion syndrome and prior scoliosis surgery**
Madeline A Chadehumbe, Donna M. McDonald-McGinn, and Raquel E Gur

9:47 **130** **Psychiatric management concerns in the transition from pediatrics to adult 22q providers**
Kerry D. Conant, Ashmita Banerjee, Matt Blessing, Gary Stobbe, and Emily Gallagher

9:54 **131** **Feasibility and acceptability of BE-WEHL-22q: a virtual wellness program for children with 22q11.2 deletion syndrome and their families**
Luc Santilli, Alain J. Benitez, Audrey Olson, Lydia Rockart, Robin Miccio, Lauren White, Donna McDonald-McGinn, and Maria Mascarenhas

10:01 **132** ***INVITED PRESENTATION***
Current findings and future directions from the IBBC and G2MH Networks
Raquel E. Gur, Philadelphia, PA, USA

10:15 **Q&A**

10:30 ***COFFEE BREAK – COVERED TERRACE***

SESSION XIV MULTIDISCIPLINARY CARE

Chairs: Anne Bassett and Donna McDonald-McGinn

11:10 **133** ***INVITED PRESENTATION***
Seeing the whole elephant: AI-powered discovery across a referral center's 22q experience
Ian Campbell, Philadelphia, PA, USA

11:25 **134** **An exploratory study using machine learning to detect clinical patterns for 22q11.2 deletion syndrome** *
Lais A. Soares, Guilherme P. Coelho, João Pedro Moretti, Vera L. Gil-da-Silva-Lopes, and Ana E. A. Silva

11:35 **135** **Multisystem medical burden in 22q11.2 deletion syndrome – managing complex care**
T. Blaine Crowley, Evie Andrewes, Audrey Olsen, Daniel E. McGinn, Lily Elman, Lydia Rockart, Lydia Hamilton, Elaine H. Zackai, and Donna M. McDonald-McGinn

11:45 **Q&A**

* *Junior Investigator*

11:55 **136** **Stakeholder survey in 240 members of and other relevant parties related to the Dutch 22q11 foundation**
Kim van Bekkum, Erik Boot, Sasja Duijff, Ania Fiksinski, Michiel Houben, Petra Oostema, and Claudia Vingerhoets

12:05 **137** **Caregiver burden and support needs in caregivers of adults with 22q11.2 deletion syndrome**
Lisa Palmer, Tracy Heung, Nikolai Reyes, Samantha D'Arcy, and Anne S. Bassett

12:15 **138** **Optimizing 22q care: the impact of a single-day multidisciplinary clinic model**
Jessica Goldberg, Valerie J Allegretti, Kelly Regan-Fendt, Jalen Clemmons, Sylvie Render, Mitch Bastillo, Elizabeth Lippner, Jennifer Miller, Naiomi Gunaratne, Margaret Ryan, Edward Jones, Chanel Howard, Ryan Cyzman, and Laura Swibel Rosenthal

12:22 **139** **Improving efficiency in the 22q deletion clinic** *
Eme Ani, Felmy Ajayi, Hui Yann, Hui Yann Yap, Chayanuch O. Charoenrat, and Alice Roueche

12:29 **140** **Geographic impacts of healthcare utilization for patients with 22q11.2 deletion/duplication in the pacific northwest**
Emily R. Gallagher, Jade Singleton, and Kristy Carlin

12:36 **141** **Shorter distance to main academic center associated with better longitudinal care and follow up in adult patients with 22q11.2 deletion syndrome** *
Jasmyn Atalla, Blaine Crowley, Kathleen Sullivan, Jennifer Heimall, Donna M. McDonald-McGinn, and Timothy Buckey

12:43 **142** **Where do we go from here? Strategies to support successful transition to adult interdisciplinary care from a pediatric 22q center**
Matthew Blessing, Kerry Conant, Gary Stobbe, and Emily Gallagher

12:50 **Q&A**

SESSION XV LAST WORDS

13:00 **143** ***INVITED PRESENTATION***
Family Voices

13:15 **144** ***INVITED PRESENTATION***
22q11.2DS: Towards restoration of the lost folio
Peter Scambler, London, UK

13:35 **Q&A**

* *Junior Investigator*

13:40 **JUNIOR INVESTIGATOR AND TOP FRIDAY PRESENTATION AWARDS**
Peter Scambler, 22q11.2 Society Trustee and Vice-Treasurer

13:50 **CLOSING REMARKS AND ANNOUNCEMENT OF 2028 MEETING LOCATION**
Donna M. McDonald-McGinn, 22q11.2 Society Chair

13:55 **Closing Breath**
Maria Mascarenhas, Philadelphia, PA, USA

14:00 ***Meeting Adjourned – See you in 2028!***

FAREWELL FARE – COVERED TERRACE
ALL CONFERENCE ATTENDEES AND ACCOMPANYING PERSONS

POSTER PRESENTATIONS

 # Top Scoring Posters

145 **Implementation of digital 22q care plan in electronic medical record to improve interdisciplinary coordination and visibility**
Lindsey H. Benedict, Hannah Berntson, Matthew Blessing, Laura Cline, Leslie Cronk, Emily Gallagher, and Suzanne Siegel

146 **Engaging children with 22q11.2-related disorders in their interdisciplinary care**
Hannah Berntson, Skyler Leonard, Maria Mills, Lex Powers, Cindy Trevino, and Matthew Blessing

147 **Nonword repetition skills of both preschoolers with 22q11.2 deletion syndrome and peers with developmental language disorder are weak, but differently associated with vocabulary**
Tessel Boerma, Marieke Huls, Emma Everaert, Iris Selten, Ellen Gerrits, and Frank Wijnen

148 **Oxycephaly associated with 22q11.2 deletion syndrome: a first reported case ***
Jette A. Boxem, Aebele B. Mink van der Molen, Elaine H. Zackai, T. Blaine Crowley, Donna M. McDonald-McGinn, and Scott P. Bartlett

149 **Sleep disruption in a mouse model of 22q11.2 deletion syndrome * #**
Lara M. Boyle, Srdjan Joksimovic, Christopher M. Cielo, Donna M. McDonald-McGinn, Raquel E. Gur, Ashlea Choi, and Shinjae Chung

150 **Importance of timely screening for mental health concerns within a multidisciplinary 22q clinic setting and the barriers surrounding identification**
Jalen D. Clemmons and Carter A. Puckett

**** Junior Investigator***

 # Top Scoring Posters

151 **Altered germ layer specification during gastrulation in 22q11.2 deletion syndrome * #**
Aidan Douglas, Eleonora Stronati, Elizabeth Abraham, Emily Megill, Olivia Mae Pericak, and Conchi Estarás

152 **Establishing novel partnerships to create a comprehensive program for adults with 22q**
Emily R. Gallagher, Matt Blessing, Kerry Conant, and Gary Stobbe

153 **Impact of chromosome 22q11.2 CNVs on height in two unrelated patients with achondroplasia ***
Audrey Olson, T. Blaine Crowley, Lydia Hamilton, Evie Andrewes, Lily Elman, Lydia Rockart, Oanh Tran, Daniel E. McGinn, Beverly S. Emanuel, Elaine H. Zackai, Vaneeta Bamba, Lorraine L. Katz, and Donna M. McDonald-McGinn

154 **Enhanced serological protection after pneumococcal polysaccharide vaccine in a child with 22q11.2 deletion syndrome and recurrent sinopulmonary infection ***
Annika Malmgren, Jenny Lingman Framme, and Solveig Oskarsdottir

155 **Cardiopulmonary findings in teenagers with right circumflex aortic arch in 22q11 deletion syndrome**
Julie Martin, Manbir Sanghera, Matthew M. Feldt, Nikita Raje, Maria Kiaffas, and Sanket Shah

156 **Very early onset inflammatory bowel disease in children with 22q11.2 deletion syndrome**
Maire Conrad, Judith Kelsen, Kathleen Sullivan, Soma Jyonouchi, Audrey Olson, Donna M. McDonald-McGinn, and Maria Mascarenhas

157 **Studying the interplay between vitamin A and hippo signaling pathways in human models of 22q11.2 deletion syndrome * #**
Emily Megill, Eleonora Stronati, Elizabeth Abraham, Aidan Douglas, Mikel Zubillaga, and Conchi Estaras

158 **Development of a screening protocol for *TANGO2* deficiency in pediatric patients with 22q11.2 deletion syndrome: initial findings and insights**
Maria Mills, Lex Powers, Matthew Blessing, Kimberly Liekweg, Lindsey Benedict, Suzanne Siegel, and Emily Gallagher

159 **Diagnosing and managing complex neuropsychiatric challenges in 22q11.2 deletion syndrome**
Lisa Palmer, Tracy Heung, Nikolai Reyes, Samantha D'Arcy, and Anne S. Bassett

160 **Binary predictive modeling for 22q11.2 deletion using structured clinical data: an experimental ensemble study with linear SVM and complement naive bayes**
Giulia T. Barcellos, Vera L. Gil-da-Silva-Lopes, João Pedro Moretti, Ana E. A. Silva, and Guilherme P. Coelho

161 **Immunodeficiency presentation in a patient with a distal 22q11.23 (LCR F-H) duplication ***
Kelly E. Regan-Fendt, Valerie J. Allegretti and Elizabeth A. Lippner

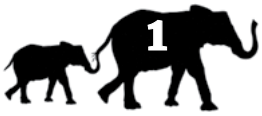
162 **Parent perspectives on educational practices for students with 22q11.2 deletion syndrome in Ontario, Canada**
Jane Summers, Katrina Palad, Sana Emami, and Jacob Vorstman

**** Junior Investigator***

 # Top Scoring Posters

163 **Trauma-related symptoms in adults with 22q11.2 deletion syndrome: exploring the efficacy of eye movement desensitization and reprocessing (EMDR) therapy**
Claudia Vingerhoets, Sasja Duijff, Sanne Vrinzen, Jeltje Spapens, Erik Boot, and Therese van Amelsvoort

164 **Words in context: measuring the vocabulary network in children with 22q11.2 deletion syndrome** *
Jantine R. Wignand, Naomi Oppeneer, Tessel D. Boerma, Michiel L. Houben and Frank N.K. Wijnen

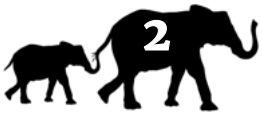


001: Unraveling the role of segmental duplicons in predisposition and phenotypic variability of the 22q11.2 deletion syndrome

Joris Robert Vermeesch[1]

[1]*Laboratory of Cytogenetics and Genome Research, Centre for Human Genetics, KU Leuven, Leuven, Belgium*

22q11.2DS is the most common genomic disorder. However, the reason for the high incidence remains unclear. The chromosome 22q11.2 microdeletion syndrome (22q11.2DS), is mediated by highly identical and polymorphic segmental duplications (SDs) known as low copy repeats (LCRs; regions A-D) that have been challenging to sequence and characterize. We have now sequence-resolved genomic architecture of 135 chromosome 22q11.2 haplotypes from diverse 1000 Genomes Project samples. We find that more than 90% of the copy number variation is polarized to the most proximal LCR region A (LCRA) where 50 distinct structural configurations are observed (~189 kbp to ~2.15 Mbp or 11-fold length variation). In addition, we demonstrate recent evolution of the region and demonstrate the presence of inversion polymorphisms, a potential driver of rearrangements. The different architectures in the population may provide insights in the predisposition for the deletion. T'ɥe high incidence and cause of neuropsychiatric phenotypes in 22q11.2DS remains an enigma. We hypothesize that the LCRs and/or rearrangement could play a role and affect the phenotypic variability. We follow two routes towards unraveling their potential role: (1) We generated haplotype-aware CRISPR/Cas9 engineered isogenic panels of H9 clones carrying deletions of LCR22-A, -B, -C, or -D. (2) we map the rearrangements in patients and explore the consequences of the variable rearrangements. Long read genome, epigenome and transcriptome analyses demonstrates the rearrangements drive genome wide changes which likely affect the 22q11.2DS phenotype indirectly and provides insights into the consequences of the LCR variability.



002: Haplotype-resolved iso-seq reveals allele-specific isoform remodeling in 22q11.2 deletion patient–parent duos *

Marta Sousa Santos[1], Erika Souche[1], David Porubsky[2,3], Natalia Olszewska[1], Evan E Eichler[2,4], and Joris R.Vermeesch[1]

[1]Laboratory of Cytogenetics and Genome Research, Centre for Human Genetics, KU Leuven, Leuven, Belgium; [2]Department of Genome Sciences, University of Washington School of Medicine, Seattle, WA, USA; [3]European Molecular Biology Laboratory (EMBL), Genome Biology Unit, Heidelberg, Germany; [4]Howard Hughes Medical Institute, University of Washington, Seattle, WA, USA.

Background: The 22q11.2 locus is enriched for low copy repeats (LCR22s) that are structurally hypervariable and mediate recurrent LCR22A–D deletions. Because paralogous sequences are highly similar, short-read RNA sequencing cannot reliably assign transcripts to the correct gene copy or haplotype, obscuring how breakpoint architecture reshapes isoform usage in 22q11.2 deletion syndrome. **Methods:** We profiled EBV-transformed lymphoblastoid cell lines from patient–parent duos carrying LCR22A–D deletions. For each individual we generated haplotype-resolved de novo assemblies, lifted over gene models, and mapped full-length iso-seq reads to personalized diploid references using haplotype-aware alignment. We quantified allele-specific isoform expression, compared the deleted versus remaining haplotype, and tested whether breakpoint position and LCR22-A structural configuration predict changes in promoter usage, splice junction choice, and 3' end formation across the locus. **Results:** Personalized diploid mapping improved assignment of reads to paralogous 22q11.2 genes and resolved isoforms that are ambiguous under linear reference mapping. We observe the expected loss of isoforms on the deleted haplotype, but also consistent remodeling on the remaining haplotype, including shifts in dominant isoforms, alternative first exon usage, and differential 3' UTR choice. Several genes show evidence of buffering, with increased expression or isoform diversity from the intact allele partially compensating for copy loss. Breakpoints that truncate distinct LCR22-A subunits are associated with predictable isoform switches in nearby genes, suggesting local cis-regulatory and structural effects beyond dosage and enabling parent-of-origin comparisons. **Conclusions:** Haplotype-resolved iso-seq in patient–parent duos enables direct measurement of allele-specific isoform consequences of 22q11.2 deletions. This framework links LCR22-A breakpoint architecture to isoform-level outcomes and prioritizes genes and isoforms with dosage compensation or breakpoint-sensitive regulation as candidates contributing to phenotypic variability.

003: Isogenic LCR22 deletions in H9 define an isoform-resolved transcript catalogue and LCR-specific regulatory programs across early development *

Marta Sousa Santos[1], Erika Souche[1], Natalia Olszewska[1], and Joris R.Vermeesch[1]

[1]*Laboratory of Cytogenetics and Genome Research, Centre for Human Genetics, KU Leuven, Leuven, Belgium.*

Background: Low copy repeats (LCR22-A to -D) within 22q11.2 mediate recurrent rearrangements, yet transcriptome analysis of this locus is hindered by its repetitiveness, incomplete representation in standard references, and substantial population-level size variability. We hypothesise that LCR22s contain transcribed elements and contribute cis-regulatory functions that shape local gene and isoform expression. **Methods:** We generated a haplotype-aware H9 genomic reference including the 22q11.2 annotation and CRISPR/Cas9 engineered an isogenic panel of H9 clones carrying deletions of LCR22-A, -B, -C, or -D. Full-length Iso-Seq reads were mapped to the H9 reference and isoforms were quantified with FLAIR to detect novel transcripts and differential isoform usage. Matched short-read RNA-seq in hESCs, neural progenitor cells (NPCs), and neurons from the same clones was integrated to relate isoform changes to gene-level expression across stages. **Results:** We built an isoform-resolved transcript catalogue spanning the LCR22s, flanking unique regions, and embedded paralogous gene families, clarifying which loci are transcriptionally active in H9 and which remain silent. Long-read data resolves full-length isoforms, enabling confident assignment of splice junctions, alternative promoters, and 3' ends that are poorly captured by short reads. Comparing isogenic deletions reveals LCR-specific regulatory footprints: the removal of each LCR produces distinct, localised changes in isoform usage and expression within 22q11.2 and its flanks, which is consistent with individual LCRs acting as modulators of transcript structure. These LCR-specific isoform programs provide mechanistic candidates that could modulate downstream developmental molecular trajectories relevant to phenotypic variability in 22q11.2 deletion syndrome. **Conclusions:** This isogenic series provides a functional map of LCR-specific control of transcription at 22q11.2 and a reference catalogue of expressed isoforms. The data nominate LCR-content–dependent isoform programs that may contribute to molecular heterogeneity in 22q11.2 deletion syndrome.

004: Resolving the exact breakpoints of the 22q11.2 deletion using CRISPR-Catch and long-read sequencing reveals chromosomal rearrangement mechanisms and individual variance in breakpoints

Alexander E. Urban [1,2,3,9], Bo Zhou [1,2], Carolin Purmann [1,2,3], Hanmin Guo [1,2,3,4,5], GiWon Shin [6], Yiling Huang [1,3], Reenal Pattni [1,3], Qingxi Meng [6], Stephanie U Greer [6], Tanmoy Roychowdhury [7], Raegan N Wood [6], Marcus Ho [1,3], Heinrich Zu Dohna [8], Alexej Abyzov [7], Joachim F Hallmayer [1], Wing H Wong [4,5], and Hanlee P Ji [6]

[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA; [2]Stanford Maternal and Child Health Research Institute, Stanford University School of Medicine, Stanford, CA, USA; [3]Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA; [4]Department of Statistics, Stanford University, Stanford, CA, USA; [5]Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA, USA; [6]Division of Oncology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA; [7]Division of Computational Biology, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA; [8]Department of Biology, American University of Beirut, Beirut, Lebanon; [9]Program on Genetics of Brain Function, Stanford Center for Genomics and Personalized Medicine, Stanford University School of Medicine, Stanford, CA, USA.

Background: The 22q11.2 deletion is mediated by large blocks of repetitive DNA sequences known as Low Copy Repeats (LCRs) or Segmental Duplications (SegDups). However, the exact breakpoints, at nucleotide resolution, lie within the SegDups which, because of their repetitive nature and size (hundreds of kbp), are impenetrable to existing analysis methods. **Methods:** We developed a generally applicable method, CRISPR/Cas9-targeted long-read sequencing (CTLR-Seq), to resolve large and complex genome regions. CRISPR-targeted very large DNA fragments are isolated and analyzed using long-read sequencing and assembly [Zhou et al., PNAS 2024]. We also grew iPSC lines from 22q11.2 deletion patients into neural organoids and carried out cell-type specific HiChIP chromosome folding analysis. Lastly, we re-analyzed the long-read DNA sequence data to detect DNA methylation patterns within the SegDups. **Results:** We applied CTLR-Seq to typical 22q11.2 deletions, from A-D. Across multiple patients we found a high degree of variability for both the rearranged SegDup sequences and the exact chromosomal breakpoint locations, which, unexpectedly, coincide with transposon-sequences. Guided by CTLR-Seq results we then performed three-dimensional chromosomal folding analysis in patient-derived neurons and astrocytes and found chromosome interactions anchored within the SegDups to be both cell type- and patient-specific. We also demonstrated that CTLR-Seq enables cell-type specific analysis of DNA methylation patterns within the SegDups, and we resolved the exact breakpoints for A-B, A-C, and B-D deletion subtypes. **Conclusions:** We have, for the first time, resolved the 22q11.2 deletions at nucleotide resolution and found a large degree of inter-patient variance, as well as functional genomics consequences of that variance. Knowledge of the exact deletion endpoints can guide studies into the mechanism of deletion-formation, the potential role of endpoint-variance as a genetic modifier associated with the phenotypic variance, and the mechanistic effects of SegDup sequence content, and its variance, across multiple molecular data modalities during disease etiology.

005: Optical mapping of nested 22q11.2 deletions reveals conserved structural architectures

Steven Pastor[1,2,3], Oanh Tran[1,2], T. Blaine Crowley[1,2], Audrey Olson[1,2], Lydia Rockart[1,2], Daniel E. McGinn[1,2], Elaine H. Zackai[1,2,4], Donna M. McDonald-McGinn[1,2,4], and Beverly S. Emanuel[1,2,4]

[1]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Biomedical and Health Informatics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

Background: The 22q11.2 locus is highly susceptible to recurrent rearrangements which are mediated by chromosome 22-specific low-copy repeats LCR22A through LCR22H (LCR22s), resulting in a spectrum of nested deletions. The most prevalent of these include A-B, B-D, and A-C events. While these deletions differ in genomic span and clinical presentation, the extent to which their underlying structural haplotypes and breakpoint architectures diverge has remained unclear to date. **Methods:** Here, we have applied high-resolution optical genome mapping to resolve haplotype structures across the 22q11.2 region in patients harboring A-B, B-D, and A-C deletions. Whole genome, *de novo* assemblies have been generated to reconstruct individual-specific LCR22 configurations and to localize deletion breakpoints with less than kilobase-scale precision. We then compared structural architectures and haplotype frequencies across patient population groups to identify potential differences in genomic predisposition amongst populations. **Results:** Across all three deletion types, we observe highly conserved LCR22 haplotype structures with no detectable enrichment of specific configurations in any deletion class. Breakpoint intervals localize to expected LCR22-mediated regions but, to date, do not exhibit group-specific structural signatures at the optical mapping level. **Conclusions:** These findings suggest that distinct nested deletions appear to arise from a shared structural substrate which does not appear to be population specific. Ongoing work focuses on sequencing across breakpoint regions to resolve nucleotide-level features and to assess the contribution of sequence motifs to recombination susceptibility. Together, this study supports a model in which 22q11.2 nested deletions are driven by common underlying genomic architectures, with breakpoint selection potentially governed by sequence-level mechanisms not captured by structural mapping alone.

006: Setting the stage: The importance of deletion size, variants on the intact chromosome 22q11.2 allele, dual diagnoses, and genome-wide modifiers

Donna M. McDonald-McGinn[1,2,3]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

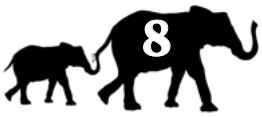
Background: 22q11.2 deletion syndrome (22q11.2DS) is common – identified in 1/1000 pregnancies, 1/1500 miscarriages, and 1/2000 livebirths. It is the 2nd most common chromosome abnormality after Down syndrome; the most common cause of syndromic palatal anomalies and schizophrenia; and the 2nd most common cause of congenital heart disease and developmental delay after Down syndrome. Based on a prevalence of 1/2000 there should be 166,000 affected Americans, including 37,000 children, which begs the question – where are they? 22q11.2 deletion syndrome (22q11.2DS) is quintessentially a multisystem disorder resulting in significant morbidity and some mortality, with broad inter and intra-familial variability, including amongst identical twins. Associated features change over time, and the focus varies by age. So how do we explain such variability and under-ascertainment? Well, 22q11.2DS most often includes loss of ~50 genes, many of which affect neural crest cell migration, and most frequently result from de novo non-allelic homologous recombination involving low copy repeats (LCRs) A, B, C, and D. Most deletions extend from LCR22A-LCR22D, including FISH probes within LCR22A-LCR22B, and the important developmental genes TBX1 (located with LCR22A-LCR22B) and CRKL (located within LCR22C-LCR22D). Here we report the importance of deletion size in a large cohort of patients with 22q11.2DS, as well as variants in key genes on the intact chromosome 22q11.2 allele associated with autosomal recessive conditions including: CDC45 (craniosynostosis), GP1BB (thrombocytopenia), LZTR1 (ptosis), SCARF1 (blepharophimosis), and TANGO2 (sudden death). We will also touch on those patients with dual diagnoses and the potential for genome-wide modifiers, all of which may explain some variability and potentially even under-ascertainment. **Methods:** Under IRB approval, findings in 1880 patients with 22q11.2DS were assessed; 328 diagnosed by FISH alone were excluded. **Results:** Standard A-D deletions were confirmed in 82% (1095/1339); 6.6% of nested deletions did not include the A-B region and would be missed by FISH; 4.7% were not mediated by LCRs. Prevalence of congenital heart disease (CHD) was statistically significant across breakpoints ($p < .01$): LCR22A-LCR22D deletions (n=1095; 66%); LCR22A-LCR22B (n=69; 73%); LCR22A-LCR22C (n=24; 76%); LCR22B-LCR22D (n=57; 26%): LCR22C-LCR22D (n=31; 38%). Hypocalcemia was reported in: LCR22A-LCR22D (52%), LCR22A-LCR22B (27%), LCR22A-LCR22C (42%), and LCR22B-LCR22D (2%). No patients with LCR22C-LCR22D deletions had hypocalcemia, palatal anomalies or structural brain anomalies; and scoliosis (8%), idiopathic seizures (3%), and ADHD (3%) were uncommon. Mean FSIQ was highest in patients with LCR22A-LCR22B and LCR22C-LCR22D deletions, although standard deviations were wide. 14% (397/461) of LCR22A-LCR22D deletions were familial, compared with LCR22A-LCR22B (22%), LCR22A-LCR22C (17%), LCR22B-LCR22D (71%), and LCR22C-LCR22D (67%). Additional variants on the non-deleted allele/genome-wide pathogenic variants significantly impacted phenotypes and management. **Conclusions:** Deletion size, examining the non-deleted allele, and screening for genome-wide variants, is key in providing targeted healthcare recommendations, identifying genotype-phenotype correlations, and providing accurate recurrence risk counseling. Concurrently patients are seeking care for features associated with 22q11.2 duplications, as well as distal deletions and duplications, all of which supports the need for clinical centers of excellence and international collaborations to better understand these conditions.

007: Do proximal nested 22q11.2 deletions have a modified adult phenotype?

Anne S. Bassett[1,2], Tracy Heung[2], Lisa Palmer[2], Samantha D'Arcy[2], Sarah Malecki[2,3], and Nikolai Reyes[2,4]

[1]Department of Psychiatry, University of Toronto, and Division of Cardiology & Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada; [2]Dalglish Family 22q Clinic, University Health Network and Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada; [3]General Internal Medicine Fellowship Program and Institute of Health, Policy Management and Evaluation, University of Toronto, Toronto, ON, Canada; [4]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada.

Background: There is evidence that individuals with proximal nested (A-B/A-C) 22q11.2 microdeletions have on average slightly higher IQ and slightly greater adult height than the majority with full extent (A-D) deletions. However, there is a paucity of evidence with respect to qualitative differences in expression. **Methods:** In a well-phenotyped cohort of 472 adults with 22q11.2 deletion syndrome having known deletion extent (i.e., after excluding 20 individuals without deletion extent data), we compared major phenotypes and other features of the n=50 with A-B/A-C deletions (25 female; median age 29.9 years) to the n=422 with A-D deletions (222 female, median age 33.6 years). **Results:** There were no significant between-group differences in age, sex, psychotic illness, moderate to severe intellectual disability, major congenital cardiac disease or mortality. However, the relative risk of developing hypothyroidism was significantly lower in the presence of an A-B/A-C deletion than for an A-D deletion (RR 0.25, 95% CI 0.08 to 0.77, p=0.015). Also, the relative risk of being in the highest IQ group was about twice that for the nested deletion than the full deletion group (RR 2.46, 95% CI 1.47 to 4.13, p=0.0007). Notably, for 12 (24%) individuals in the nested deletion group, the deletion was inherited or transmitted, and for a further 5 (10%) an additional variant was called on the microarray. **Conclusion:** The results suggest that, for individuals with a "typical" 22q11.2 deletion, the deletion extent can have clinically relevant effects on long-term outcomes. There are potential implications for genetic counselling, with further support for the utility of clinical genome-wide microarray, including for the many individuals with only targeted (FISH) 22q11.2 deletion detection. The results also indicate that studies of disease (e.g., autoimmune) mechanisms will require consideration of 22q11.2 deletion extent.

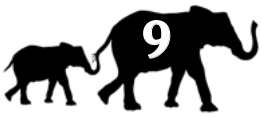


008: Clinical phenotypes of 22q11.2 typical and atypical deletions and duplications

Thérèse van Amelsvoort[1], Emma von Scheibler[1,2], Rianne van Roij[1], Winde Mercken[3],Tjitske Kleefstra[4], and David Linden[1]

[1]Mental Health & Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands; [2]Koraal, Institution for people with Intellectual Disability, Sittard, The Netherlands; [3]Department of Clinical Genetics, Radboud University Medical Centre, Nijmegen, The Netherlands; [4]Department of Clinical Genetics, Erasmus Medical Centre, Rotterdam, The Netherlands.

Background: The 22q11.2 region contains approximately 100 genes and eight low copy repeats (LCR22-A to LCR22-H). Although the clinical phenotype of the typical deletion has been extensively described in large samples, resulting in clinical guidelines and establishment of specialised clinical services, the phenotypes of the atypical deletion and the duplications are less understood. It is of great clinical relevance to add to the documentation of these phenotypes in order to inform clinical service provision. Furthermore the 22q11.2 locus is one of the most-studied LCR regions of the human genome, particularly because of its paradigmatic relevance for psychiatric and cardiac genetics. Differentiating clinical phenotypes within this region and comparing deletions and duplications is a crucial first step towards the elucidation of gene-phenotype associations and dosage effects to inform further mechanistic investigation. **Methods:** We conducted a multi-centre retrospective chart review in two clinical genetic centres in the Netherlands. Eighty-one participants were enrolled in the study and divided over four groups, typical deletion or duplication (including LCRA-B), atypical deletion or duplication (excluding LCRA-B). Data were recorded on demographics, molecular diagnosis and lifetime history of phenotypic manifestations. **Results:** Eighty-one participants consisted of 27 participants with a typical deletion (33.3%), 10 with an atypical deletion (12.3%), 12 with a typical duplication (14.8%) and 32 with an atypical duplication (39.5%); 18 (22.2%) had an additional genetic variant, or 'second-hit'. We found that both typical and atypical duplication carriers had high rates of epilepsy (25.0% and 12.5%), cardiac disease (8.3% and 12.5%), movement disorders (33.3%, and 18.8%) and autism (25.0% and 21.9%). Atypical deletion carriers had slightly lower rates of cardiac and higher rates of urinary tract malformations than typical deletion carriers. **Conclusion:** Our results add to the current limited knowledge of the atypical deletion and duplication phenotype and may help to inform patients.

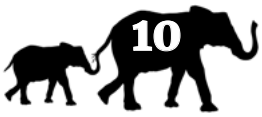


009: Genotype-phenotype correlation in 22q11.2 deletion syndrome: unravelling the clinical heterogeneity

Deepthi Jyothish[1], Elizabeth Brettle[1], Hannah Titheradge[2], Asma Hamad[2], Neha Gupta[1,3], Hakim-Moulay Debhi[4], and Charlotte Clarke[4]

[1]General Paediatrics Department, Birmingham Children's Hospital, Birmingham, UK; [2]Department of Clinical Genetics, Birmingham Children's Hospital, Birmingham, UK; [3]University of Birmingham Medical School, Birmingham, UK, Statistics Department; [4]University of Central London, National Institute for Health and Care Research, London, UK; [5]Great Ormond Street Hospital Biomedical Research Centre, London, UK.

Background: 22q11.2 DS results from non-allelic, homologous recombination between low-copy-repeats (LCRs) A to H, with LCR A–D being the commonest deletion. Genetic and molecular contributors to the marked phenotypic variability remain poorly understood. This study compared phenotypic differences between individuals with common LCR A–D deletion and those with atypical deletions. Greater understanding of genotype–phenotype correlations may enhance prognostic accuracy, informing clinical care and genetic counselling. **Method:** We conducted a retrospective cohort study involving 75 patients. A standardised data collection tool was developed. Clinical information was extracted from electronic health records and laboratory reports. Clinical phenotypes across multiple organ systems were coded as dichotomous variables. Prevalence of each phenotype was compared and Fisher's exact test was used to assess associations between LCR deletion type and phenotype. **Results:** 17 patients lacking genetic deletion data were excluded, leaving a final sample of 58 patients: 48 with LCR A–D deletion and 10 with alternate deletion sizes/breakpoints. Mean age at study entry was 8.4 years (SD 4.1). Mean age at diagnosis was 2.7 years (SD 3.5). The cohort was 62% male and 69% White British. No statistically significant differences were found at body system level. However, at individual abnormality level, ventricular septal defects and immunodeficiencies—including impaired T cell function, humoral immunity deficits, and low immunoglobulin M —were significantly more prevalent in the LCR A–D group. This group also had a higher frequency of multiple cardiac anomalies. **Conclusions:** Individuals with LCR A–D deletion are likely to have a higher prevalence of immunodeficiencies and multiple congenital cardiac anomalies, particularly ventricular septal defects. Early detection of immune dysfunction influences vital decision-making on live vaccinations and infection management. Evaluating genotype–phenotype correlations using advanced genetic analysis is crucial for understanding clinical heterogeneity, early identification of multi-system morbidity, management, prognosis and counselling.

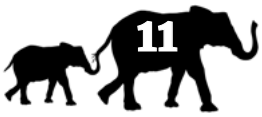


010: 22q11.2-22q11.23 distal deletions and duplications: An emerging important population *

Daniel E. McGinn[1,2], T. Blaine Crowley[1,2], Audrey Green[1,2], Lily N. Elman[1,2], Evie Andrewes[1,2], Lydia Rockart[1,2], Oanh Tran[1,2], Beverly S. Emanuel[1,2,3], Elaine H. Zackai[1,2,3], and Donna M. McDonald-McGinn[1,2,3]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

Background: Chromosome 22q11.2–22q11.23 copy number variants (CNVs) distal to LCR22D (e.g., D–E, D–F, E–F) are relatively uncommon and under-characterized compared with proximal LCR22A–LCR22D variants associated with 22q11.2 deletion and duplication syndromes. Moreover, existing data are largely laboratory-derived, limiting clinical guidance. Conversely, families are increasingly seeking anticipatory guidance despite the greater variability and uncertainty associated with distal CNVs. Here we describe findings in our cohort of patients with distal 22q11.2–22q11.23-CNVs. **Methods:** We retrospectively reviewed records on 137 individuals from 95 families with distal chromosome 22q11.2–22q11.23-CNVs, including 53 with distal deletions and 84 with distal duplications, beginning at LCR22D through LCR22H. Demographics, inheritance, and clinical features were analyzed. **Results:** Most distal deletions (80%) and duplications (67%) were *de novo*. Across both groups, common features included gastrointestinal problems (77%), ENT abnormalities (70%), neurologic findings (70%), developmental (50%) and speech delay (47%), and behavioral challenges (25%). Distal deletions were associated with higher rates of gastrointestinal (91%), endocrine (82%), ENT (76%), speech/palatal (75%), and cardiac (50%) findings, with developmental (91%) and psychiatric (57%) diagnoses more frequent in probands compared with relatives. Distal duplications demonstrated similar but generally milder and more variable phenotypes, primarily affecting development. Recurrent phenotypic clusters were observed for specific CNVs, including short stature, microcephaly, auricular anomalies, and developmental delay when a deletion included the LCR22D–LCR22E region. Five patients had deletions including *SMARCB1* but none had a malignancy. **Conclusions:** Distal 22q11.2-CNVs are not variants-of-unknown-significance but are clinically distinct from proximal LCR22A–LCR22D CNVs, and actionable, exhibiting some recurrent findings especially when involving a deletion in the LCR22D-LCR22E region. Prospectively pooling data from multiple centers will allow for an improved understanding of associated features, variability, and prognoses, including malignancy risk when involving *SMARCB1*, refining anticipatory guidance and genetic counseling for this emerging population and their families.

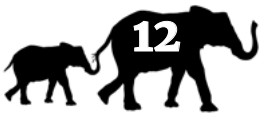


011: Expression and methylation studies in 22q11.2 deletion syndrome

Beata Nowakowska[1]

[1]*Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland*

22q11.2 deletion syndrome (22q11.2DS) is characterized primarily by broad inter and intrafamilial phenotypic variability, including amongst identical twins, making predictions of clinical presentations extremely difficult, if not impossible. Sequencing methodologies have provided evidence for the association of changes in single genes within the chromosome 22q11.2 region as contributing to phenotypic variability, for example: variants in *CDC45* result in atypical phenotypic features such as craniosynostosis, short stature, imperforate anus, and thumb differences, while mutations in *SNAP29* cause cerebral dysgenesis and keratoderma, and finally, pathogenic variants in *TANGO2* lead to dystonia, thyroid disease, hypoglycemia, rhabdomyolysis, metabolic encephalopathy, and arrhythmia leading to sudden death. However, the identification of variants in individual genes within the deleted region alone still does not explain the large clinical diversity amongst all patients with 22q11.2DS. Here, we present the results of our expression analysis and whole genome sequencing performed on biologic samples from 190 deeply phenotyped patients with 22q11.2DS, where we divided patients into the endophenotypic cohorts according to the observed phenotype, e.g. patients with and without overt cleft palate, and performed a differential gene expression analysis between such groups of patients. We focused on phenotypic features present in more than ~15% of patients. For each of the characteristics we recruited at least 30 patients with and without the phenotypic feature of interest. Results of whole transcriptome profiles will be presented, hopefully supporting our hypothesis that identification of gene expression changes associated with a specific clinical characteristic will ultimately inform our understanding of clinical variability across this population of patients.



012: The 22q11.2 methylome *

Senne Meynants[1], Erika Souche[1], Marta Sousa Santos[1], Nicolas Dierckxsens[1], Ann Swillen[1,2], Elfi Vergaelen[1,2], Jeroen Breckpot[1,2], and Joris R. Vermeesch[1,2]

[1]Department of Human Genetics, KU Leuven, Leuven, Belgium; [2]Centre for Human Genetics, University Hospital UZ Leuven, Leuven, Belgium.

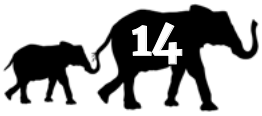
Background: The 22q11.2 deletion syndrome (22q11.2DS) is caused by rearrangements between segmental duplications, also known as low copy repeats on chromosome 22 (LCR22s). Recent advances using long-read sequencing (LRS) technologies enabled complete assembly of the region, including the LCRs. Mapping the rearranged alleles demonstrated multiple paralogs mediate non-allelic homologous recombination (NAHR) and palindrome (PATRR) driven rearrangements. Not only the rearrangements, but also methylation changes are known to occur in 22q11.2DS (Rooney et al., 2021). In order to map and understand the methylation changes in 22q11.2DS we set out to analyse both genome wide and LCR specific methylation in both wild type and rearranged alleles. **Methods**: We developed a workflow to (i) construct genome wide and LCR22 methylation maps from Oxford nanopore derived long read sequencing data and (ii) chart methylation across the rearranged haplotype in patient-parent duos and trios by mapping patient and parental haplotype specific reads to the patient's personal de novo assembly before plotting methylation frequencies along the repeat composition. **Results**: Using 200 haplotypes, we provide characteristic LCR methylation profiles with unmethylated promotor regions in genes with neurological function (e.g. *RTN4R* and *PRODH*). Furthermore, we demonstrate haplotype-specific methylation profiles surrounding the deletion breakpoint. **Conclusions**: We present a pipeline that leverages long reads and de novo assemblies for complete 22q11.2 region methylome characterization both at population and patient-parent level. This method enables mapping of paralog methylation states and allows assessing whether the local methylation patterns are altered upon rearrangements. Those insights will contribute towards understanding of phenotypic variability in 22q11.2DS.

013: Impact of ancestry on prevalence of 22q11.2 deletion syndrome *

Lydia Rockart[1,2,3], T. Blaine Crowley[1,3], Daniel E. McGinn[1,3], Audrey Olson[1,3], Oanh Tran[1,3], Steven Pastor[1,3], Laura Schultz[4], Laura Almasy[5], Raquel Gur[6,7], Kai Wang[8], Ian M. Campbell[1,3,9,10], Kathleen Valverde[1,2], Elaine H. Zackai[1,3,10], Sulagna C. Saitta[11], Loydie A. Jerome-Majewska[12], Beverly S. Emanuel[1,3,10], and Donna M. McDonald-McGinn[1,2,3,10]

[1]The 22q and You Center, Children's Hospital of Philadelphia, [2]Master of Science in Genetic Counseling Program, The Perelman School of Medicine of the University of Pennsylvania, [3]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Research Institute, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [6]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [7]Lifespan Brain Institute (LiBI) of the Children's Hospital of Pennsylvania (CHOP) and Penn Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [8]Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [9]Department of Biomedical and Health Informatics at Children's Hospital of Philadelphia; [10]Department of Pediatrics, The Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [11]Departments of Human Genetics, Pediatrics and Obstetrics and Gynecology, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; [12]Department of Pediatrics, Division of Endocrinology and Metabolism, McGill University, Montreal, Canada

Background: 22q11.2 deletion syndrome (22q11.2DS) results from non-allelic homologous recombination (NAHR). We previously reported a lower prevalence of 22q11.2DS in patients who self-identify as Black, postulating under-ascertainment due to absence of associated craniofacial features. More recently we examined low-copy-repeats (LCRs) within the 22q11.2 region using optical mapping and found population-specific variability in copy-number and orientation of LCRs, which may contribute to lower prevalence of 22q11.2DS in Black patients by reducing the likelihood of NAHR. To exclude other contributions to under-ascertainment, we examined age at diagnosis, prevalence of associated features, AI-powered syndrome-specific facial analysis, and genomic ancestry. **Methods**: Under an IRB-approved protocol, we examined data from subsets of 1,880 patients with 22q11.2DS followed at our Center. Continental ancestry was identified using KING in 274 genomes. Face2Gene analysis was performed on 125 unique photographs. Optical maps of LCR22A and LCR22D were compared across 106 proband and parent genomes. **Results:** European American ancestry were overrepresented in our 22q11.2DS cohort compared with our hospital's population (84.7% vs. 50.4%). African ancestry was underrepresented (9.9% vs. 25.2%). 95% of individuals self-identifying as Black had African ancestry and >99% self-identifying as White had European/American ancestry. Mean age at diagnosis was younger for Black patients (2.6 years vs. 3.7 years). There were no significant differences in prevalence of major clinical features including congenital heart disease between Black and White patients. Face2Gene identified 22q11.2DS-associated craniofacial features in both Black and White patients with comparable accuracy. Optical genome mapping identified significantly shorter lengths of homology and longer inter-LCR22 distances in Black genomes. **Conclusions**: Ancestral background in our 22q11.2DS cohort does not match our hospital population, which is not attributable to under-ascertainment due to absence of craniofacial or other features, and Black patients were diagnosed earlier. These findings, in combination with optical genome mapping data, suggest a genomic structural difference accounting for the observed discrepancy.



014: Demographic, socioeconomic, and clinical profiles of individuals with 22q11.2 deletion and duplication syndromes: a large multi-institutional EHR study

Hanadys Ale[1,2], Marta Telatin[1], Brianna Santiago[2], and Jennifer Keelin[2]

[1]Division of Immunology, Allergy and Rheumatology, Joe DiMaggio Children's Hospital, Memorial Healthcare System, Hollywood, FL, United States; [2]Florida International University Herbert Wertheim College of Medicine Miami, FL, United States.

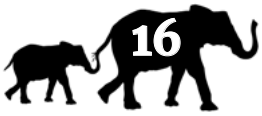
Background: Although the clinical features of chromosome 22q11.2 copy number variants (CNVs) are well characterized, limited data exist on how race, ethnicity, and socioeconomic factors influence diagnosis, management, or access to care. To address this gap, we examined potential disparities in the evaluation and management of individuals with 22q11.2 CNVs using a large, multi-institutional electronic health record dataset. **Methods:** A retrospective analysis of de-identified data from Epic Cosmos, a multi-institutional dataset comprising records from over 300 million patients across the United States, Canada, Lebanon, and Saudi Arabia was conducted. Patients with 22q11.2 deletion (ICD-10 D82.1, Q93.81, Q93.59) or 22q11.2 duplication (Q92.2, Q92.8) were identified from May 1, 2015, to April 30, 2025. Demographics, geographic distribution, insurance status, clinical diagnoses, and provider utilization were analyzed. **Results:** The cohort included 65,860 individuals with 22q11.2 deletion syndrome and 40,489 with 22q11.2 duplication syndrome. White patients comprised the majority (Deletion: 77%; Duplication: 77.7%), followed by Black (13.1%) and Asian patients (3.8%). Most were non-Hispanic (Deletion: 76%; Duplication: 78.3%). Sex distribution was approximately equal, with 50% male and 50% female in both cohorts. Pediatric patients predominated (Deletion: 77.5% <18 years; Duplication: 67.8% <18 years), but adults ≥65 years were also represented (Deletion: 4.4%; Duplication: 13.7%). Geographically, most patients lived in the South of the United States (Deletion: 42.8%; Duplication: 40%), particularly Texas, Florida, California, and Ohio, with the majority residing in metropolitan areas (Deletion: 69.5%; Duplication: 70.5%). Commercial insurance was most common (Deletion: 65.7%; Duplication: 67.3%). Pediatricians were the most involved providers (Deletion: 39.2%; Duplication: 32.8%). **Conclusions:** This study represents one of the largest real-world characterizations of 22q11.2 syndromes, demonstrating broad demographic, geographic, and clinical diversity. These findings support the need for lifelong multidisciplinary care, targeted resources for socioeconomically vulnerable populations, and improved EHR data capture to optimize care and outcomes in this complex population.

015: An exposome-wide analysis of environmental predictors of IQ in 22q11.2 and 16p11.2 CNV carriers *

Yelyzaveta Snihirova[1], Sinan Guloksuz[1,2], David EJ Linden[1], Ann Swillen[3], Marianne BM van den Bree[4], Raquel E Gur[5], Ruben C Gur[5], Carrie E Bearden[6,7,8], Jacob AS Vorstman[9], Jonathan Sebat[10], Sébastien Jacquemont[11,12], Donna McDonald-McGinn[13], Anne S Bassett[14], Mieke van Haelst[15], Claudia Vingerhoets[1], and Thérèse van Amelsvoort[1]

[1]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Research Institute, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; [2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; [3]Centre for Human Genetics, University Hospital Gasthuisberg and Department of Human Genetics, KU Leuven, Leuven, Belgium; [4]Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK; [5]Lifespan Brain Institute of the Children's Hospital of Philadelphia and Penn Medicine, University of Pennsylvania, Philadelphia, PA, USA; [6]Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA; [7]Department of Psychology, University of California, Los Angeles, CA, USA; [8]Neuroscience Interdepartmental Program, University of California, Los Angeles, CA, USA; [9]Department of Psychiatry, Program in Genetics and Genome Biology, Research Institute, The Hospital for Sick Children, Toronto, ON, Canada; [10]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA; [11]Department of Pediatrics, University of Montreal, Montreal, QC, Canada; [12]Sainte Justine Hospital Research Center, Montreal, QC, Canada; [13]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania; 22q and You Center, Clinical Genetics Center, and Section of Genetic Counseling, CHOP, Philadelphia, PA, USA; [14]Dalglish Family 22q Clinic and Toronto General Hospital Research Institute, University Health Network; Clinical Genetics Research Program and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health; Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [15]Department of Human Genetics, Amsterdam Reproduction & Development Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

Background: Copy number variants (CNVs) at the 22q11.2 and 16p11.2 loci confer substantial risk for neurodevelopmental, psychiatric, and cognitive impairments, yet carriers show marked inter-individual variability in cognitive outcomes. This variability suggests that the phenotype of the carriers is substantially modified by environmental context. However, environmental exposures are rarely examined systematically in rare CNV research. **Methods:** We investigated the influence of socioeconomic and psychosocial exposures on cognitive function in 1,356 unrelated carriers of 16p11.2 and 22q11.2 deletions and duplications recruited as part of project 2 of the G2MH network (https://genes2mentalhealth.com) across seven international centers. We conducted an exposome-wide association study (ExWAS) of 33 candidate environmental exposures across three cognitive domains (full-scale, verbal, and performance IQ). Each exposure was tested in separate linear regression models adjusted for age, sex, and recruitment site, with multiple imputation for missing data and false discovery rate control. Exposures surviving correction were subsequently examined in multivariable models, additionally adjusting for CNV group. **Results:** Socioeconomic indicators emerged as the most robust and consistent predictors of cognitive outcomes. The highest education level showed the strongest associations across all IQ domains. Household income, employment-related variables, current living situation, and parental occupation indicators also showed independent associations. After correction for multiple testing, eight exposures were associated with full-scale IQ, six with verbal IQ, and four with performance IQ, with substantial overlap across domains. In multivariable models, socioeconomic exposures jointly explained approximately 19% of the variance in full-scale IQ ($\Delta R^2 \approx 0.19$), indicating a considerable contribution of environmental context to cognitive variability among CNV carriers. **Conclusions:** These findings demonstrate that cognitive outcomes in individuals with rare pathogenic CNVs are strongly shaped by socioeconomic context, highlighting the importance of contextual and potentially modifiable factors in understanding how genetic variation influences phenotypes in CNV carriers.



016: Characterizing environment and its relationship to psychopathology in 22q11.2 deletion syndrome

Arielle Ered[1,2], Tyler M. Moore[1, 2], Austin T. Moran[1], Claudine B. Van Arman[1], Alyssa M. Neppach[1,2], Mia Schwartzberg[1], R. Sean Gallagher[1], Simon Smerconish[1,2], Kosha Ruparel[1, 2], Scott Troyan [1, 2], Amy Cassidy[1,2], Lauren K. White[2], T. Blaine Crowley[3], Daniel E. McGinn[3], Audrey Olson[3], Oanh Tran[3], Elaine H. Zackai[3,4], Beverly S. Emanuel[3,4], Ruben C. Gur[1,2], Donna M. McDonald-McGinn[3,4], and Raquel E. Gur[1, 2]

[1]Neurodevelopment & Psychosis Section, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [2]Lifespan Brain Institute, Penn Medicine and Children's Hospital of Philadelphia, Philadelphia, PA, USA. [3]22q and You Center, Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA. [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

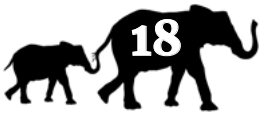
Background: In the general population, environmental factors are consistently linked to physical and mental health outcomes. Studies of environment, particularly those focused on neighborhood factors, are limited in individuals with 22q11.2 Deletion Syndrome (22qDS). As neighborhood factors have been found to predict psychosis symptoms, this remains an important area of exploration for gene x environment interactions in 22qDS, which substantially elevates risk for psychotic disorders. **Methods:** A sample of 278 (51% male, mean age=18.47 years) individuals with 22qDS was collected through the Penn/CHOP site of the Gene to Mental Health (G2MH) study. Street addresses were geocoded for census block group and connected to the American Community Survey year nearest to when the addresses were collected. Neighborhood characteristics including urbanicity, percent married, percent in poverty, median family income, population density, and other factors were derived and an environment score was generated, such that higher scores indicate greater adversity. Environment score, controlling for age and sex, was examined in regression models to predict positive psychosis spectrum symptoms on the Structured Interview for Psychosis-risk Syndromes. **Results**: Participants were largely from suburban/rural (69%), wealthy (79%) neighborhoods. Environment score was not significantly associated with positive psychosis spectrum symptoms (β=.07, p=.34). **Conclusions**: In individuals with 22qDS, environment appears to have less impact on psychosis spectrum outcomes compared to the role of the deletion itself; however, this may be a result of our largely higher SES sample. We will examine measures of individual-level environment such as family chaos, expand the sample to include individuals with a broader range of environmental conditions, and examine the impact of environment on other psychopathology domains, as well as the interaction of environment with sex and deletion size.

017: Combined and differential effects of polygenic, socioeconomic, and developmental markers in individuals with 22q11.2 and 16p11.2 copy number variants

Authors: Vincent-Raphaël Bourque[1, 2], Anjali Srinivasan[3], Samuel J R A Chawner[4], Laura Almasy[5], Laura Schultz[5], Ruben Gur[5], Marianne B M van den Bree[4], Donna M McDonald-McGinn[5], Therese van Amelsvoort[6], Ann Swillen[7], Carrie E Bearden[8], Raquel E Gur[5], Genes to Mental Health Network (G2MH), Jonathan Sebat[3], Jacob A S Vorstman[2], and Sébastien Jacquemont[1]

[1]CHU Sainte-Justine, Montreal, QC, Canada; [2]The Hospital for Sick Children, Toronto, ON, Canada; [3]University of California San Diego, La Jolla, CA, USA; [4]Cardiff University, Wales, United Kingdom; [5]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Maastricht University, Netherlands; [7]KU Leuven, Belgium; [8]University of California, Los Angeles, CA, USA

Background: Recurrent copy number variants (CNVs) have effects that span multiple diagnostic domains, e.g., intellectual disability, ADHD, and psychosis. To guide individual-specific care, clinicians need models differentiating risks for these diagnostic outcomes. Early developmental, polygenic, and socioeconomic factors are associated with these outcomes in the general population, but their predictive value and interrelationships remain poorly understood once a high-impact rare variant is identified. **Methods:** We trained and validated models to predict neurodevelopmental and mental health diagnoses among carriers of recurrent CNVs. To do so, the G2MH Network prospectively assembled an international "genetics-first" cohort of individuals with 16p11.2 and 22q11.2 CNVs (n=1,235, median age 17 [IQR: 11, 27], 52% female) assessed for lifetime diagnostic outcomes. Models included 10 developmental, 6 polygenic, and 3 socioeconomic variables, and were adjusted for the baseline effect of the CNV, age, and sex. **Results:** Polygenic, socioeconomic, and developmental factors showed cumulative contributions to predicting cognitive impairment. Developmental markers did not predict mental health outcomes, whereas polygenic scores were the strongest predictors. Models achieved substantial gains in positive predictive value compared with baseline risk: e.g., cognitive impairment, 45%→73%; ADHD, 43%→65%; psychosis spectrum, 27%→42%; identifying up to 50% of cases. To characterize polygenic effects, then we analyzed a subset of up to 434 families. We observed evidence consistent with non-random partner assortment in carrier individuals (r=0.2) which may increase polygenic mental health risk in offspring. Non-transmitted maternal alleles related to cognition were associated with protective effects (odds ratio 0.54, 95% CI: 0.33-0.90) on cognitive outcomes in their CNV carrier children. **Conclusions:** As molecular genetic findings are increasingly integrated into clinical care, our results support the translation of group-level findings to person-level prediction, paving the way for more individualized care of this population.

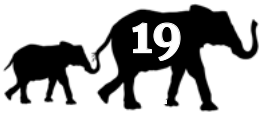


018: Investigating the non-deleted chromosome 22q11.2 allele *

Lily N. Elman[1,2], Audrey Green[1,2], Evie Andrewes[1,2], Lydia Rockart[1,2], Lydia Hamilton[1,2], T. Blaine Crowley[1,2], Bekah Wang[1,2], Daniel E. McGinn[1,2], Beverly S. Emanuel[1,2,3], Elaine H. Zackai[1,2,3], Beata Nowakowska[4], and Donna M. McDonald-McGinn[1,2,3]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [4]Institute of Mother and Child, Warsaw, Poland

Background: We previously reported a 22q11.2 deletion on one chromosome and a pathogenic variant on the non-deleted allele resulting in dual diagnoses. These autosomal recessive (AR) conditions included Bernard Souilier-*GP1BB*, CEDNIK-*SNAP29*, Noonan-*LZTR1*, and CGS-*CDC45*. Five additional genes are associated with AR disorders (*PI4KA, PRODH, SCARF2, SLC25A1, TANGO2*). The critical importance of *TANGO2*-Deficiency-Disorder (TDD) was presented at the 22q11.2 Society Conference in 2024. Subsequently, we have recommended screening the non-deleted allele in all patients with a 22q11.2 deletion within the LCR22A-LCR22D region to identify those patients with a concomitant AR condition. **Methods:** We partnered with a commercial laboratory to develop a custom gene panel on a whole genome sequencing (WGS) backbone. A subset of patients had concurrent or sequential WGS based on atypical phenotypic features. **Results:** 135 tests were ordered; 94 (70%) were completed; 6 are in progress. No pathogenic variants were identified within the 22q11.2 region but 3 VUSs (*SLC25A1, PI4KA*, and *GP1BB*) were found. Genome-wide, 11/44 (25%) studies identified pathogenic variants (16p11.2 deletion, *LRP5*, *PALB2*, biallelic *GJB2*, *FLG*, *CRELD1*, *LDLR*, *F2*, *NFKB1*, *TTR*, *LHON* + XYY), 5 with at least 1 additional VUS. Thirteen additional patients had a VUS, of whom 2 were found to also be carriers for genetic conditions and another had a ROH. Two others had ROH and 2 were identified as carriers. Overall, 18 (41%) were reportedly negative, importantly including one patient with a known deletion in Exon 9 of *TANGO2* via research studies. **Conclusions:** Identifying a patient's diagnosis in its entirety, regardless of the burden associated with effecting such investigations, is key to providing personalized healthcare and accurate genetic counseling. This is especially true when a condition, such as TDD, is amenable to preventative therapeutics. Having confidence in the results though is paramount and something we have not yet achieved in the commercial setting.



019: Autosomal recessive conditions unmasked by 22q11.2 deletion: a population-level analysis using a national EHR network

Hanadys Ale[1,2,3], Jessica Colon[2], Jorge Haddad Gomez[2], Emily Woolhiser[2], Andres Wong[3], Virna Kneller[2], and Shwetha Maharaj[2]

[1]Division of Immunology, Allergy and Rheumatology, Joe DiMaggio Children's Hospital Hollywood, FL, USA; [2]Memorial Healthcare System, Hollywood, FL, USA; [3]Florida International University Herbert Wertheim College of Medicine Miami, FL, USA.

Background: 22q11.2 deletion syndrome (22q11.2DS) results in hemizygosity for multiple genes within the deleted interval. When a pathogenic variant is present on the remaining allele of a recessive disease gene in this region, the deletion can "unmask" an autosomal recessive disorder, leading to dual diagnoses and atypical phenotypes. Although described in case reports (e.g., Bernard–Soulier syndrome), the population-level impact of this mechanism remains unclear. We used a large federated electronic health record (EHR) to examine the co-occurrence of gene-associated conditions localized to the 22q11.2 region in these patients. **Methods:** A retrospective cross-sectional analysis was conducted using Epic Cosmos from January 1, 2016 through January 1, 2026. Patients with confirmed 22q11.2DS were identified using diagnosis codes. Thirteen autosomal recessive conditions associated with genes within the 22q11.2 region were queried, including GP1BB, SNAP29, TANGO2, PRODH, SCARF2, TXNRD2, LZTR1, and PI4KA. **Results:** Among 28,761 patients with 22q11.2DS, dual molecular diagnoses were identified across all queried conditions. CEDNIK syndrome (SNAP29) was most prevalent (n=1,245; 4.3%), followed by schizophrenia-associated neuropsychiatric diagnoses (n=836; 2.9%), TANGO2/PI4KA/TXNRD2-related malformation syndromes (n=799; 2.8%), and PRODH-related neuropsychiatric disorders (n=722; 2.5%). Van den Ende–Gupta syndrome (SCARF2) was identified in 635 patients (2.2%), polymicrogyria with optic nerve hypoplasia in 381 (1.3%), Bernard–Soulier syndrome (GP1BB) in 323 (1.1%), and isolated coloboma in 208 (0.7%). Less prevalent conditions included short-stature syndromes (n=136; 0.5%), malignancy risk variants (n=98; 0.3%), macrothrombocytopenia type 2 (n=65; 0.2%), epileptic encephalopathy (n=22; 0.1%), and male infertility (n=16; 0.06%). The cohort was predominantly pediatric (70.1% <19 years), 52.3% female, and 68.5% White. **Conclusions:** This population-level analysis demonstrates measurable co-occurrence of disorders linked to genes within the 22q11.2 interval among individuals with 22q11.2DS. These findings support the concept that hemizygosity may contribute to the clinical expression of recessive or gene-associated conditions and have implications for genetic evaluation and clinical surveillance.

020: Screening for *TANGO2* and other autosomal recessive conditions in individuals with 22q11.2 deletion syndrome

Valerie J. Allegretti[1], Jaime C. Duncan[1], Laura H. Swibel Rosenthal[2,4], and Kelly E. Regan-Fendt[1,3]

[1]Edwards Family Division of Genetics & Rare Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [2]Division of Otolaryngology – Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [3]Department of Pediatrics at Northwestern Memorial Hospital, Chicago, IL, USA; [4]Department of Otolaryngology at Northwestern Memorial Hospital, Chicago, IL, USA.

Background: We implemented sequencing of genes associated with autosomal recessive conditions within the 22q11.2 region in patients diagnosed with 22q11.2 deletion syndrome. Specifically, we coordinated analysis of 11 genes associated with autosomal recessive disorders: *CDC45, CLDN5, CRKL, GP1BB, LZTR1, PRODH, SCARF2, SLC25A1, SNAP29, TANGO2*, and *TBX1*. **Methods:** The benefits and limitations of testing were reviewed with families, who were given the option to accept or decline. Prior authorization was pursued when required, accompanied by a letter of medical necessity outlining the clinical rationale for testing. **Results:** Testing was offered to 35 patients; 2 declined due to prior out-of-pocket expenses for genetic testing, perceived low risk in the absence of symptoms, or a preference to avoid additional testing. In these cases, multivitamin supplementation including vitamin B was recommended to mitigate potential manifestations of TANGO2 deficiency. Of the 33 patients who elected testing, 31 required prior authorization (2 patients had traditional Medicaid plans that do not require preauthorization at our institution). Among the 31 authorization requests, 7 were denied (22.6%). Appeals were submitted for two cases, resulting in one reversal and one upheld denial. Of the 6 final denials, 3 were issued by commercial insurers and 3 by Medicaid managed care organization (MCO) plans. Notably, some insurers approved testing for certain patients but denied coverage for others despite submission of identical CPT and ICD-10 codes, demonstrating inconsistency in coverage determinations. **Conclusion:** This testing has the potential to identify individuals with TANGO2 deficiency, a condition associated with life-threatening metabolic crises. Given its clinical significance, incorporation of this testing into standardized management guidelines for 22q11.2 deletion syndrome may support more consistent insurance approval and improve patient safety.

021: TANGO2 deficiency with 22q11.21 microdeletion: metabolic and neuropsychiatric considerations

Valerie J. Allegretti[1], Renee J. Wakulski[1], Joshua J. Baker[1,3], Laura H. Swibel Rosenthal[2,4], and Kelly E. Regan-Fendt[1,3]

[1]Edwards Family Division of Genetics & Rare Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago IL, USA; [2]Division of Otolaryngology – Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [3]Department of Pediatrics at Northwestern Memorial Hospital, Chicago, IL, USA; [4]Department of Otolaryngology at Northwestern Memorial Hospital, Chicago, IL, USA.

Background: We report a patient with TANGO2 deficiency caused by a pathogenic variant in *TANGO2* and a 226 kb microdeletion at chromosome 22q11.21 involving exon 2 of *TANGO2*. This deletion is considerably smaller than the canonical 22q11.2 deletion associated with 22q11.2 deletion syndrome. In addition to *TANGO2*, the deleted region encompasses *TXNRD2, COMT, GNB1L, ARVCF, MIR4761, RTL10,* and *MIR185*. **Methods:** The patient demonstrates clinical features consistent with TANGO2 deficiency, including recurrent metabolic crises, cardiomyopathy, and intellectual disability. Current management includes supplementation with B-complex vitamins and adherence to a low-fat diet. At our institution, four patients with TANGO2 deficiency receive triheptanoin (C7; Dojolvi) in addition to standard therapy. There are also additional cases treated with triheptanoin identified through inter-institutional communication. The 22q11.21 microdeletion introduces additional considerations. Although it does not include *TBX1*, it encompasses *COMT*, for which haploinsufficiency has been associated with increased risk of psychiatric disorders, including schizophrenia and anxiety. Such psychiatric risk is not typically emphasized in isolated TANGO2 deficiency. **Results:** In light of this patient's 22q11.21 deletion, psychiatric surveillance has been recommended. For metabolic management, triheptanoin is hypothesized to bypass impaired long-chain fatty acid metabolism and promote anaplerosis. Since initiation of triheptanoin three years ago, the patient has not experienced further hospitalizations for metabolic crisis, though causality cannot be definitively established. Among all four patients with TANGO2 deficiency receiving triheptanoin, our center is evaluating the relationship between QTc, CK, and cardiac function during times of crisis. **Conclusion:** Triheptanoin may reduce metabolic decompensation and improve cardiac outcomes in TANGO2 deficiency. In patients with coexisting 22q11.21 deletions, proactive psychiatric monitoring, or other 22q11.2 deletion syndrome management, should be considered. This case underscores the importance of comprehensive genomic evaluation and suggests potential benefit of emerging metabolic therapies in this population.

022: 22q and TANGO2 - understanding TANGO2 deficiency disorder via genotype-phenotype correlations in 22q11.2 deletion syndrome

Beata A. Nowakowska[1], Maciej Geremek[1], Theresa A. Grebe[2], Robert Śmigiel[3], T. Blaine Crowley[4], Daniel E. McGinn[4], Audrey Olson[4], Raquel Gur[4], Bernice Morrow[5], Anne Bassett[6], and Donna M. McDonald-McGinn[4,7]

[1]Institute of Mother and Child, Warsaw, Poland; [2]Phoenix Children's Hospital, Phoenix, AZ, USA; [3] Wroclaw Medical University, Wroclaw, Poland, [4]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Albert Einstein College of Medicine, New York, NY, USA; [6]University of Toronto, Toronto, Canada; [7]Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

Background: *TANGO2* deficiency disorder (TDD) results from biallelic pathogenic variants in *TANGO2*. TDD is a life-threatening condition, described in 2016, leading to episodic metabolic crises, rhabdomyolysis, hypothyroidism, hypoglycemia, seizures, dysarthria, intermittent ataxia, cardiac arrhythmias, and sudden death. It is thought to reflect secondary impairment of cellular energy metabolism, resembling mitochondrial and fatty acid oxidation disorders. It typically presents with neurodevelopmental regression and recurrent metabolic crises triggered by infection. Recent reports suggest that Vitamin B supplementation may prevent such metabolic crises. The 22q11.2 deletion syndrome (22q11.2DS) results in haploinsufficiency of ~50 genes, including *TANGO2*. Consequently, 22q11.2DS increases the risk of TDD due to the possibility of a variant in *TANGO2* on the non-deleted chromosome 22q11.2 allele. Thus, 22q11.2DS provides a unique opportunity to understand prevalence of *TANGO2* variants and genotype-phenotype correlations for TDD. **Methods:** We examined whole genome sequencing from ~1700 individuals with 22q11.2DS to detect pathogenic variants in TANGO2. We performed RNA sequencing on 260 patients with 22q11.2DS, including a subset of those identified with a TANGO2 variant. **Results:** Ten variants were identified including 3 deletions in exons 3-9, 6 missense variants, and an atypical small deletion in exon 9. The latter 7 variants were not previously described as pathogenic. All patients with an exon 3-9 deletion and 2/6 with missense variants were symptomatic. Five other patients still require deep phenotyping for TTD symptomatology. **Conclusions:** Given the potential severity of TDD and recognizing the possibility of preventable treatment, it is imperative to diagnose everyone with 22q11.2DS and TDD.

023: Clinical consensus guidelines for acute management of TANGO2 deficiency disorder

Samuel J. Mackenzie[1], Ashton B. Ariola[2], Deena L. Chisholm[3], Jonathan Scaccia[4], Mike Morris[3], Nourhan Suleiman[5,6], Sebastian C. Tume[6,7], Svjetlana Tisma-Dupanovic[8], Miriam Hull[6,9], Donna M. McDonald-McGinn[10], Scott Ceresnak[11], Angela L. Hewitt[1], Elizabeth G. Ames[12],Kimberly M. Houck[6,13], Alyssa Smith[14], Seema R. Lalani[15], Megha K. Kanjia[16], Georgia Sarquella-Brugada[17], Christina Y. Miyake[6,18], Divakar S. Mithal[19,20], Kuntal Sen[21], Joshua K. Meisner[22], and Lina Ghaloul-Gonzalez[23]

[1]Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA; [2]SUNY Upstate Medical University, Syracuse, NY, USA; [3]TANGO2 Research Foundation, Hadlyme, CT, USA; [4]Dawn Chorus Group; [5]Section of Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Houston, TX, USA; [6]Department of Pediatrics, Baylor College of Medicine Houston TX, USA; [7]Division of Critical Care Medicine, Texas Children's Hospital Houston, TX USA; [8]Department of Pediatric Cardiology, Nemours Children's Cardiac Center, Orlando, FL, USA; [9]Pediatric Movement Disorders Clinic, Section of Child Neurology, Texas Children's Hospital, Houston, TX, USA; [10]Children's Hospital of Philadelphia and Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [11]Division of Pediatric Cardiology, Department of Pediatrics, Stanford University School of Medicine, Lucile Packard Children's Hospital, Palo Alto, CA, USA; [12]C.S. Mott Children's Hospital, Michigan Medicine, University of Michigan, Ann Arbor, MI, USA; [13]Division of Neurology and Developmental Neuroscience, Texas Children's Hospital, Houston, TX, USA; [14]Division of Genetic and Genomic Medicine, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA; [15]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; [16]Department of Anesthesiology, Perioperative, and Pain Medicine Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; [17]Arrhythmia, Inherited Cardiac Diseases and Sudden Death Unit, Cardiology Department, Hospital Sant Joan de Déu, Barcelona, Spain; [18]Genetics Arrhythmia Program, Texas Children's Hospital, Houston, TX, USA; [19]Division of Neurology, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA; [20]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [21]Division of Neurogenetics and Neurodevelopmental Pediatrics, Children's National Hospital, Washington DC, USA; [22]Division of Pediatric Cardiology, Department of Pediatrics, University of Michigan, Ann Arbor, MI, USA; [23]Division of Genetic and Genomic Medicine, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

Background: TANGO2 deficiency disorder (TDD) is a rare, life-threatening metabolic disorder that, when untreated, is associated with movement disorders, seizures, and recurrent acute metabolic crises that involve rhabdomyolysis, encephalopathy, and life-threatening cardiac arrhythmias. Individuals with 22q11.2 deletion syndrome (22q11.2DS) are at significantly increased risk for TDD given that the *TANGO2* locus is within the 22q11.2 deletion, making them haploinsufficient at baseline. Despite growing recognition of TDD, standardized, evidence-informed guidance for acute management remains limited. Our objective was to develop consensus-based clinical guidelines focused on the recognition and management of acute manifestations of TDD. **Methods:** We conducted a comprehensive literature review of published cases, cohort studies, mechanistic investigations, and existing expert recommendations related to TDD. Three multidisciplinary working groups (Neurology, Cardiology, and Genetics/ICU/Nutrition) that included clinical experts and caregivers of individuals with TDD were convened to draft domain-specific clinical statements. Draft statements were discussed during an in-person consensus meeting in Houston, Texas in December 2025. Areas of overlap were identified to ensure consistency across disciplines, and statements were refined for clarity and scope. A modified Delphi process was used to formalize consensus. All participants were asked to rate each statement on agreement, strength of recommendation, and clarity, and to provide structured comments. **Results:** The initial voting phase is currently underway. Feedback from this round will inform iterative revisions, a second voting phase, and the finalization of recommendations. These will address the acute management of TDD, including management of paroxysmal neurological symptoms, crisis recognition, cardiac monitoring strategies, metabolic stabilization, and ICU-level interventions. They will also include recommendations for screening and treatment for individuals with 22q11.2DS awaiting genetic testing for comorbid TDD. **Conclusions:** By integrating the available evidence with structured expert consensus, this effort aims to standardize acute care, reduce preventable complications, and improve outcomes for individuals with TDD with and without 22q11.2DS.

024: Multifactorial role of Tbx1 in the second heart field

Sophie Astrof[1]

[1]*Department of Cell Biology, Rutgers University, Newark, NJ, USA*

Tbx1 is a major disease gene responsible for the proper morphogenesis of the cardiovascular system. Phenotypes resulting from the deletion of Tbx1 recapitulate many of the disease sequela in 22q11.2 deletion syndrome (DS) patients. Some patients with 22q11.2DS are diagnosed with primary lymphedema, a disorder characterized by abnormal lymph drainage resulting in the accumulation of fluids in lower extremities. However, the etiology of lymphedema in 22q11.2DS is not well understood. The expression of Tbx1 in the second heart field (SHF) is essential for the proper formation of the heart and the aortic arch arteries. Recently, we discovered that the SHF is also important for the development of the lymphovenous junctions, the structures regulating the drainage of the lymphatic fluid into the circulation. There are two lymphovenous junctions, one on the right and one on the left, at the base of the neck. Each lymphovenous junction contains two openings, guarded by valves, regulating lymphatic flow into blood. Defects in the formation of the lymphovenous openings or valves can result in primary lymphedema. We found that the expression of Tbx1 in the SHF is required for the morphogenesis of the lymphovenous junction and will discuss the mechanisms underlying this regulation.

025: Tbx1 acts upstream of distal enhancers in the embryonic mesoderm for cardiac outflow tract formation

Bernice E. Morrow[1]

[1]*Department of Genetics, Albert Einstein College of Medicine, Bronx, NY*

Background: TBX1 is an essential T-box transcription factor gene that is responsible for congenital heart disease in patients with 22q11.2DS. In mouse embryos, it is expressed in the cells comprising the cardiopharyngeal mesoderm (CPM) within the pharyngeal apparatus. Inactivation of Tbx1 in these cells results in a persistent truncus arteriosus, which also occurs in patients with 22q11.2DS. **Methods:** We performed functional genomic studies consisting of single cell RNA-seq, ATAC-seq and TBX1 ChIP-seq. **Results:** We identified differentially expressed genes in Tbx1 mutant CPM cells including multilineage progenitors that are dependent on Tbx1 function. Several thousand putative enhancers were identified, some of which were near differentially expressed genes reduced in expression when Tbx1 was inactivated. Some of these putative distal enhancer regions contained consensus T-sites or TBX1 binding sites and therefore might be directly regulated by TBX1. To further understand the regulatory role of Tbx1 in the CPM and ascertain if they could function as enhancers, we overlapped our data with functional genomic data in the VISTA database consisting of many human and mouse datasets that were filtered for putative enhancers in mammalian fetal hearts. We found 731 distal enhancers, some of which were linked to differential gene expression when Tbx1 was inactivated in the CPM. A subset of these enhancers was tested by mouse embryonic transgenesis to determine where and when those enhancers function to regulate gene expression. We found that 21 of the 731 enhancers had expression in the cardiac outflow tract or heart. We have now generated transgenic mouse embryos to test the function of additional putative enhancers found by our functional genomic studies that have not been previously evaluated. **Conclusions:** We found that Tbx1 is required for cell fate progression during cardiac outflow tract development by acting directly and indirectly upstream of distal enhancers in mouse models.

026: Broad phenotype of congenital heart disease in fetuses and infants with 22q11.2 deletion syndrome: an international cohort study *

Marco Masci[1,2], Stephanie Galloway[3], Ronald Wapner[3], Alessandra Toscano[2], T. Blaine Crowley[4], Elizabeth Goldmuntz[4], Anne S. Bassett[5], Donna M. McDonald McGinn [4], and Lindsay R. Freud[1]

[1]The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; [2]Bambino Gesu Children's Hospital, IRCCS, Rome, Italy; [3]New York-Presbyterian Hospital, Columbia University Irving Medical Center, New York, NY, USA; [4]Children's Hospital of Philadelphia and Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [5]Centre for Addiction and Mental Health, Toronto, ON, Canada.

Background: We sought to describe the phenotypic spectrum of congenital heart disease (CHD) in a large international cohort of fetuses and infants diagnosed with 22q11.2 deletion syndrome (22qDS) ≤1 year of age. **Methods:** Phenotypic data was ascertained on fetuses and infants with laboratory-confirmed 22qDS from 2006-2019 from 30 international centers. Type of CHD was classified, and timing of diagnosis of CHD (prenatal vs. postnatal) was compared. Association with deletion size was investigated, where available. **Results:** Of the 625 patients, 529 (85%) had CHD: 357 were diagnosed prenatally (67%) and 172 (33%) postnatally. In those diagnosed prenatally with CHD (n=357), there were two fetal demises (<1%), 275 (77%) were live-born. Most (322/357, 90%) were also prenatally diagnosed or suspected of having 22qDS. 68% of patients with CHD (361/529) had conotruncal defects typically associated with 22qDS and an additional 13% (70/529) had an isolated ventricular septal defect (VSD). 37% (n=197) had an arch anomaly, either isolated or associated with other CHD. There were also rare cases of transposition (n=2), double outlet right ventricle +/- mitral hypoplasia (n=8), or other single ventricle lesions (n=1), without co-existing arch anomalies. Conotruncal defects were more commonly diagnosed prenatally, except for those with interrupted aortic arch (IAA), while VSDs were more commonly diagnosed postnatally. Of patients with CHD and known breakpoints (n=378), 363 (96%) had standard A-D or proximal nested deletions (LCR22A-LCR22B or LCR22A-LCR22C). Of four patients with LCR22C–LCR22D deletions, three (75%) had major CHD. **Conclusions:** CHD associated with perinatally diagnosed 22qDS is broad and may occur with nested deletions not detectable by FISH. Prenatal diagnosis of CHD should prompt genetic counselling and recommendation of chromosomal microarray as a starting point. If 22qDS is diagnosed or suspected, then careful attention should be paid to exclude IAA, which is a challenging but ductal-dependent diagnosis.

027: Primary pulmonary artery anomalies in 22q11.2 deletion syndrome *

Cristina Angellotto[1,2], T. Blaine Crowley[1], Daniel E. McGinn[1], Marta Unolt[2], Carolina Putotto[2], Elaine H. Zackai[1], Cristina Digilio[2], Paolo Versacci[2], Jill Savla[1], Robert Kelly[3], Bernice Morrow[4], Bruno Marino[2], and Donna M. McDonald-McGinn[1].

[1]Children's Hospital of Philadelphia and Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [2]Ospedale Pediatrico Bambino Gesù and Policlinico Umberto I, Rome, Italy; [3]Marseille Institute of Developmental Biology and Aix-Marseille University, Marseille, France; [4]Albert Einstein College of Medicine, New York City, NY, USA.

Background: Major pulmonary artery (PA) anomalies are common in 22q11.2 deletion syndrome (22q11.2DS). Traditionally, they were regarded as secondary manifestations of complex conotruncal defects, particularly tetralogy of Fallot, pulmonary atresia, and truncus arteriosus, attributed to right ventricular outflow tract obstruction and abnormal flow dynamics. However, severe PA defects occur in patients without such intracardiac lesions. We hypothesized that these isolated pulmonary vascular phenotypes represent a primary developmental manifestation of sixth pharyngeal arch dysplasia, arising from disrupted genetic mechanisms characteristic of 22q11.2DS. **Methods:** Through a multicenter collaboration, under IRB–approved protocols, we enrolled seven probands with severe pulmonary artery defects and molecularly confirmed standard chromosome 22q11.2 deletions (LCR22A–LCR22D). Five patients were recruited from Children's Hospital of Philadelphia (CHOP) and two from Sapienza University and Bambino Gesù Children's Hospital in Rome. Inclusion criteria included major pulmonary arterial dysgenesis (agenesis, hypoplasia, or discontinuity) in children with an intact ventricular septum or a simple ventricular septal defect. Patients with TOF ± PA or with TA were excluded to avoid hemodynamic confounders. Echocardiography, cardiac catheterization angiography, magnetic resonance imaging, and computed tomography with high-resolution volumetric imaging were used to delineate sixth pharyngeal arch–derived vascular morphology. **Results:** Sixth pharyngeal arch dysplasia characterized all phenotypes including pulmonary arterial agenesis (*n* = 3), discontinuous PA morphology (*n* = 2), and anomalous systemic arterial origin (*n* = 2). Left-sided involvement predominated (6/7, 86%). Concurrent pharyngeal arch malformations included complete vascular rings with aberrant subclavian branching (n=2). Ventricular septal defects were present in 3 patients. Early diagnosis and surgical intervention yielded optimal outcomes. **Conclusions:** Pulmonary artery defects in 22q11.2DS arise as a primary developmental feature of sixth pharyngeal arch dysplasia rather than secondary consequences of conotruncal disease. This novel observation underscores the need for early precision-guided cardiac evaluation and targeted therapeutic intervention for this complex but informative condition.

028: Branch pulmonary artery anomalies in 22q11 deletion-diagnosis, management and medium-term outcomes – a case series

Sanket S. Shah[1], Manbir Sanghera[2], Matthew M. Feldt[1], Julie Martin[1], Maria Kiaffas[1], and Nikita Raje[1]

[1]Children's Mercy Hospital-University of Missouri Kansas City, Kansas City, MI, USA; [2]Kansas City University, Kansas City, MI, USA.

Background: Branch Pulmonary artery [PA] anomalies are often associated with 22q11 deletion syndrome and require surgical or catheter-based interventions. **Methods**: We evaluated branch PA anomaly patients between 2010-2025, 628 patients with 22q11.2DS and 22q11.2DupS. We identified and followed 3 patients: with at least 5-year follow-up after initial diagnosis of significant branch PA anomaly. **Results**: Case 1: A fetal echo identified aortic origin of the right PA. The child had a surgical reimplantation of RPA to main PA in the neonatal period and subsequently required stent angioplasty of RPA twice, but at the last visit, the child remains asymptomatic. Case 2: A neonate with moderate to severe Left PA stenosis was diagnosed at 3 weeks of age. Since the child was asymptomatic, the Left PA stent angioplasty was deferred till age 3 years. At the most recent evaluation, the child remains asymptomatic, and no repeat intervention has been required for the last 7 years. Case 3: A child from Asia with Tetralogy of Fallot and absent left pulmonary artery and right pulmonary artery stenosis underwent staged intracardiac repair infancy and was adopted by USA family. Over the last 5 years, after 2 surgeries on right PA and 2 angioplasties, the child has intermittent cyanosis, clubbing, and cachexia. **Conclusions**: Chromosome 22q11 deletion is associated with isolated anomalies of branch PA. Diagnosis can often be suspected on fetal or post-natal echo but cross-sectional imaging with CT/MRI is vital for precise anatomical details and physiological assessment. A combination of surgical/interventional cardiology procedures at appropriate ages are warranted for optimizing the PA flows and remaining symptom free.

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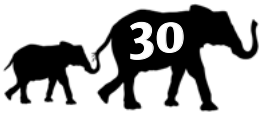
029: Prenatal diagnosis of 22q11.2 deletion syndrome: what can we learn about pregnancy options from the international 22q11.2 PVPOS study?

Natalie Blagowidow[1], T. Blaine Crowley[2,3], Stephanie Galloway[4], Daniel E. McGinn[2,3], Kimberly Gaiser[2,3], Oahn Tran[2,3], Elaine H. Zackai[2,3,5], Beverly S. Emanuel[2,3,5], Erica Schindewolf[6], Julie Moldenhauer[6,7], PVPOS Consortium[8], Qi Yan[4], Ron Wapner[4], Anne S. Bassett[9], Lindsay R. Freud[10], and Donna M. McDonald-McGinn[2,3,5]

[1]Greater Baltimore Medical Center, Baltimore, MD, USA; [2]22q and You Center, Children's Hospital of Philadelphia; [3]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]NewYork-Presbyterian Hospital, Columbia University Irving Medical Center, New York City, NY, USA; [5]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [6]Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [7]Department of Obstetrics and Gynecology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [9]Centre for Addiction and Mental Health and Toronto General Hospital, University of Toronto, Toronto, Canada; [10]Hospital for Sick Children, University of Toronto, Toronto, Canada

[8]Ann Swillen, Jeroen Breckpot, Antoni Borrell, Neeta L Vora, Bettina Cuneo, Hilary Hoffman, Lisa Gilbert, Beata Nowakowska, Maciej Geremek, Anna Kutkowska-Kaźmierczak, Joris R Vermeesch, Koen Devriendt, Tiffany Busa, Sabine Sigaudy, Trisha Vigneswaran, John M Simpson, Jeffrey Dungan, Nina Gotteiner, Karl-Philipp Gloning, Maria Cristina Digilio, Marta Unolt, Carolina Putotto, Bruno Marino, Gabriela Repetto, Magdalena Fadic, Sixto Garcia-Minaur, Ana Achón Buil, Mary Ann Thomas, Deborah Fruitman, Taylor Beecroft, Pui Wah Hui, Solveig Oskarsdottir, Rachael Bradshaw, Amanda Criebaum, Mary E Norton, Tiffany Lee, Miwa Geiger, Leslie Dunnington, Jacqueline Isaac, Louise Wilkins-Haug, Lindsey Hunter, Claudia Izzi, Marika Toscano, Tullio Ghi, Julie McGlynn, Francesca Romana Grati, J William Gaynor, and Elizabeth Goldmuntz

Background: Pregnancies diagnosed with 22q11.2DS can be challenging to evaluate and counsel due to multi-system involvement and broad variability. Here we examined a multi-national cohort to better define pregnancy outcomes. **Methods:** Pregnancies diagnosed with 22q11.2DS between 2006-2019 were identified via the Prenatal v. Postnatal Outcomes Consortium Study (PVPOS). Prenatal histories were reviewed including demographics, family history, gestational age (GA) at diagnosis, and clinical findings. **Results:** 262 women from 13 countries with a fetal diagnosis of 22q11.2DS were identified. 161/262(62%), with a mean age of 29.5 years, continued the pregnancy (CtP). The mean age for woman interrupting the pregnancy (ItP) was 31.5 years and they were less likely to have a personal history of 22q11.2DS (n= 3;3%) compared with the CtP group (n=19;12%). Two paternally inherited deletions were identified per group, while >30% of parents had no genetic testing. The average GA at 22q11.2DS diagnosis was 23.5 weeks for those who CtP, of whom 13% were diagnosed before 20 weeks, 1% in the first trimester; and 19.5 weeks for those who ItP, of whom 28% were diagnosed before 20 weeks GA, 9% in the first trimester. Cardiac anomalies (CA) were identified in 79% of the CtP group and 74% of the ItP group. The ItP group was more likely to have second or multiple additional anomalies detected beyond CA - 19% versus 9%. Pregnancies with only non-CA were identified in 10% of the ItP group and 7% in the CtP group. 22q11.2 deletion size was similar for both groups, with detailed information available for 52%. **Conclusions:** Prenatal diagnosis can provide families the opportunity to have a detailed evaluation of their pregnancy, and genetic counseling regarding the variable aspects of this complex condition. Early diagnosis also allows patients time to consider options, and plan for optimal management of the pregnancy and delivery.



030: Prenatal diagnosis and outcomes in a large cohort of patients with 22q11.2 copy number variants *

Daniel E. McGinn[1,2], T. Blaine Crowley[1,2], Renee Wright[3], Audrey Olson[1,2], Oanh Tran[1,2], Beverly S. Emanuel[1,2,4], Elaine H. Zackai[1,2,4], Natalie Blagowidow[5], Nahla Kahlek[3,6], and Donna M. McDonald-McGinn[1,2,3]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [5]Harvey Institute for Human Genetics at Greater Baltimore Medical Center, Baltimore, MD, USA; [6]Department of Obstetrics and Gynecology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Background: Diagnosis of 22q11.2 copy-number-variants (22q-CNV) is optimally made early. Here we report outcomes in pregnancies ascertained prenatally and delivered at CHOP. **Methods:** Under an IRB protocol, we reviewed our database to identify fetuses with 22q11.2-CNVs delivered at CHOP. **Results:** Between 2008, when our Special Delivery Unit opened, and 2026, 125 pregnant women were evaluated due to suspected/confirmed fetal 22q11.2-CNVs. Mean travel distance was 102 miles(SD+/-248 miles; range-1-2066 miles; median distance-50 miles; 14% within 10 miles, 50% within 50 miles). Referral indications included any combination of: prenatal diagnosis of 22q-CNV(N=22), congenital heart disease(CHD)(N=79), high-risk-NIPT(N=11), CNS findings(N=6; two neural-tube-defects), renal-anomalies(N=5), airway-abnormalities(N=3), positive family history(N=2; 22qCNV, 45,X), microgastria, cleft lip/palate, omphalocele. **Outcomes:** 10 mothers were lost to follow-up, 6 discontinued the pregnancy, 2 are pregnant, and 15 delivered locally (6 at Penn-Medicine due to maternal high-risk factors). Of the 92 delivered at CHOP, 84 had fetuses with 22q11.2DS(91%; 82%-LCR22A-LCR22D) and 8 had 22q11.2DupS(75%-LCR22A-LCR22D). Of the 11 high-risk-NIPTs, 3 were confirmed prenatally and 8 postnatally. Prenatal findings at CHOP included: CHD(N=82;89%), thymic aplasia or hypoplasia(N=16;37%), polyhydramnios(N=16;37%), renal anomalies(N=10;23%), enlarged cavum-septum-pellucidum(N=7;16%), esophageal atresia(N=2), microgastria with tracheal atresia. **Inheritance** (when both parents were tested): *de novo*(N=42;71%), familial(N=17)(maternal[6], paternal[9], and 2 unrelated mothers with 22q11.2DupS and fetuses with 22q11.2DS). Only 1/17(6%) parents were diagnosed with a 22q11.2-CNV prior to identification in the fetus; 5 additional relatives were detected following parental diagnoses. Postnatally, 94% of children had CHD. TOF was most common(38%). Nine children expired (10%)(8/9 with CHD, 1 with tracheal atresia and microgastria) – higher than our overall cohort(4%). Mean age at death was 4 months. Most common postnatal features, besides CHD, were GERD/dysphagia(49%) and hypocalcemia(48%). Two children had overt cleft palate not appreciated on ultrasound. **Conclusions:** This cohort of prenatally ascertained and neonatally evaluated children provides a unique opportunity to examine early diagnosis and familial CNVs.

031: The impact of non-invasive prenatal testing (NIPT) for 22q11.2 copy number variants

Donna M. McDonald-McGinn[1,2,3], T. Blaine Crowley[1,2], Daniel E. McGinn[1,2], Audrey Olson[1,2], Lydia Hamilton[1,2], Lily Elman[1,2], Evie Andrewes[1,2], Oanh Tran[1,2], Beverly S. Emanuel[1,2,4], Elaine H. Zackai[1,2,4], Anne Bassett[5], and Natalie Blagowidow[6]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [5]Center for Addiction and Mental Health and University of Toronto, Toronto, CA; [6]Harvey Institute for Human Genetics at Greater Baltimore Medical Center, Baltimore, MD, USA

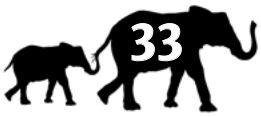
Background: Data supports offering 22q11.2DS NIPT to all pregnant patients. Here we examined our cohort to ascertain patients with 22q11.2-CNVs identified via NIPT. **Methods:** Under IRB approval, we reviewed records on 468 children with a laboratory confirmed 22q11.2-CNV born between January 1, 2014 (following introduction of 22q11.2DS-NIPT) and April 1, 2026. **Results:** 46/380(12%) children with 22q11.2DS and 2/88(2%) with 22qDupS had a high-risk NIPT for a 22q11.2-CNV. 13/48(27%) had prenatal confirmatory studies via amniocentesis. The remainder (73%) deferred prenatal testing and were confirmed postnatally. Mean age at diagnosis, inclusive of prenatal studies, was 4 weeks (range-19 weeks' gestation to 4.5 years). Mean age at postnatal confirmation was 10 weeks. **CNV size:** 38/46(83%) had a standard LCR22A-LCR22D deletion, the remainder had nested deletions [LCR22A-LCR22B (N=3), LCR22A-LCR22C (N=1), LCR22B-LCR22D (N=2), and LCR22C-LCR22D (N=2)]. Both duplications were standard LCR22A-LCR22D. **Inheritance (where both parents were tested):** 27/38(71%) were *de novo*; 8 were maternal and 3 paternally inherited. Of the 11 parents identified following NIPT, only 2(18%) were known to be affected prior to NIPT. Two affected siblings were subsequently diagnosed. 9/11(82%) parents had some associated symptomatology. **Management:** Twelve mothers (28%) made a change in delivery plans and 3(7%) underwent specialty maternal-fetal-medicine consultations. **Associated prenatal features included:** CHD(56%), polyhydramnios(21%), thymic aplasia/hypoplasia(14%), renal anomalies(12%), enlarged cavum-septum-pellucidum(5%), and bilateral club foot. Postnatal echocardiography revealed normal anatomy in 40%. Significant CHD included TOF(N=10), IAA (N=3), truncus arteriosus (N=2). Most common postnatal findings included: gastrointestinal problems [dysphagia/feeding difficulty(81%), GERD(58%), significant constipation(47%), nasal regurgitation(37%)], hypocalcemia(35%), lymphopenia(26%), chronic otitis media(23%), and hypotonia(21%). Developmentally, 4 children were too young to assess; 35/39(90%) had developmental delay including half of school-aged children requiring educational support; 2 had autism. **Conclusions:** NIPT facilitates prenatal diagnostic testing, consideration for changes in prenatal management, appropriate newborn evaluations, detection of previously undiagnosed relatives, and subsequent genetic counseling.

032: Cell-free DNA screening for the 22q11.2 microdeletion: disparities in access to testing

Katelyn Hashimoto[1], Patrick Kelly[1], Brittany Prigmore[1], Kathleen D. Kueck[1], Thea N. Golden[1], and Sheetal Parmar[1]

[1]*Natera, Inc., Austin, TX, United States.*

Background: Data demonstrate clinical validation and utility for cfDNA screening for the 22q11.2 microdeletion comparable to the common trisomies. Current guidelines for 22q11.2 deletion syndrome (22q11.2DS) are inconsistent. While the American College of Medical Genetics and Genomics (ACMG) recommends offering cfDNA screening for 22q11.2DS to all pregnant people, the Society of Maternal and Fetal Medicine (SMFM) and the American College of Obstetrics and Gynecology (ACOG) do not endorse cfDNA screening for microdeletions. In California (CA), an ACOG guideline-based program provides screening and follow-up for common aneuploidies. cfDNA screening for 22q11.2DS is not included in the State program. However, testing for additional conditions, including 22q11.2DS, may be performed outside the program with a separate order ("supplemental order"), potentially at increased cost. We assessed ordering patterns and patient access to 22q11.2DS screening across racial and ethnic groups. **Methods:** Retrospective review of CA supplemental 22q11.2DS screening data (1/2023-1/2026) from a single commercial laboratory. Test order, race, and ethnicity were identified from the requisition form. The percent of patient orders with supplemental 22q11.2DS screening by race and ethnicity was calculated. **Results:** The percent of CA patients who accessed 22q11.2DS screening by ethnicity was 12.4% Black; 13.8% Hispanic; 31.4% White; and 51.4% Asian. The access rate for 22q screening among White and Asian patients, combined, was 3.1x ($p < 0.001$) and 2.8x ($p < 0.001$) higher than Black and Hispanic patients, respectively. **Conclusions:** ACMG supports cfDNA screening for 22q11.2DS while SMFM/ACOG do not. Restricting coverage is associated with inequitable ordering patterns and reduced access to 22q11.2DS screening for Black and Hispanic patients compared with White and Asian patients. Guideline support of 22q11.2DS screening may improve access and reduce disparities in care.



033: Reduced dosage of *Kmt2d* modifies *Tbx1* haploinsufficiency towards phenotypes of 22q11.2DS *

Daniella Miller[1], Kevyn Jackson[1], Timothy C. Cox[2], and Bernice E. Morrow[1]

[1]Departments of Genetics, Albert Einstein College of Medicine, New York City, NY, USA; [2]Departments of Oral & Craniofacial Sciences and Pediatrics, University of Missouri-Kansas City, Kansas City, IL, USA.

Background: Haploinsufficiency of *TBX1*, which occurs in 22q11.2 deletion syndrome (22q11.2DS), leads to a heterogeneous spectrum of clinical manifestations, including craniofacial anomalies, immunodeficiency, and congenital heart defects. The variability in syndromic presentation between patients may be partially explained by variants in chromatin regulatory genes that act to further modify TBX1 function. To investigate this relationship, we selected *KMT2D* as a candidate gene due to its role in the etiology of Kabuki syndrome which shares overlapping features with 22q11.2DS. **Methods:** To assess for a possible developmental relationship, we conditionally inactivated *Kmt2d* in the *Tbx1* lineage in mice and assessed for phenotypic and transcriptomic changes. **Results:** We demonstrate fully penetrant perinatal lethality in these mutant mice, as well as increased incidence of craniofacial dysmorphism, thymus and parathyroid gland hypoplasia, and aortic arch anomalies. We also noted low penetrance of cardiac interventricular septal dysmorphology that implicates *Tbx1* function in the apex of the heart. At early stages, mutant embryos had defects of the caudal pharyngeal apparatus, including abnormal patterning of the 3rd pouch endoderm, hypoplastic 4th arches, and defective 4th arch arteries. Finally, analysis of single cell RNA-sequencing (scRNAseq) revealed dysregulation, and largely downregulation, of genes involved in basic cellular functions, suggesting that *Tbx1* and *Kmt2d* developmentally converge upon essential biological processes. Comparison of our scRNAseq data to a previously published, stage-matched *Tbx1* null mouse dataset further supported this significant overlap in function, particularly within the cell types of the epithelium, endothelium, multi-lineage primed progenitors, and anterior second heart field. **Conclusions:** Overall, these results indicate that reduced dosage of *Kmt2d* perturbs the developmental landscape of the *Tbx1* heterozygote, eliciting phenotypes that are shared between 22q11.2DS and Kabuki syndrome. This supports the theory that variants in the genome, particularly those that impact chromatin modification, can modify the phenotypic presentation of 22q11.2DS.

034: Mechanisms underlying variability in 22q11.2 deletion syndrome

Tatiana Ferebee[1], Pooja Chauhan[1], Elias Oxman[1], and Irene Zohn[1]

[1]*Center for Precision Medicine and Genomics Research, Children's National Hospital, Washington, DC, USA.*

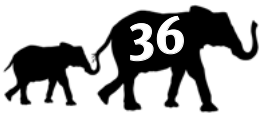
Background: One of the mysteries of 22q11.2 deletion syndrome (22qDS) is its variable presentation. For example, it remains unknown why some patients have critical congenital heart defects (CHDs), while others have mild or no CHDs. One possible mechanism is that 22qDS serves as the initial "hit," increasing susceptibility to CHDs with subsequent environmental or genetic insults. Our hypothesis is that haploinsufficiency of *DGCR8*, a miRNA-processing enzyme required for mature miRNA production, contributes to this variability in 22qDS. Cardiac progenitors are altered in 22qDS, resulting in CHDs. These progenitors normally develop under a precise gradient of retinoic acid, the biologically active metabolite of vitamin A. We propose that miRNAs play essential roles in "buffering" retinoic acid to create this gradient by mediating negative feedback loops. Thus, in the 22qDS embryo, miRNA-mediated negative feedback may be blunted, resulting in delayed buffering of increased vitamin A exposure. This, combined with *Tbx1* haploinsufficiency, results in an increased incidence and severity of CHDs. **Methods:** To test the idea that *Dgcr8* haploinsufficiency increases susceptibility to environmental exposures, we exposed mouse embryos from the *LgDel* model of 22q11.2, *Tbx1*$^{-/+}$, *Dgcr8*$^{-/+}$, or *Tbx1*$^{-/+}$; *Dgcr8*$^{-/+}$ to increased retinoic acid during critical periods of cardiac progenitor development and determined the incidence and severity of CHDs. We also measured changes in gene expression in the second heart field during cardiac specification. **Results:** Our results show that haploinsufficiency of *Dgcr8* alters the buffering of vitamin A exposure, as evidenced by altered gene expression in cardiac progenitors. Moreover, low doses of vitamin A that did not cause significant cardiac phenotypes in wild-type embryos resulted in CHDs in *Tbx1*$^{-/+}$;*Dgcr8*$^{-/+}$ and *LgDel* embryos. **Conclusions:** Changes in miRNA processing due to *DGCR8* haploinsufficiency may reduce the 22qDS embryo's ability to buffer environmental exposures, contributing to CHDs and phenotypic variability in 22qDS.

035: Nutritional implications for genetic counseling in 22q11.2 deletion syndrome: evidence from a mouse model *

Maria Victòria Llull-Albertí[1], Emilia Amengual-Cladera[1], Angelika Merkel[2], Jessica Hernandez-Rodriguez[1,3], Marc Ventayol-Guirado[1], Juan Antonio Jimenez-Barceló[1], Jairo Enrique Rocha[1,4], Aina Vaquer-Picó[1], Víctor José Asensio-Landa[1,3], Laura Torres-Juan[1,3], Fernando Santos-Simarro[1,3], María García de Paso-Mora[1,3], Icíar Martínez-López[3], and Damian Heine-Suñer[1,3]

[1]Grup Genòmica de la Salut, Institut d'Investigació Sanitària de les Illes Balears (IdISBa), Palma, Illes Balears, Espanya; [2]Unitat de Bioinformàtica, Fundació Josep Carreras Contra la Leucemia, Badalona, Barcelona, Espanya; [3]Unitat de Diagnòstic Mol·lecular i Genètica Clínica (UDMGC), Hospital Universitari de Son Espases, Palma, Illes Balears, Espanya; [4]Grupo de Biología Computacional I Bioinformàtica (BIOCOM), Universitat de les Illes Balears, Palma, Illes Balears, Espanya.

Background: Current clinical guidelines for the management of adults with 22q11.2 deletion syndrome (22q11.2DS) emphasize the importance of genetic counseling, particularly in the reproductive context, due to the 50% transmission risk in each pregnancy and the inability to predict phenotypic expression in offspring. This unpredictability highlights the limited evidence regarding the influence of gestational factors on syndrome expressivity. Recent studies have explored potential genetic and environmental modifiers, including retinoic acid, folic acid, and vitamin B12, which may contribute to clinical variability. A better understanding of how environmental factors, especially maternal diet, influence the 22q11.2DS phenotype is essential to improve reproductive management and genetic counseling. **Methods:** We used a mouse model of 22q11.2DS, termed Df1/+, to evaluate the effect of maternal vitamin A (vitA) and vitamin B12 (vitB12) dietary imbalance (supplementation or deficiency) on the incidence of aortic arch defects (AADs), a common congenital heart defect observed in 22q11.2DS patients and Df1/+ model. To determine whether genes or genomic regions were altered under each vitamin dosage condition, **we** integrated RNA-seq and DNA methylome analyses from embryonic hearts and placentas of Df1/+ embryos across experimental groups. **Results:** We observed that changes in maternal vitA and vitB12 serum levels during gestation differentially influence the risk of developing a more severe 22q11.2DS phenotype, and that this effect depends on the maternal genotype (deletion carrier or non-carrier). Diet-maternal genotype interaction effects were also detected at the level of differential gene expression and DNA methylation of genes involved in cardiac and placental development. **Conclusions:** These findings suggest that nutritional recommendations for pregnant women with 22q11.2DS may require adjustment compared with standard guidelines due to potential diet–genotype interaction. Although further research is needed to elucidate the underlying molecular mechanisms, our results support revisiting dietary recommendations in this population to improve clinical guidelines and genetic counseling.



036: Studying vitamin A signaling in human heart models of 22q11.2DS

Conchi M. Estaras[1], Emily Megill[1], Eleonora Stronati[1,2], Elizabeth Abraham[1], Aidan Douglas[1], and Mikel Zubillaga[1]

[1]Cardiovascular Sciences Department, Aging + Cardiovascular Discovery Center, Temple University, Philadelphia, PA, USA; [2]Department of Child and Adolescence Psychiatry, The Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: Congenital heart defects (CHDs) affect approximately 70–80% of individuals with 22q11.2 deletion syndrome (22q11.2DS). A hallmark of these defects is their striking phenotypic variability, ranging from mild septal defects to severe conotruncal malformations, even among patients carrying the same genetic deletion. The mechanisms underlying this variability remain poorly understood and likely reflect the interplay of genetic background and non-genetic modifiers. Notably, maternal vitamin A exposure has been shown to modulate cardiac phenotypes in mouse models of 22q11.2DS, implicating altered retinoic acid (RA) signaling as a potential contributor to disease variability. **Methods**: To directly interrogate RA pathway activity and sensitivity in the context of 22q11.2DS, we employed human developmental models including human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and patterned heart organoids. These systems were combined with phenotypic analyses, single-cell transcriptomics, and targeted metabolomic profiling of intracellular retinoids. **Results**: 22q11.2DS models recapitulated key aspects of aberrant cardiac development and exhibited heightened sensitivity to vitamin A exposure. Single-cell transcriptomic analyses revealed altered expression of RA-responsive gene networks during cardiac lineage specification. Intracellular quantification of retinoid metabolites further suggested that dysregulated RA availability and/or metabolism contributes to this increased responsiveness, indicating additional layers of metabolic control within this genetic background. **Conclusions:** Collectively, our findings support a model in which vitamin A metabolism and RA signaling act as critical modifiers of cardiac developmental outcomes in human 22q11.2DS, providing a mechanistic framework to explain phenotypic variability in congenital heart defects.

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037: Dietary intake patterns in children with 22q11.2 deletion syndrome: widespread micronutrient imbalances revealed following 72-hour dietary recall analysis

Luc Santilli,[1] Alain J. Benitez,[1,2] Audrey Olson,[3] Lydia Rockart,[3] Robin Miccio,[1] Lauren White,[2,4] Donna McDonald-McGinn,[2,3,5] and Maria Mascarenhas[1,2,3]

[1]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia; Philadelphia, PA, USA.

Background: Children with 22q11.2 deletion syndrome (22q11.2DS) frequently experience feeding difficulties and food selectivity, yet comprehensive characterization of dietary intake remains limited. We characterized baseline nutrient intake patterns. **Methods:** Nineteen children with laboratory confirmed 22q11.2DS (ages 7–14) enrolled in the BE-WEHL-22q program completed 72-hour dietary recalls analyzed using the Nutrition Data System for Research (NDSR). Intake was compared to age- and sex-specific Dietary Reference Intakes (DRIs). Nutrient adequacy was classified as insufficient if less than 85% DRI, adequate if between 85–120%, or excessive if greater than 120%. **Results:** Mean energy intake was 1,657 kcal. Protein was generally adequate (89.5%; mean 15.2% energy intake). However, widespread micronutrient imbalances were identified. Fiber intake was insufficient for nearly all subjects (94.7%; mean 46% AI), likewise vitamin D (89.5%; mean 41% RDA), potassium (68.4%; mean 74.9% AI), water (57.9%), calcium (57.9%), choline (52.6%), and vitamin A (47.4%). Pantothenic acid showed wide variability, with 31.6% insufficient and 42.1% excessive. Folate was excessive in 52.6% yet insufficient in 10.5%. Sodium exceeded recommendations in 94.7% (mean 198% of AI), and B vitamins were consistently excessive: niacin (94.7%), riboflavin (89.5%), thiamin (78.9%), and B12 (73.7%). Among macronutrients, 84.2% exceeded saturated fat guidelines (mean 12.0% of energy vs. <10%); 63.2% exceeded added sugar limits (mean 11.8% vs. <10%). Fat exceeded the recommended range in 47.4%; carbohydrates fell below range in 26.3%. **Conclusions:** Children with 22q11.2DS demonstrate striking nutrient imbalances, with near-universal deficiency in fiber, vitamin D, and potassium alongside excess sodium, B-vitamins, and saturated fat. The pattern of B-vitamin excess concurrent with fiber and whole-food deficiencies suggests heavy reliance on fortified or ultra processed foods. Despite adequate protein intake, deficiencies in water, calcium, choline, and vitamin A highlight the need for targeted dietary intervention and provide the foundation for evaluating BE-WEHL-22q's impact on dietary quality.

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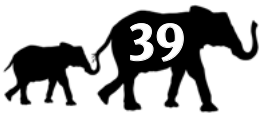
038: Vitamin B12 status in adults with 22q11.2 deletion syndrome

Samantha D'Arcy[1], Tracy Heung[1,3], Lisa Palmer[1], Nikolai Reyes[1,2,3,4,], and Anne S. Bassett[1,2,3,5]

[1]Dalglish Family 22q Clinic, Toronto General Hospital, Toronto, ON, Canada; [2]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [3]Clinical Genetics Research Program, Centre for Addiction & Mental Health, Toronto, ON, Canada; [4]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada; [5]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada.

Background: 4-5% of Canadian adults have vitamin B12 deficiency. Treatment of this deficiency is important as it can have lasting effects on neurocognitive function. As neurocognitive features are common in adults with 22q11.2 Deletion Syndrome (22q11.2DS), understanding the prevalence of B12 deficiency in this population will be an important part of preventing and managing these treatable conditions. **Methods:** Through the course of regular clinical assessment, vitamin B12 levels were collected for adults with 22q11.2DS. Vitamin B12 deficiency was defined as <148 pmol/L, marginal levels as ≥148 but <222 pmol/L, and above normal as >652 pmol/L. In individuals with levels <222 pmol/L, vitamin B12 levels post-3 months of treatment with supplemental B12 (1000 mcg/daily) were also collected, where available. **Results:** Of 180 consecutive adults (median age 28 years, n=100 females) with 22q11.2DS who were screened for vitamin B12 levels, n=10 (5.6%) had vitamin B12 deficiency, with a further 31 (17.2%) having marginal levels; n=10 (5.6%) had above normal levels. Of the 41 individuals with marginal levels or lower, 17 who underwent treatment with supplemental B12 had 3 months post-treatment B12 levels available. Of these, 10 (59%) achieved levels >222 pmol/L within 3 months, while 4 (24%) remained deficient or marginal, and 3 (18%) developed above normal levels. **Conclusions:** The results indicate that just under one in every four adults with 22q11.2DS may have marginal or deficient vitamin B12 levels, underscoring the importance of regular screening. Understanding the predictors of vitamin B12 deficiency in 22q11.2DS will be helpful for developing more targeted screening and management strategies for this population. Early identification of this readily treatable vitamin deficiency could help optimize neurocognitive functioning, a worthy goal for these patients.



039: First characterization of the gut microbiome in children with 22q11.2 deletion syndrome

Alain J. Benitez[1,2] Luc Santilli,[1] Scott G. Daniel,[1] Audrey Olson,[3] Lydia Rockart,[3] Robin Miccio,[1] Lauren White,[2,4] Donna McDonald-McGinn,[2,3,5] and Maria Mascarenhas[1,2,3]

[1]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia; Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (22q11.2DS) is a multisystem disorder characterized by immune dysfunction, increased risk of neurodevelopmental and psychiatric conditions, and prominent gastrointestinal involvement. Despite the immunologic vulnerability and psychiatric risk in 22q11.2DS, both of which suggest that altered host–microbiome interactions may contribute to disease expression, the gut microbiome has not been characterized in affected individuals. Defining gut microbial composition and function in 22q11.2DS may clarify disease mechanisms and identify novel therapeutic targets. Here we present pilot data characterizing the microbiome in 22q11.2DS and examine possible changes as a function of a wellness intervention program. **Methods:** Stool samples were collected from children with 22q11.2DS prior to and 1 month after an 8-week wellness intervention. DNA was extracted (~200 mg stool; Qiagen DNeasy PowerSoil Pro) and sequenced on an Illumina NovaSeq 6000 (2×150 bp). Shotgun data were processed with Sunbeam and taxonomic abundance estimated using Kraken. Linear mixed-effects models assessed relative abundance group differences. **Results:** Samples from 19 participants (19 pre-, 8 post-intervention) were analyzed (mean age 10.4 years; 53% female; 90% White). Gut microbiome showed substantial variability, dominated by Bacillota, Bacteroidota, and Actinomycetota. Alpha diversity did not differ by antibiotic exposure, probiotic use, or sex. Beta diversity differed by sex ($p=0.02$) and probiotic exposure ($p=0.04$), but not antibiotics. Male sex and probiotic use were associated with higher relative abundance of *Blautia* spp., *Ruminococcus* sp. SR1/5, and unclassified Clostridia; males also showed lower *Alistipes onderdonkii* and unclassified *Bacteroides*. **Conclusions:** In this pilot study, alpha diversity was preserved across subgroups; however, gut microbial community composition differed significantly by sex and probiotic exposure with enrichment of Firmicutes-associated taxa in males. Host biological factors and probiotic exposure may influence microbial community composition in this cohort. Forthcoming analyses will provide result validation, comparison with age and sex matched controls, and evaluate intervention effect.

040: Microbiota–metabolite remodeling links Tbx1 haploinsufficiency to brain dysfunction in 22q11.2 deletion syndrome

Stefano Leo[1], Sabrina Bianco[2,3], Sara Cioffi[4], Gemma Flore[4], Sara Veneziano[4], Michele Costanzo[2,3], Marianna Caterino[2,3], Margherita Ruoppolo[2,3], Lucia Mele[4], Lucia Marra[4], Marchesa Bilio[4],Rosa Ferrentino[4], Elizabeth Illingworth[5], Antonio Baldini[2], and Gabriella Lania[4]

[1]*European Biomedical Research Institute of Salerno, Salerno, Italy;* [2]*University of Naples Federico II, Department of Molecular Medicine and Medical biotechnology, Naples Italy;* [3]*CEINGE-Biotecnologie Avanzate Franco Salvatore s.c.a.r.l., Naples, Italy;* [4]*Institute of Genetics and Biophysics of National Research Council Naples, Italy;* [5]*University of Salerno, Department of Chemistry and Biology, Fisciano, Italy*.

Background: 22q11.2 deletion syndrome (22q11.2DS) is a major genetic risk factor for neurodevelopmental disorders, yet the mechanisms linking gene dosage to brain dysfunction remain unclear. Using a Tbx1$^{+/-}$ mouse model, we previously found that haploinsufficiency produces behavioral abnormalities accompanied by profound remodeling of the brain metabolome, suggesting that metabolic dysregulation may contribute to neural phenotypes[1].Because gut microbiota are key regulators of host metabolism[2], we investigated whether microbial metabolites participate in these alterations. **Methods:** Whole-metagenome shotgun sequencing was performed on fecal samples taken from 13 Tbx1$^{+/-}$ and 14 Tbx1$^{+/+}$ mice matched by sex and age. In parallel, high resolution mass spectrometry was conducted on whole brains from 2-month-old Tbx1$^{+/-}$ (n=4) and Tbx1$^{+/+}$ (n=4) mice. **Results:** Microbiota sequencing revealed a marked significant compositional shift (PERMANOVA *pval* < 0,01) in Tbx1 mutant mice, including enrichment of taxa predicted to produce lactate and acetate and depletion of butyrate-producing and mucin-degrading bacteria, consistent with altered microbial metabolic capacity. Brain proteomic analysis further identified significant changes in proteins involved in synaptic signaling, neuronal plasticity, mitochondrial function, and energy metabolism. Dysbiosis was usually associated with altered systemic levels of SCFAs and lactate, which were also elevated in mutant brains. Integrative multi-omics analysis therefore supports a link between microbiota-associated metabolites and brain phenotype in Tbx1$^{+/-}$ animals. **Conclusion:** These findings support a model in which Tbx1 haploinsufficiency may influence neurodevelopmental outcomes in 22q11.2DS through microbiota–metabolite–brain interactions, highlighting the gut–brain axis as a potential mechanistic and therapeutic target.

041: Primate-specific RNA dysregulation and innate immune activation in 22q11.2 deletion syndrome

Sara Heras[1]

[1]*Facultad de Farmacia, University of Granda, Granada, Spain*

DGCR8, a core component of the microRNA (miRNA) biogenesis machinery is affected by the 22q11.2DS microdeletion. Although DGCR8 haploinsufficiency has been associated with altered miRNA production, its contribution to the developmental and immune phenotypes of the 22qDS remain unknown. We have generated human pluripotent stem cell models carrying a single functional *DGCR8* allele to investigate its role in early development. DGCR8+/− human embryonic stem cells exhibit increased apoptosis, impaired self-renewal, and defective differentiation in both naïve and primed pluripotent states. Small RNA profiling reveals a preferential depletion of primate-specific miRNAs, accompanied by reduced expression of the primate-restricted endogenous retrovirus HERVH, which is required for pluripotency maintenance. Mechanistically, HERVH downregulation is driven by loss of primate-specific miRNAs, revealing a regulatory axis not conserved in mouse models and highlighting the importance of human-specific RNA networks in stem cell identity. Beyond its canonical role in miRNA biogenesis, we have identified DGCR8 as a suppressor of the innate immune pathway, the type I interferon response. Mechanistically, we have found that inactivation of DGCR8 leads to the accumulation of immunogenic double stranded RNAs, that the immune system misrecognizes as a threat, activating the type I IFN response. In agreement with a role of DGCR8 in immune regulation, cells derived from 22qDS patients display an exacerbated IFN signature that inversely correlates with DGCR8 expression levels, linking RNA homeostasis to innate immune activation. Together, these findings establish DGCR8 as a central regulator of primate-specific RNA networks in pluripotency and suppression of immunogenic TE-derived dsRNA. This dual function provides a mechanistic framework connecting human-specific RNA regulation with developmental abnormalities and innate immune dysregulation in 22q11.2 deletion syndrome.

042: Immunologic correlates of psychotic illness in 22q11.2 deletion syndrome

Anne S. Bassett[1], Katherine Beigel[2], Kelly Maurer[2], Nouf Alsaati[3], Raquel Gur[4], T. Blaine Crowley[5], Donna McDonald McGinn[5], and Kathleen E. Sullivan[2]

[1]University of Toronto, Clinical Genetics Research Program at the Centre for Addiction and Mental Health, and Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada; [2]Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Psychiatry, Neurodevelopment & Psychosis Section, Perelman School of Medicine and Lifespan Brain Institute, University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Clinical Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (22q11.2DS) is the most common recognized genetic etiology for schizophrenia and related psychotic illnesses. While 22q11.2DS is associated with immunodeficiency, especially in children, the relationship of the immune system effects to psychotic illness is not well understood. Evidence from epidemiologic data in the general population suggests that inflammation may contribute to the development of schizophrenia. This study examined differences in the immune landscape in patients with 22q11.2DS and psychotic illness. **Methods:** Under an IRB approved protocol, unbiased methodologies, including single cell RNA-sequencing and antibody arrays, were used to determine differences between patients with 22q11.2DS and psychotic illness (22q-P, maximum n=17) and those without psychosis (22q-NP, maximum n=17), and healthy donors (HD, maximum n=18). **Results:** There were significantly higher levels of antibodies, both to known autoantigens and to other antigens, in the 22q-P group compared to the other two groups. The 22q-P group also exhibited expansions of T cell clones, with the clones expressing genes related to inflammation and cytotoxic functions. These expanded T cell clones differed qualitatively from those in both the 22q-NP and HD groups. Notably, T cell epitopes differed in the 22q-P group with respect to having more self-reactive epitopes in the expanded clones. **Conclusions:** These initial results indicate there is a highly altered immune landscape in individuals with 22q11.2DS with psychotic illness. The results implicate inflammatory mediators and increased self-reactivity mechanisms in the susceptibility to, and development of, psychotic illness in 22q11.2DS. Consistency with previous epidemiologic data suggests potential for broader applicability in the general population.

043: Haploinsufficiency-Driven RNA Metabolism is Associated with Immune Dysregulation and Psychosis Risk in 22q11.2 Deletion Syndrome *

Christina Michalski[1], David A. Parker[2], Leah Cheng[1], Mojahidul Islam[3], Sidney Imes[1,4], Gabrielle Ruban[1,4], Heath Dunlop[5], Bruce Cuthbert [1,4], Brett Henshey[4,5], Grace Lee[5], Nicholas M. Massa[4], Opal Y. Ousley[1], Elaine F. Walker[6], David R. Goldsmith[1], Joseph F. Cubells[1,2], Erica Duncan[1,4], Bradley D. Pearce[7], Ashish A. Sharma[3], and Zhexing Wen[1,2,8,9]

[1]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA; [2]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA; [3]Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, USA; [4]Atlanta Veterans Affairs Health Care System, Decatur, GA, USA; [5]College of Arts and Sciences, Emory University, Atlanta, GA, USA; [6]Department of Psychology, Emory University, Atlanta, GA, USA; [7]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA; [8]Department of Cell Biology, Emory University School of Medicine, Atlanta, GA, USA; [9]Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA.

Background: 22q11.2 deletion syndrome (22qDS) is a high genetic risk factor for schizophrenia. Prior studies demonstrated immune dysregulation in 22qDS; however, the mechanistic relationship between immune perturbations and neuropsychiatric symptoms remains incompletely understood. **Methods:** We studied a cohort of individuals with 22qDS (n=34) and age- and sex-matched controls (n=33). Participants were assessed for psychosis symptoms using the Structured Interview for Psychosis-Risk Syndromes (SIPS). Plasma cytokines were quantified and peripheral blood mononuclear cells (PBMCs) were profiled by single-cell RNA sequencing. Differential gene expression and gene set enrichment analyses were performed, adjusting for age and sex with correction for multiple comparisons. **Results:** 22qDS was characterized by a pro-inflammatory plasma cytokine profile with elevated IL-1β, IL-2, IL-6, IP-10, and IL-17A compared to controls. As expected, genes located within the 22q11.2 deletion interval were expressed in control PBMCs but significantly downregulated in 22qDS. Subset-specific differential gene expression analyses revealed upregulation of inflammatory pathways across immune compartments in 22qDS. Monocytes demonstrated enrichment of NF-κB and IFN-γ signaling, consistent with the elevated plasma levels of IL-1β and IL-6. Naïve and memory T cell compartments exhibited upregulation of IL-2–STAT5 signaling. Additionally, pathways downstream of IL-1β, IL-6, and TGF-β were enriched in naïve CD4 T cells, consistent with enhanced Th17 polarization and elevated plasma IL-17A. RNA processing pathways were significantly downregulated across PBMC subsets in 22qDS donors, including genes within the 22q11.2 region (e.g., DGCR8, ESS2). Interestingly, within the 22qDS participants, low expression of RNA metabolism and protein translation pathways was associated with increasing SIPS scores. **Conclusions:** Our findings suggest that haploinsufficiency of 22q11.2 region genes disrupts RNA processing in immune cells, promoting inflammatory activation and elevated IL-17A. These data implicate immune-intrinsic consequences of 22qDS as contributors to inflammatory and neuropsychiatric phenotypes and support further research into therapeutic strategies targeting immune pathways.

044: Discriminating psychosis in 22q11.2 deletion syndrome using monocyte inflammation-related gene expression *

Emma Saillart[1], Elfi Vergaelen[1,2], Stephan Claes[1,2], Elske Vrieze [1,2], and Ann Swillen[3]

[1]Mind-Body Research, Psychiatry Research Group, Department of Neuroscience, Faculty of Medicine, KU Leuven, Leuven, Belgium; [2]University Psychiatric Center KU Leuven, University Hospital Leuven, Leuven, Belgium; [3]Center for Human Genetics, University Hospital Leuven/Department of Human Genetics, KU Leuven, Leuven, Belgium.

Background: The 22q11.2 deletion syndrome (22q11.2DS) is associated with a high prevalence of psychotic disorders and immune dysregulation characterized by disturbed T-cell development, altered T- and B-cell function, and an increased prevalence of autoimmune disorders. Given growing evidence for immune involvement in the development of psychosis in 22q11.2DS, we aimed to determine whether monocyte immune-related gene expression profiles can discriminate adults with 22q11.2 deletion syndrome based on psychosis status. **Methods:** Adults with 22q11.2DS were classified into two groups based on clinical assessment of psychotic symptoms. Individuals with a history of schizophrenia spectrum disorder or meeting criteria for being at risk for psychosis based on the Comprehensive Assessment of At-Risk Mental States (CAARMS) were classified as having psychotic symptoms (n = 16). Individuals without a history of psychosis and with low CAARMS risk scores were classified as non-psychotic (n = 20). Gene expression levels in monocytes of 17 inflammation-related genes were assessed. To identify immune markers contributing to the discrimination of psychosis status, sparse partial least squares discriminant analysis (sPLS-DA) was performed using the mixOmics package in R. Model parameters were optimized using repeated five-fold cross-validation based on the balanced error rate (BER). Model significance was assessed using permutation testing. **Results:** 36 participants (33.3% female) with 22q11.2DS were included (mean age 38.8 ± 5.3 years; mean BMI 27.1 ± 5.9). sPLS-DA identified a two-component model discriminating individuals with and without psychosis with a BER of 0.338 (balanced accuracy = 0.662). The mean cross-validated AUC was 0.751 ± 0.283, and permutation testing supported model significance (p = 0.027). **Conclusions:** These findings suggest that monocyte immune gene expression markers show moderate ability to discriminate adults with 22q11.2DS with versus without psychotic symptoms. Further studies in larger cohorts are needed to investigate the role of immune-related pathways in psychosis in 22q11.2DS.

045: Immune dysregulation in chromosome 22q11.2 related disorders: insights from the USIDNet registry

Nikita Raje[1], Vaibhavi Vichare[2], Roshini Abraham[3], Ivan Chinn[4], Megan A. Cooper[5], Ramsay Fuleihan[6], Avni Y. Joshi[7], Monica G. Lawrence[8], Rebecca Marsh[9], Luigi Notarangelo[10], Jennifer M. Puck[11], Charlotte Cunningham Rundles[12], Kelly Walkovich[13], and Kathleen Sullivan[14]

[1]Depeartment of Pediatrics, Division of Allergy Immunology Pulmonary Sleep Medicine, Children's Mercy Hospital, University of Missouri, Kansas City, MO, USA; [2]Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Nationwide Children's Hospital, Columbus, OH, USA; [4]Department of Pediatrics, Division of Immunology, Allergy, and Retrovirology, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA; [5]Department of Pediatrics, Division of Rheumatology/Immunology, Washington University, St. Louis, MO, USA; [6]Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, Columbia University Irving Medical Center, New York City, NY, USA; [7]Mayo Clinic Rochester, MN, USA; [8]Division of Asthma, Allergy & Immunology, University of Virginia School of Medicine, VA, USA; [9]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; [10]National Institutes of Health, Bethesda, MD, USA; [11]Division of Allergy/Immunology and Blood and Marrow Transplantation, Dept. of Pediatrics, and UCSF Benioff Children's Hospital, University of California San Francisco, San Francisco, CA, USA; [12]Department of Medicine, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York City, NY, USA; [13]University of Michigan, MI, USA; [14]Division of Allergy Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: Chromosome 22q11.2 deletion syndrome is the most common microdeletion chromosomal anomaly. Frequent infections are a major feature of immunodeficiency noted in chromosome 22q11.2 deletion syndrome and related disorders (22qRD), including 22q11.2 duplication, DiGeorge syndrome, and velocardiofacial syndrome. Immune dysregulation is also observed in 22qRD but has not been well characterized in large multicenter registry cohorts. The aim of this project was to describe the noninfectious immune manifestations among patients with 22qRD in USIDNet, a database that selectively enrolls individuals with immune system abnormalities. **Methods:** We performed a retrospective analysis of USIDNet individuals with ICD codes corresponding to 22qRD and retrieved encounters related to recurrent fevers, cytopenias, or autoimmunity. Descriptive statistics were used to summarize clinical features and encounter frequencies. **Results:** From 2018–2024, the USIDNet cohort included 1,456 patients with 22qRD, including 1,428 with 22q11.2 deletion and 9 with 22q11.2 duplication. We reviewed 20,163 encounters for these patients. The number of encounters ranged from 0–299 (0 indicating no encounters, diagnosis listed only in the problem list). Out of 1,456 patients, 134 had thrombocytopenia with 366 unique encounters, and another 18 had easy bruising or bleeding accounting for 17 unique encounters. A total of 145 reported recurrent fevers with 335 unique encounters; 27 reported arthritis or joint swelling/redness with 246 unique encounters; 77 had diarrhea with 142 unique encounters; and 34 had thyroiditis with 120 unique encounters. **Conclusions:** Chromosome 22q11.2related disorders can be associated with a range of noninfectious immune complications, including recurrent fevers, autoimmunity, cytopenias, endocrinopathy, and arthritis. Thus, immune dysregulation may contribute to overall morbidity in this patient population.

046: Immune system activation following trauma in 22q11.2 deletion syndrome

Adi Drapisz[1], Yana Paltavets[1,2], Shira Dar[3], Doron Gothelf[1,2,4], and Michal Taler[2,3,4]

[1]Behavioral Neurogenetics Center, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; *[2]Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel; [3]Pediatric Molecular Psychiatry Laboratory, Sheba Medical Center, Tel Aviv, Israel; [4]The Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel.*

Background: 22q11.2 deletion syndrome (22q11.2DS) is associated with increased trauma exposure, elevated PTSD rates, and baseline immune dysregulation. Previous studies have shown that trauma can trigger immune activation across various populations. However, the relationship between trauma exposure and immune activation in individuals with 22q11.2DS remains poorly understood. We examined whether trauma exposure is associated with altered cytokine levels in this population. **Methods:** Thirty participants with molecularly confirmed 22q11.2DS were recruited from a tertiary clinical center. Trauma-related symptoms were assessed using the Child PTSD Symptom Scale (CPSS). Participants were dichotomized into high-trauma (CPSS >21) and low-trauma groups based on established clinical cutoffs. Peripheral blood samples were collected and serum concentrations of IL-6, IL-1β, and TNF-α were quantified using standard immunoassay techniques. Cytokine levels were compared between trauma groups using group-based analyses. **Results:** Participants with high trauma exposure exhibited significantly elevated IL-6 ($p = 0.01$) and TNF-α ($p = 0.022$) levels compared to those with low trauma exposure. IL-1β showed a similar pattern but did not reach statistical significance. **Conclusions:** Research examining trauma in rare genetic syndromes remains limited and scarce. Given the unique vulnerabilities of the 22q11.2DS population, including pre-existing immune dysfunction and elevated psychiatric risk, raises a need for further investigation. Understanding the interplay between trauma, immune activation, and psychiatric outcomes in this population could inform targeted interventions and improve clinical care for these individuals.

047: Identification of whole gene deletion of TBX1 with autoimmune cytopenias in a large pediatric cohort

Emily M Harris[1], Amanda B Grimes[2], Yi-Lee Ting[3], Taylor Kim[4], Rachael F Grace[1], Kristin Shimano[5], and Michele P. Lambert[6]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA; [2]Department of Pediatrics, Section of Hematology/Oncology, Baylor College of Medicine, Houston, TX, USA; [3]Labcorp, USA; [4]University of Southern California and Children's Hospital of Los Angeles, Los Angeles, CA; [5]University of San Francisco, San Francisco, CA USA; [6]Department of Pediatrics, Perelman School of Medicine at UPENN and Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: Individuals with 22q11.2DS have an increased risk of autoimmune cytopenias and variable clinical phenotypes. Identification of a deletion of TBX1 via next-generation sequencing (NGS) may raise concerns for 22q11.2DS. We examined the prevalence of TBX1 whole gene deletion in a cohort of children undergoing evaluation for immune cytopenias. **Methods:** This was a retrospective study of pediatric patients who had clinical genetic testing through a commercial clinical laboratory (Invitae, now part of Labcorp) who were tested for the indication of autoimmune cytopenias. Patients had any of the following targeted NGS panels performed: Inborn Errors of Immunity and Cytopenias panel, Primary Immunodeficiency Panel, ALPS Panel, Phagocytic Disorders Including Neutropenia Panel, Autoinflammatory and Autoimmunity Syndromes Panel, and/or Common Variable Immunodeficiency Panel containing 9-1558 genes; and were identified by the loss of a single copy of TBX1. **Results:** There were 715 patients with immune cytopenias identified who had targeted NGS panels. Median age at time of testing was 12 years (range 0-21) and 47.4% (n=339) were female. The frequency of patients with pathogenic or likely pathogenic variants was 30.1% (215/715) in the total cohort and was not different by disease type. The frequency of molecular IEI diagnosis in the entire cohort was 7.7% (55/715). The most common genetically identified variant was deletion of a single copy of TBX1 (n=8), accounting for 14.5% of molecular IEI diagnoses. Of these 8 patients, 3 had ITP, 1 had AIHA, and 4 had ES; the median age was 12 years (4-20) and 25% (n=2) were female. **Conclusions:** Genetically defined IEI are identified in approximately 30% of children with autoimmune cytopenias and the most common was deletion of TBX1, which is commonly deleted in 22q11.2DS. The confirmation of 22q11.2DS by microarray would significantly alter the management of these patients.

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048: Immune cytopenias in a large cohort of patients with 22q11.2DS: management, outcomes and unique considerations

T. Blaine Crowley[1], Praharsha Konde[2], Samantha Gaerian[2], Donna McDonald-McGinn[1], and Michele P. Lambert[2]

[1]Division of Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: Immune cytopenias including Immune Thrombocytopenia (ITP), Autoimmune Hemolytic Anemia (AIHA), or Evans syndrome (ES), can complicate the diagnosis of 22q11.2DS. We describe the prevalence, management and outcomes of patients with autoimmune cytopenias and 22q11.2DS at our center. **Methods:** This was a retrospective study including pediatric patients who were followed at our center. Patients who were seen at the Division of Hematology and carried a diagnosis of ES, ITP or AIHA in addition to 22q11.2DS were identified by review of electronic medical records in compliance with an IRB approved study. **Results:** Within our database of 1840 patients with 22q11.2DS seen at the center, 14 patients had autoimmune cytopenias: 9 patients were identified with ES. 2 patients had isolated AIHA and 3 patients had isolated ITP. Of those patients with isolated ITP, two of three patients had excellent response to IVIG and did not require retreatment. One of the 3 patients had a relapse. All patients received IVIG due to concern for bleeding and/or need for concomitant anti-platelet therapy. There were 2 patients with isolated autoimmune hemolytic anemia with a relapsing/remitting course requiring several courses of corticosteroids and/or anti-CD20 antibody. Of the 9 patients with ES, 7 presented with combined cytopenias at the time of diagnosis. One patient had eventual diagnosis of SLE. Four patients had complex congenital heart disease including 3 with TOF and one with truncus arteriosus. All of these patients required rituximab, corticosteroids and other immune modulation long term. Two patients died, one with ES and one with ITP. **Conclusions:** Children with 22q11.2DS are at increased risk of development of autoimmune cytopenias. Isolated, single lineage cytopenias, may be managed similarly to children without the deletion. In patients with refractory disease or ES, multimodal management is important to maintain disease control but may still be associated with mortality.

049: Proteome wide autoantibody profiling in the 22q11.2 deletion syndrome

Jenny Lingman Framme[1, 2], Viktoria Hennings[3], Anna-Carin Lundell[3], Karolina Thörn[3], Christina Lundqvist[3], Susanne Lindgren[1, 3], Vanja Lundberg[1, 3], Esbjörn Telemo[3], Anders Fasth[1], Sólveig Óskarsdóttir[1], and Olov Ekwall[1,3]

[1]Department of Pediatrics, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; [2]Department of Pediatrics, Halland Hospital Halmstad, Halmstad, Region Halland, Sweden, [3]Department of Rheumatology and Inflammation Research, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

Background: The 22q11.2 deletion syndrome (22q11DS) is associated with immunodeficiency related to thymus hypoplasia and an increased risk of autoimmune disease. A fraction of infants with 22q11DS present in newborn screening using T-cell receptor excision circles (TRECs), indicating low output of naïve T cells. **Purpose**: To investigate if low TRECs at birth was associated with higher prevalence of autoantibodies at follow-up in 22q11DS, and to identify syndrome-specific novel autoantibodies or patterns of autoantibodies. **Method:** A planar array containing 42,100 antigens was screened for IgG reactivities with pooled plasma from i) 10 individuals with 22q11DS and low number of TRECs at birth, ii) 10 individuals with 22q11DS and normal TRECs at birth and iii) 9 healthy controls. Antigens with seroreactivity in both 22q11 groups (n=380) were further analyzed using a bead array on individual samples. A second validation was performed on five selected antigens in an extended cohort of 50 individuals with 22q11DS and 50 controls. **Results:** Individuals with 22q11DS had autoantibodies towards a higher number of antigens than controls, and low TRECs at birth was associated with stronger reactivities in 22q11DS. Overall, 146 antigens were validated as autoantigens in the bead array, and a proportion of these antigens shared molecular functions related to receptor binding. Reactivity towards specific antigens was shared by up to 8 out of 20 22q11 individuals, and two 22q11 individuals had 6 reactive antigens in common. **Conclusions**: Individuals with 22q11DS, particularly those with low TRECs in newborn screening, had higher number of autoantibodies, implying autoimmune predisposition.

050: Spatial multiomic studies of the thymus in individuals with 22q11.2 deletion syndrome

Viktoria Hennings[1,2], Jenny Lingman Framme[1,3], Sólveig Óskarsdóttir[1], and Olov Ekwall[1,2]

[1]Department of Pediatrics, The Sahlgrenska Academy at University of Gothenburg, Sweden; [2]Department of Rheumatology and Inflammation Research, The Sahlgrenska Academy at University of Gothenburg, Sweden; [3]Department of Pediatrics, Halland Hospital Halmstad, Sweden.

Background: The 22q11.2 deletion syndrome (22q11DS) is the most common primary thymus disorder. Although complete athymia is rare in 22q11DS, most individuals have thymus hypoplasia, leading to T lymphopenia of varying severity. The spatial organization of the thymus tissue and the mechanisms contributing to thymic dysfunction in 22q11DS remain incompletely described. **Methods:** A multiomic approach was applied to investigate the spatial organization and cellular composition of the thymus in individuals with 22q11DS. Using 10X Visium spatial transcriptomics and protein co-detection with the Phenocycler platform, we analyzed thymic tissue from two children with 22q11DS and compared with healthy controls (n=8). **Results:** Consistent with findings from mouse models, the transcriptomic profiles of the 22q11DS thymuses revealed upregulation of genes and pathways critical for cortical collagen formation, extracellular matrix remodeling, and mesenchymal and endothelial cell proliferation. The thymuses of 22q11DS patients exhibited decreased medullary areas and poor separation between the medulla and cortex. Deconvolution analysis, informed by single-cell RNAseq datasets, allowed us to identify differences in cell abundances and spatial co-localizations. These findings were further validated at the protein level using a 30-marker spatial proteomics approach. **Conclusions:** The results provide new insights into the cellular mechanisms and pathways involved in the maintenance and regulation of the human thymus, as well as the thymic pathophysiology in 22q11DS.

051: Investigation of autoimmune alterations in 22q11.2 deletion syndrome in a single Brazilian center: preliminary results from 17 individuals *

João Pedro Moretti[1] and Vera Lúcia Gil-da-Silva-Lopes[1]

[1]*Department of Medical Genetics and Genomics Medicine, School of Medical Sciences, State University of Campinas (Unicamp), Campinas, São Paulo, Brazil.*

Introduction: 22q11.2 deletion syndrome (22q11.2DS OMIM #611867) has an estimated prevalence of 1:2200 live births. This is a chronic health condition that requires management and monitoring of complications throughout one's life. In addition to the defects most associated with this microdeletion, thymic hypoplasia, which results in immune dysregulation encompassing both immunodeficiency and autoimmunity phenotypes, has gained increasing importance. **Objectives:** To screen the prevalence and characterize the profile of autoimmunity in 22q11.2DS in a single Brazilian Genetic Center. **Methods:** This is a transversal study involving 17 individuals from the Craniofacial Dysmorphologic Outclinic in a tertiary hospital in the Brazilian Southeast (Hospital de Clínicas, Unicamp). Individuals were screened for chronic arthropathy using a validated 12-question tool (Len et al., 2006). Additionally, all probands were evaluated for cytopenia through hemogram. **Results:** Of 17 individuals (6 male and 11 female), ages ranged from 4 to 59 years. Five of them (29%) met the threshold of 5 points, suggesting chronic arthropathy, and 1 patient already had juvenile idiopathic arthritis (JIA). Evaluation of cytopenias showed four affected individuals (23%), all with low-grade thrombocytopenia; one proband (5%) had persistent bicytopenia with thrombocytopenia and anemia. **Discussion:** The underlying mechanisms behind autoimmunity in 22q11.2DS are yet to be clarified; immunophenotyping assays have indicated that patients harbor both cellular and humoral impairments. The most common immune defects are reduced suppressive function of regulatory T cells (Treg) alongside depletion of naïve CD4+ T and B memory cells populations; contraction of these lineages has been linked with juvenile idiopathic arthritis and immune cytopenias in inborn errors of immunity cohorts, aligning with the autoimmune profile of 22q11.2DS patients. **Conclusion:** The results reinforce the importance of dissemination among healthcare professionals for the early evaluation and monitoring of autoimmune manifestations in 22q11.2 deletion syndrome, thereby promoting early diagnosis and improved quality of life.

052: Cardiac complexity predicts increased immune diagnostic burden in 22q11.2 deletion syndrome *

Jasmyn Atalla[1], Blaine Crowley[2,3], Kathleen Sullivan[1,2,4], Jennifer Heimall[1,4], Donna M. McDonald-McGinn[2,3,4], and Timothy Buckey[1,4]

[1]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (DS) is the second most common cause of congenital heart disease (CHD) and a multisystem disorder that contributes to substantial overall disease burden. Additionally, 22q11.2DS is the most common cause of DiGeorge syndrome and the second most common chromosomal abnormality after Down syndrome found in 1/2148 livebirths. Up to 75-80% of 22q11.2DS patients have immune system abnormalities. We aim to determine whether CHD complexity is associated with a higher burden of allergic, immunologic, and autoimmune diagnoses. **Methods:** We performed a retrospective chart review of adults (≥18 years) with confirmed 22q11.2DS seen at the 22q and You Center at Children's Hospital of Philadelphia (CHOP). Exclusion criteria included 22q11.2 duplication, residence more than 100 miles from CHOP, no documented visit between 2001-2025. We assessed CHD severity (based on structural complexity) and its association with allergic, immunologic, and autoimmune disorders identified through diagnosis codes. These variables were compared by chi-square analysis. **Results:** A total of 419 adults met inclusion criteria; 54 of 419 (13%) had a documented autoimmune diagnosis, 118 (28%) had an allergic condition, and 121 (29%) had an immune disorder. Twenty-five patients (6%) had an unknown cardiac history – so presumed normal/mild CHD. Of those with CHD, 37 individuals (9%) had a documented autoimmune diagnosis, 75 (18%) had an allergic diagnosis, and 87 (21%) had an immune condition. Analysis of CHD complexity revealed no statistically significant association with lifetime autoimmune diagnoses ($p=0.08$) or allergic diagnoses ($p=0.32$). In contrast, CHD complexity was significantly associated with immune diagnoses ($p=0.001$), suggesting that individuals with more structurally complex congenital heart disease experience a higher burden of immune-related conditions over their lifetime. **Conclusions:** These findings highlight a potential link between cardiac severity and immune system involvement in adults with 22q11.2DS, underscoring the importance of longitudinal cardiovascular and immunologic care in this population.

053: Platelet function and bleeding risk in adults with 22q11.2 deletion syndrome: a cross-sectional investigational study *

Emma N.M.M. von Scheibler[1,2], Jeltje C.C. Spapens[1], Magdolna Nagy[3], Irene M.L.W. Keularts-Körver[4], Floor C.J.I. Heubel-Moenen[5], Johan W.M. Heemskerk[3], Agnies M. van Eeghen[6,7], Thérèse A.M.J. van Amelsvoort[1], and Erik Boot[1,6,8]

[1]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Institute (MHeNs), Maastricht University, Maastricht, The Netherlands; [2]Koraal, Maasveld, Maastricht, The Netherlands; [3]Department of Biochemistry, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands; [4]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht University, Maastricht, The Netherlands; [5]Department of Internal Medicine–Hematology, Maastricht University Medical Center, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands; [6]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [7]Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, The Netherlands; [8]The Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada.

Background: 22q11.2 deletion syndrome (22q11.2DS) is associated with macrothrombocytopenia and increased bleeding tendency, but studies have focused primarily on children. Additionally, the role of candidate genes in the deleted region such as GP1BB remain unclear. Furthermore, schizophrenia and psychoactive medication may independently affect platelet function. This study aimed to compare platelet function and bleeding risk in adults with 22q11.2DS versus controls, between patients with and without schizophrenia spectrum disorder, and in relation to age. **Methods:** We included 24 adults with molecularly confirmed typical 22q11.2DS (12 females, mean age =30.2, SD = 13.1) and 19 age-matched healthy controls (11 females, mean age =31.8, SD =15.1), excluding those using anticoagulant or antiplatelet medication. Platelet parameters were assessed through complete blood count analysis, flow cytometry for GPIbβ expression, and whole blood perfusion over collagen and Von Willebrand Factor /fibrinogen surfaces at arterial shear rates. Bleeding risk was evaluated using the ISTH-BAT questionnaire. **Results:** Bleeding scores were significantly higher in adults with 22q11.2DS (p <0.001). Platelet count was significantly lower (p <0.001) and mean platelet volume was significantly higher in the 22q11.2DS group compared to controls (p <0.001). GPIbβ expression showed no significant difference between groups. Additional analyses examining platelet adhesion, aggregation, and associations with schizophrenia and age are currently being finalized. **Conclusions:** This is the first study to comprehensively assess platelet function in adults with 22q11.2DS. Our findings demonstrate macrothrombocytopenia and increased bleeding risk compared to controls. GPIbβ expression was preserved despite GP1BB haploinsufficiency. Complete results including advanced platelet function analyses and correlations with schizophrenia and age will provide novel insights into the underlying mechanisms and clinical implications for adult 22q11.2DS patients.

054: Immunologic outcomes following thymectomy in patients with 22q11.2 deletion syndrome

Anne Jennings[1,2], T. Blaine Crowley[1], Audrey Olson[1], Lydia Rockart[1], Daniel E. McGinn[1], Oanh Tran[1], Elaine H. Zackai[1,3,4], Beverly S. Emanuel[1,3,4], J. William Gaynor[1,5,6], Kathleen E. Sullivan[1,4,7], Kathleen Valverde[2], and Donna M. McDonald-McGinn[1,2,3,4]

[1]The 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Master of Science in Genetic Counseling Program, The Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, The Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Cardiothoracic Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Department of Surgery, The Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [7]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: Patients with 22q11.2 deletion syndrome (22q11.2DS), may present perinatally with thymic aplasia/hypoplasia. Others with congenital heart disease undergo routine thymectomy during cardiothoracic surgery. Here we examined the impact of thymectomy on short- and long-term immunologic outcome in patients with 22q11.2DS with thymic aplasia/hypoplasia and those who underwent thymectomy during cardiothoracic surgery to patients with 22q11.2DS with no evidence of thymic aplasia/hypoplasia and sans thymectomy during cardiothoracic surgery. **Methods:** We performed a retrospective chart review, under an IRB approved protocol, to identify individuals with a laboratory confirmed 22q11.2 deletion, with and without neonatal cardiothoracic surgery performed between 1998 and 2024 with available immunologic laboratory data including, at minimum, a lymphocyte panel. **Results:** 706 patients met inclusion criteria. Group A included 135 patients with thymic aplasia/hypoplasia/thymectomy (64-absent thymus noted prenatally/neonatally and 71 underwent intraoperative thymectomy). Group B included 571 patients with no history of thymic aplasia/hypoplasia or cardiothoracic surgery and available immune data. T cell count data consisted of absolute CD3+, CD3+/CD4+, CD3+/CD8+, and CD19+, assessed neonatally and longitudinally. Patients in Group A initially had lower absolute CD3+, CD3+/CD4+, CD3+/CD8+, and CD19+ cell counts compared to Group B, however, over time, immune cell counts in Group A normalized and converged with those of Group B. **Conclusion:** This study suggests that there may be an additive effect of 22q11.2DS and cardiac surgery on T cell counts in infancy. However, while thymic hypoplasia/aplasia/thymectomy may initially impact the neonatal T cell counts, importantly the immune system appears to reconstitute and normalize. Whether this is accompanied by qualitative changes to the T cells is unknown and will require additional inquiry. Future investigations will also include examination of infection history, immunoglobulins and B cell counts, humoral deficits, and atopy to further examine immune function across these two sub-cohorts.

055: TLB-101, a GMP allogeneic iPSC-derived thymic epithelial cell product for the potential treatment of congenital thymic insufficiency

Francisco Leon[1], Holger A. Russ[2], Jessie M. Barra[2], Alexander S. Baker[2], Antonio Jimeno[3], J Jason Morton[3], Nathaniel Alzofon[3], Philip Ball[1], Lara Silverman[1], Paul Dunford[1], Christian Blount[1], and Yeh-Chuin Poh[1]

[1]Tolerance Bio Inc, Philadelphia, PA, USA; [2]Diabetes Institute, College of Medicine, University of Florida, Gainesville, FL, USA; [3]Division of Medical Oncology, Department of Medicine, University of Colorado, Aurora, CO, USA.

Background: Congenital thymic insufficiency -underdeveloped or absent thymus at birth- can occur due to genetic abnormalities or environmental factors. The most common cause is chromosomal abnormalities in the 22q11.2 region, which has an incidence of approximately 1 in 2000 live births. The thymus is critical for establishing the adaptive immune system by educating developing T cells resulting in a diverse yet self-tolerant T cell repertoire. Without treatment, children with athymia generally do not survive beyond the first 2-3 years of life primarily due to infection. Patients with thymic hypoplasia often present with reduced naïve T lymphocytes, regulatory T cells and humoral immunity, leading to infections, autoimmunity and atopy. **Methods:** Thymus cells derived from induced pluripotential stem cells (iPSC) could offer a novel option to reconstitute the T cell immune system in these patients. To this end, we are developing TLB-101, a GMP allogeneic iPSC-derived thymic epithelial cell product for the potential treatment of congenital thymic insufficiency. **Results:** We have developed a good manufacturing practice (GMP) 3D/suspension manufacturing process in bioreactors to produce iPSC-derived thymic cells at scale. When implanted into athymic mice, the iPSC thymic cells induce the generation of diverse-repertoire T cells. In vitro, iPSC-derived thymic organoids exhibit key features of negative selection, including AIRE-driven expression in TECs induces expression of tissue-restricted self-antigens. In vivo, positively-selected T cells have been shown to infiltrate and attack a malignant tumor. **Conclusions:** These findings provide proof-of-principle to continue advancing towards future clinical efforts in patients with congenital thymic insufficiency.

056: Therapeutic restoration of immune function through iPSC-derived human thymic epithelial cells (iTECs) - an update on bringing iTECs to the clinic

Wenqing Wang[1], Abdulvasey Mohammed[1], Martin Arreola[1], Hanh Dan Nguyen[1], Zihao Zheng[1], Yujin Moon[1], Kelsea M. Hubka[1], Humza Ali Khan[2], Mark Krampf[1], Agnieszka Czechowicz[1], Anca Pasca[1], Li Li[1], Virginia Winn[3], Sean Bendall[2], Rosa Bacchetta[1], Vittorio Sebastiano[3], and Katja G. Weinacht[1]

[1]Stanford School of Medicine, Department of Pediatrics, Stanford, CA, USA; [2]Stanford School of Medicine, Department of Pathology, Stanford, CA, USA; [3]Stanford School of Medicine, Department of Obstetrics and Gynecology, Stanford, CA, USA.

Background: The thymus is essential for de novo T-cell generation and establishing central tolerance. Thymic function declines beginning in the second decade of life and can be further impaired by cytotoxic therapies, radiation, infection, and graft-versus-host disease. In its most severe form, defective thymic development, as seen in genetic disorders such as 22q11 deletion syndrome, results in congenital athymia. Currently, transplantation of allogeneic cultured thymus tissue is the only therapy available for these patients. However, grafts are derived opportunistically from pediatric cardiac surgery and cannot be HLA-matched, contributing to significant morbidity from autoimmunity and graft failure. Thus, broadly applicable strategies to restore thymic function in an HLA-compatible manner remain lacking. Notably, a recent large-scale study demonstrated that thymectomy in adults doubled the risk of cancer and nearly tripled all-cause mortality within five years (Kooshesh et al., NEJM, 2023), underscoring the critical role of thymic integrity in human health. **Methods:** Here we present a preclinical platform for differentiating iPSCs into functional human thymic epithelial cells (TECs) suitable for direct implantation. **Results:** Xenografted into athymic, human hematopoietic stem cell-engrafted NSG-Foxn1null mice, iPSC-derived TECs (iTECs) promoted full de novo human immune reconstitution with highly diverse TCRab effector and regulatory T-cells. iTECs instructed the development of T-cells capable of discriminating “self” from “non-self,” exhibiting cytotoxicity toward allo-antigens while maintaining tolerance to self-antigens. In vivo, iTECs matured into cortical and medullary compartments with spatially defined thymopoietic and tolerance-inducing niches. These findings provide proof-of-concept for iTECs as a transplantable cell therapy, capable of executing core functions of the human thymus, and establish a rationale for clinical strategies to restore immune function across congenital, acquired, and age-related immune decline. **Conclusions:** Regenerating thymic function from autologous or HLA-compatible iPSCs therefore holds tremendous therapeutic promise. Patients with congenital athymia represent the ethical and regulatory entry point into the clinic. Efforts to obtain an IND for patients with congenital athymia are under way.

057: Postoperative hypocalcemia in children with 22q11.2 deletion syndrome: results following initiation of an institution-wide evidence-based clinical pathway

Jill Arganbright[1], Meghan Tracy[1], Max Feldt[1], Nikita Raje[1], and Janelle Noel-MacDonnell[1]

[1]*Children's Mercy Hospital, Kansas City, MO, United States.*

Background: The 22q guidelines recommend perioperative calcium monitoring, however little has been published on postoperative hypocalcemia for children with 22q11.2 deletion syndrome (22q11DS). With this, our pediatric institution established an evidence-based clinical pathway requiring ionized calcium postoperatively for all children with 22q11.2DS, which went live on June 1, 2025. The aim of this paper is to evaluate the effectiveness of the clinical pathway on improving postoperative calcium testing rates, better understand the frequency and degree of postoperative hypocalcemia in children with 22q11.2DS, and identify whether this is associated with specific types of surgeries. **Methods:** Chart review of patients in our 22q Center's repository from February 1, 2015 to February 1, 2026. Inclusion criteria was a confirmed diagnosis of 22q11DS who underwent any non-cardiac surgical procedure. Data extracted included co-morbidities, surgical details, and calcium testing results within 48 hours of the surgery. **Results:** 264 patients were included who underwent 1,190 procedures (1,158 pre-pathway and 32 post-pathway). Prior to the pathway, 20% of the surgeries had postoperative testing compared to 65% following pathway initiation which represents a 225% increase in testing. Of those that were tested, the rates of postoperative hypocalcemia were similar (pre-pathway=52.9% vs. post-pathway=66.7%) and not associated with protocol timing (p=0.2287). Postoperative hypocalcemia occurred after multiple types of surgical procedures with variable lengths ranging from 20 minutes to 3 hours. **Conclusions:** A clinical pathway can dramatically improve postoperative calcium testing and adherence to the 22q guideline recommendations. Postoperative hypocalcemia is common amongst children with 22q11.2DS and occurs following multiple types of surgeries; interestingly, this occurred even after very brief surgical procedures. Ongoing data collection, with the potential for future multisite collaboration, will allow better identification of patient/surgical factors that may increase a child's risk for developing postoperative hypocalcemia and further help develop mitigation strategies for children with 22q11.2DS.

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058: Peri-operative pathway for hypocalcemia management in youth with 22q11.2 deletion/duplication syndrome: preliminary outcomes following palate repair *

Douglas Villalta[1,2], Donna M. McDonald-McGinn[2,3], T. Blaine Crowley[3], Audrey Olsen[3,7], Daniel E. McGinn[3], Elaine H. Zackai[2,3,7], Lisa Elden[4,5,7], Oksana Jackson[5,6,7], Edna E. Mancilla[1,7], Vaneeta Bamba[2,3,7], Ian Campbell[2,3,7], and Lorraine E. Levitt Katz[1,2,7]

[1]Division of Endocrinology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Genetic and Genomic Medicine and 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Division of Otolaryngology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Department of Surgery, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [6]Division of Plastic and Reconstructive Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [7]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

Background: Hypocalcemia is associated with 22q11.2 Deletion/Duplication Syndrome (22q11.2DS/DupS). There is an increased risk of hypocalcemia during periods of biological stress, such as perioperatively. We developed a clinical pathway to standardize perioperative care and prevent unrecognized postoperative hypocalcemia. **Methods:** A multidisciplinary team from Endocrinology, Genetics, Otolaryngology, Anesthesiology, and Plastic Surgery created the pathway. We performed a case control study (N=39 patients with 22q11.2DS/DupS) undergoing palatal repair pre- and post-induction of the pathway (06/01/2021) between 12/22/2016-4/28/2025 examining prevalence of hypocalcemia (calcium < 8.5 mg/dL), risk category of hypocalcemia, endocrinology consultations, baseline calcium measurement 3 months before surgery, and calcium nadir. Risk of hypocalcemia was based on history of hypocalcemia with procedures/illness, duration of procedure, baseline hypocalcemia medications, delay of transition to enteral nutrition. Patients were ordered prophylactic calcium/calcitriol supplementation if needed prior to procedure. **Results:** There were thirty-two cases of palatal repair prior to pathway initiation and 14 following pathway implementation. There were 19 low-risk, 23 intermediate-risk, and 4 high-risk patients at the time case was reviewed. Post-operative hypocalcemia was identified in 34% pre-pathway v. 79% post-pathway. By risk group, post-operative hypocalcemia was identified in 71% pre-pathway v. 100% in intermediate-risk cases. No low-risk patient case had an endocrinology consultation after publication v. 19% pre-pathway, and 71% of patient cases had a calcium check within 3 months of operative procedure compared to 40% pre-pathway. **Conclusions:** Our QI pathway resulted in an improved detection of hypocalcemia. Moreover, there was an increase in pre-operative calcium checks following implementation of the pathway to stratify the patient's risk of hypocalcemia. We saw a decreased need for endocrinology consultation in low-risk patients. Identification of patients at the highest risk of developing hypocalcemia post-operatively can streamline the prevention of postoperative hypocalcemia.

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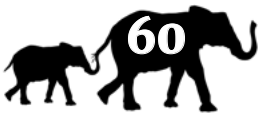
059: Recurrent postpartum hypocalcemia in association with 22q11.2 deletion syndrome *

Evie Andrewes[1,2], Audrey Olson[1,2], T. Blaine Crowley[1,2], Daniel E. McGinn[1,2], Oanh Tran[1,2], Beverly S. Emanuel[1,2,3], Elaine H. Zackai[1,2,3], Michele P. Lambert[1,3,4], Vaneeta Bamba[1,3,5], Lorraine L. Katz[1,3,5], Natalie Blagowidow[6], Lorraine Dugoff[7], and Donna M. McDonald-McGinn[1,2,3]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [4]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Endocrinology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Greater Baltimore Medical Center, Baltimore, MD, USA; [7]Department of Obstetrics and Gynecology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

Background: Hypocalcemia, a cardinal feature of 22q11.2DS reported in ~50% of patients and associated with provoked seizures, often occurs during times of biological stress such as neonatally, with illness, perioperatively, during adolescence, and in pregnancy. **Methods:** Here we report recurrent postpartum hypocalcemia in association with 22q11.2DS. **Results:** A Gravida-9 Para-1 TAB-8 34-year-old with a history of thrombocytopenia, tetralogy of Fallot, and 22q11.2DS diagnosed in childhood, presented to L&D for induction at 37-weeks' gestation with severe preeclampsia. On postpartum day (PD) 3, she became tachycardic and a right pulmonary embolism was identified. She was anticoagulated and discharged on PD5. Calcium at discharge was 7.3mg/dL (reference range: 8.9-10.3mg/dL.). Two weeks later, she was admitted to surgical intensive care with severe bleeding and anemia due to retained products of conception requiring dilation and curettage. Calcium was 6.3mg/dL. Two years later she presented to L&D at 37 weeks' gestation with concerns for severe preeclampsia in the setting of worsening thrombocytopenia, necessitating delivery. The birth was complicated by uterine rupture requiring emergency Cesarian-section and massive transfusion. She was treated with seizure prophylaxis and discharged on postpartum day 13 with a stable calcium of 8.9mg/dL. Two weeks later, she presented to the emergency room with bilateral flank pain and hematuria due to a UTI. Calcium was 6.6mg/dL. Of note, a genetics consultation was requested following delivery of all three children. The latter two were found to have 22q11.2DS. In addition to providing recommendations for evaluation and treatment for the children, a recommendation to follow the maternal calcium was provided. **Conclusions:** This patient highlights the need for long-term follow-up, including careful monitoring for hypocalcemia in pregnancy and post-partum, likely best provided by an endocrinologist.



060: Thyroid carcinoma and 22q11.2 deletion syndrome – A critical association

Andrew Bauer[1,2,3], T. Blaine Crowley[1,4], Audrey Olson[1,4], Lily Elman[1,4], Evie Andrews[1,4], Daniel E. McGinn[1,4], Elaine H. Zackai[1,3,4], Beverly Emanuel[1,3,4], Michele P. Lambert[1,3,5], Kathleen E. Sullivan[1,3,6], Vaneeta Bamba[1,2,3], Lorraine L. Katz[1,2,3] Julio Ricarte-Filho, Jenny Li and Donna M. McDonald-McGinn[1,3,4]

[1]22q and You Center, Children's Hospital of Philadelphia; [2]Division of Endocrinology, Children's Hospital of Philadelphia; [3]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania; [4]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia; [5]Division of Hematology, Children's Hospital of Philadelphia; [6]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Background: Malignancy has been reported in 22q11.2DS [thyroid(6), hepatoblastoma(5), lymphoma(3), pineoblastoma(2), Wilms(2), neuroblastoma, xantho-astrocytoma, pineocytoma/glioma, renal, ovarian, smooth-muscle, squamous-cell-tongue, melanoma-vulvar, osteosarcoma, ALL] (McDonald-McGinn-2006; Lambert-2008; Sarli-2023; Feng-Gu-2024; Liu-2024) including thyroid carcinoma (TC) in 5/33 patients described by Liu, of whom 3/5 were originally reported by Sarli (papillary(2), follicular; mean age 10y), who concluded 22q11.2DS poses an increased risk for head/neck neoplasms, recommending annual/biannual imaging. Notably, 22q LOH is the most common chromosomal loss in follicular TC (Kitamura-2001; Hemmer-1999); similarly in poorly differentiated (Ibrahimpasic-2019) and anaplastic (Kitamura-2000). Associations with papillary TC are low but perhaps higher in follicular variants of PTC. Here we report metastatic papillary TC in a 6-year-old-male and 4 additional patients to illustrate this significant association. **Methods:** Under IRB approval we reviewed our cohort of 1880 patients with 22q11.2DS to ascertain those with TC. **Results:** We identified 5/1880 (mean age 14.4y) with differentiated TC, including one previously reported 7-year-old-female (papillary and follicular, Lambert-2018); 4/5 had a standard deletion (LCR22A-LCR22D), the 5th had FISH only; all had T-cell lymphopenia; 3/5 had growth hormone therapy. Of the 4 unpublished patients, 2 were males and TC was papillary(2), papillary microcarcinoma, and follicular. **Conclusions:** The overall probability of malignancy is elevated in 22q11.2DS. Now, in the largest case series to date, we report thyroid malignancy in 5/1880 (0.3%) patients with 22q11.2DS, a risk that is forty-two times greater than the general population risk (13.5/100,000 overall) in males and ten times higher in females, confirming a critical association between TC and 22q11.2DS. The risk for 22q11.2DS associated TC may be related to T-cell lymphopenia, chronic inflammation, predisposing autoimmune thyroid disease, and/or additional genetic factors. Future discussion within the 22q11.2DS community should focus on screening patients for thyroid disease, to include TC, to increase our understanding of clinical risk factors, as well as genetic predispositions.

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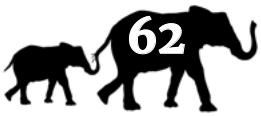
061: Testosterone deficiency in males with 22q11.2 deletion syndrome: a case series

Evana Valenzuela[1], Hanadys Ale[2], Lauren Waidner[3], Lauryn Bachman[3], and Jeremy Purrow[3]

[1]Division of Endocrinology, Memorial Healthcare System, Hollywood, FL, United States; [2]Division of Allergy and Rheumatology, Joe DiMaggio Children's Hospital, Memorial Healthcare System, Hollywood, FL, United States; [3]Florida International University Herbert Wertheim College of Medicine Miami, FL, United States.

Background: 22q11.2 deletion syndrome (22q11.2DS) is a complex multisystem disorder characterized by congenital heart disease, immunodeficiency, and neurodevelopmental manifestations. Endocrine abnormalities such as hypoparathyroidism, growth hormone deficiency, and thyroid dysfunction are well recognized. In contrast, hypogonadism has rarely been reported, with only isolated cases in the literature, often confounded by comorbid conditions. The association between 22q11.2DS and testosterone deficiency therefore remains poorly defined. **Methods:** We describe an expanded clinical series of male patients with genetically confirmed 22q11.2DS evaluated for testosterone levels in a tertiary multidisciplinary clinic. Clinical features, comorbidities, and biochemical findings were reviewed. **Results:** Two patients demonstrated overt hypogonadism with frankly low testosterone levels. A 25-year-old male with Tetralogy of Fallot and hypoparathyroidism was found to have low testosterone incidentally during evaluation for balanitis; pituitary imaging and additional hormonal studies were otherwise unremarkable. A 20-year-old male with growth hormone deficiency, scoliosis, and neurodevelopmental disorders similarly exhibited low testosterone without identifiable secondary causes. A third patient, 24-year-old with Tetralogy of Fallot and growth hormone deficiency also exhibited very low levels of testosterone (141ng/dL). Additional two other patients demonstrated low-normal testosterone levels (318–425 ng/dL) with partial virilization, including facial hair development, suggesting variable androgen effects or compensatory mechanisms. In contrast, patients with markedly low levels lacked facial hair. **Conclusions:** These observations suggest that hypogonadism and suboptimal testosterone levels may represent an underrecognized endocrine feature of 22q11.2DS. Potential mechanisms include disruption of the hypothalamic–pituitary–gonadal axis, primary testicular dysfunction, or haploinsufficiency of genes within the deleted region (e.g., SNAP29). Larger studies systematically assessing testosterone, LH, and FSH are needed to define prevalence and determine whether routine gonadal screening should be incorporated into clinical care guidelines.

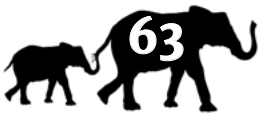


062: Delineating the incidence, accrual, and pathways to development of cardiovascular disease for 22q11.2 microdeletion using population-based and clinical data *

Sarah L. Malecki,[1,2,3,4] Tracy Heung,[4] Samantha Morais,[5] Refik Saskin,[5] Drew Wilton,[5] Therese A. Stukel,[2,5] Eyal Cohen,[2,3] Amol A Verma,[2,6] and Anne S. Bassett[4,7,8]

[1]General Internal Medicine Fellowship Program, University of Toronto, Toronto, ON, Canada; [2]Institute of Health, Policy Management and Evaluation, University of Toronto, Toronto, ON, Canada; [3]Child Health Evaluative Sciences and Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada; [4]Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada; [5]ICES, Toronto, ON, Canada; [6]Li Ka Shing Knowledge Institute & Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, ON, Canada; [7]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [8]Dalglish Family 22q Clinic, Division of Cardiology, & Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada.

Background: Most children with 22q11.2 microdeletion (22q) survive to adulthood, but adult health data remain limited. We investigated the incidence and accrual of cardiovascular outcomes in people with molecularly confirmed 22q compared with general population-comparators and further explored pathways to heart failure within the 22q cohort. **Methods:** Using a retrospective cohort study design, we linked 365 adult 22q-cases (median age 32 y; 51% female) to health administrative data for ~15 million individuals with universal healthcare, identifying 3,650 matched population-comparators. We used Poisson regression to estimate incidence rate ratios (IRRs) and 95% CI for five cardiovascular/risk conditions, and recurrent event modelling to assess their relative rate (RR) of accrual over a median 28 years of health data. We explored the progression from diabetes to heart failure and death among the clinical 22q cohort (n=405) using multi-state modelling and time-to-event analysis. **Results:** Accrual of cardiovascular conditions occurred at a significantly greater relative rate (RR) in 22q-cases than population-comparators (RR 3.8, 95% CI 2.9–4.8), even when restricting to 22q-cases with neither major congenital heart disease (CHD) nor schizophrenia (RR 3.6, 95% CI 2.4–5.4). Incidence was significantly greater in 22q-cases for hypertension and diabetes by age 18–24 (IRR 2.98, 95% CI 1.45–6.14; IRR 3.21, 95% CI 1.42–7.24, respectively), and by age 35–44 for heart failure. Among the clinical 22q cohort, heart failure was only observed among those with CHD, with no preceding diabetes. In a cause-specific model, the hazard of heart failure was lower for females (HR 0.13, 95% CI 0.04-0.47). **Conclusions:** A population-based approach provided new evidence for accumulating illnesses over young adulthood in 22q. Events observed during clinical follow-up did not show evidence of traditional cardiovascular disease development pathways in 22q, but longer follow-up is needed to further investigate established aging pathways.



063: Use of GLP-1 agonists and associated outcomes in adults with 22q11.2 deletion syndrome

Samantha D'Arcy[1], Tracy Heung[1,3], Lisa Palmer[1], Nikolai Reyes[1,2,3,4], and Anne S. Bassett[1,2,3,5]

[1]Dalglish Family 22q Clinic, Toronto General Hospital, Toronto, ON, Canada; [2]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [3]Clinical Genetics Research Program, Centre for Addiction & Mental Health, Toronto, ON, Canada; [4]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada; [5]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada.

Background: Obesity is a common metabolic feature of 22q11.2 Deletion Syndrome (22q) that can lead to reduced quality of life. As the use of GLP-1 agonists (GLP1) for weight loss has increased in recent years, many people with 22q are using this treatment to manage their weight as well as hyperglycemia. **Methods:** In adults with 22q known to be taking GLP1, we collected information on the type of GLP1 used, administration and dosage. Weight and hemoglobin A1c values were collected over time, pre and post initiation of treatment, as part of regular clinical assessment. We also collected qualitative data regarding tolerance of GLP1 and discontinuation of treatment. **Results:** Of the 18 adults (5 female; median age = 34) with 22q taking GLP1, 83% were using weekly semaglutide injections, with doses ranging from 0.25 mg to 2.4 mg. 44% of individuals taking GLP1 had a history of metformin use, and 33% continued to use it during GLP1 treatment. Individuals experienced a mean 5.48% total body weight loss (range -12.66% - +2.95%), Regarding hemoglobin A1c, individuals saw a mean reduction of 0.5% (range –2.1 - +1.4). 5 individuals (28%) discontinued the medication due to adverse reactions or perceived lack of efficacy. **Conclusions:** Initial data suggests that GLP1 agonists may be a useful intervention for adults with 22q to manage metabolic conditions. Factors such as impulsivity and environmental barriers to healthy eating continue to be important influences on outcomes. Understanding weight trends specific to adults with 22q using GLP1 agonists are important as use of these medications continues to grow, to give people more accurate information with which to make decisions regarding their medical care.

064: Body composition and bone density in children with 22q11.2 deletion syndrome: evidence for reduced lean mass *

Helena-Jamin Ly[1,2], Anna Svedlund[1], Annika Malmgren[2], and Solveig Oskarsdottir[2]

[1]Department of Pediatrics, Göteborg Pediatric Growth Research Center (GP-GRC), Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [2]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

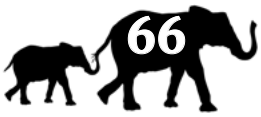
Background: Bone health and body composition in children with 22q11.2 deletion syndrome (22q11.2DS) remain insufficiently described, and available data suggest reduced bone mineral density in this population. Further characterization of skeletal health and body composition is therefore needed. This study aims to describe bone mineral density and body composition in children with 22q11.2DS using dual-energy X-ray absorptiometry (DXA) measurements. **Methods:** We performed a retrospective chart review of children and adolescents with 22q11.2DS who underwent DXA as part of routine clinical follow-up from October 2023. In total, 29 examinations from children aged 5.3–18.1 years were included. Bone mineral density and body composition were assessed using pediatric DXA protocols, and results were compared with age- and sex-specific European reference data. **Results:** Body composition analysis demonstrated near-normal fat mass index (mean SDS -0.33), but a marked reduction in lean mass index, with a mean SDS of -2.0 and 46% of the cohort falling below -2 SDS, indicating substantially decreased muscle mass compared with European reference values. Children with 22q11.2DS showed a mean Total Body Less Head (TBLH) bone mineral density (BMD) Z-score of -1.16 ± 1.02, with 57% falling below -1 and 21% below -2. Lumbar spine BMD was similarly reduced (-1.04 ± 1.17), with 48% below -1 and 24% below -2, and hip BMD followed the same pattern (-1.09 ± 1.07), with 54% below -1 and 21% below -2 Z-scores, indicating a consistent pattern of moderately reduced BMD across skeletal sites. A weak positive association was observed between TBLH BMD Z-scores and ionized calcium levels (r = 0.25). **Conclusion:** Markedly reduced lean mass was observed in children with 22q11.2DS, providing objective evidence for a clinically recognized phenotype, while bone density was also reduced, supporting the need for further research into musculoskeletal health.

065: Vertebral fractures in youth with 22q11.2 deletion syndrome: a case series *

Amanda Spatz[1,2], Edna Mancilla[1,2], Donna M. McDonald-McGinn[2,3,4], Vaneeta Bamba[1,2], and Lorraine E. Levitt Katz[1,2]

[1]Division of Endocrinology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, PA, Pennsylvania, USA; [3]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: 22q11.2 Deletion Syndrome (22q11.2DS) is the most common microdeletion syndrome, with a prevalence of 1:2000 live births. Orthopedic problems include scoliosis, club foot and cervical and vertebral anomalies, but the syndrome is not typically associated with skeletal fragility. Vertebral fractures in the general pediatric population are diagnostic of osteoporosis, and more than 60% of pediatric vertebral fractures occur between ages 15 to 17 years. **Methods:** This case series of vertebral fractures in 4 patients with 22q11.2DS includes chart review of medications, comorbidities, anthropomorphic data, and metabolic parameters. **Results:** Four patients (3M, 1F) aged 5 months to 13 years were incidentally identified to have asymptomatic vertebral fractures. Three of four patients had prior history of low calcium levels: one with transient neonatal hypoparathyroidism and two with ongoing primary hypoparathyroidism, requiring daily calcium, calcitriol, and vitamin D treatment. A 5-month-old male with a compression fracture incidentally found on chest X-ray for wheezing was identified to have multiple healing fractures, prompting evaluation for Osteogenesis Imperfecta v. Non-Accidental Trauma; WES testing revealed 22q11.2DS, and no mutations in genes associated with skeletal fragility were found. Three of four patients were taking inhaled corticosteroids for asthma e.g. Flovent and 2 of 4 proton-pump inhibitors. One of the four patients had low BMI from malnutrition and is optimizing feeds. Only one patient had a DXA scan performed which revealed normal bone density; two are due for DXA scans. **Conclusions:** These cases highlight the need for careful assessment of bone health in this high-risk population. Children with 22q11.2DS often have comorbidities such as hypoparathyroidism, malnutrition, gastrointestinal and cardiac disease, which may be risk factors for vertebral fractures.



066: Cervical spinal cord compression in association with 22q11.2 deletion syndrome *

Jette A. Boxem[1, 2], Michiel L. Houben[3], Malcolm L. Ecker[4], Gregory Heuer[5], Erin S. Schwartz[6], Tom Schlosser[7], Gregory Heuer[5], E. Zackai[2], T. Blaine Crowley[2], Donna M. McDonald-McGinn[2], Aebele B. Mink van der Molen[1], and Alexander M. Tucker[5].

[1]Department of Plastic Surgery, University Medical Center Utrecht, The Netherlands; [2]Department of Genetics, Children's Hospital of Philadelphia, United States of America; [3]Department of Pediatrics, University Medical Center Utrecht, The Netherlands; [4]Division of Orthopedic Surgery, Children's Hospital of Philadelphia, United States of America; [5]Division of Neurosurgery, Children's Hospital of Philadelphia, United States of America; [6]Division of Neuroradiology, Children's Hospital of Philadelphia, United States of America; [7]Department of Orthopedic Surgery, University Medical Center Utrecht, The Netherlands.

Introduction: Cervical spine anomalies are common in patients with 22q11.2 deletion syndrome (22q11DS), but the clinical course and risk of spinal cord compression remain poorly defined in this population. Current guidelines recommend cervical spine screening around 4 years of age, yet cases of compression are often detected later. This study aims to characterize the clinical and radiological presentation of patients with 22q11DS who develop cord compression to aid early recognition and to answer the following question: what are the clinical and radiological features of 22q11DS patients who develop cervical spinal cord compression? **Methods:** a retrospective chart review including patients with 22q11DS and cervical spinal cord compression that were in need of surgery. Clinical and radiological findings were reviewed. **Results:** 5 patients were identified with spinal cord compression**.** Three patients presented with neurological symptoms, two of which could be attributed to cord compression, while two patients were asymptomatic. All patients older than four years underwent routine cervical spine screening, in accordance with current clinical guidelines for 22q11DS. Four of five patients showed no evidence of cervical instability on radiographs at initial evaluation. **Conclusion:** Current screening practices, including cervical spine imaging at the age of four years, may not be sufficient to detect cord compression as most of our patients presented in adolescence and did not show signs of instability during initial evaluation. These findings suggest that continued clinical vigilance beyond childhood is warranted, with particular attention to neurological examination during adolescence to facilitate timely diagnosis and intervention.

067: Early vertebral rotation before the adolescent growth spurt in children with 22q11.2DS: implications for development of scoliosis *

Annemie J. Sluijter[1], Peter P.G. Lafranca[1,2], René M. Castelein[1], Moyo C. Kruyt[1,3], Keita Ito[4], Michiel L. Houben[5], and Tom P.C. Schlösser[1]

[1]Department or Orthopedic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Department of Orthopedic Surgery, St. Antonius Ziekenhuis, Utrecht, The Netherlands; [3]Department of Developmental Bioengineering, Twente University, Enschede, The Netherlands; [4]Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands; [5]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.

Background: Adolescent idiopathic scoliosis (AIS) is a three-dimensional, rotational deformity of the spine that develops in otherwise healthy children during the adolescent growth spurt. Compared to the general population, children with 22q11.2DS have a 20-fold increased risk of developing scoliosis during their growth, with a prevalence of around 50%. Their curve morphology resembles that of the curve in AIS. It remains unknown whether abnormalities in spinal development are already present prior to the adolescent growth spurt. The prospective EARLYBIRD study investigates spinal growth in children with 22q11.2DS, starting before the growth spurt. **Methods**: In this prospective cohort study, spinal growth is followed in children with 22q11.2DS, from ages 8–10 (girls) or 9-11 (boys) years, and without clinical signs of scoliosis at inclusion. Using artificial intelligence, a synthetic CT scan was generated from bone MRI data. Axial vertebral rotation from vertebral level T2 to T12 was measured systematically using a semi-automated method and compared with a control group consisting of trauma CT scans from children without spinal pathology. **Results:** A total of 17 children (10 boys, 7 girls, mean age 9.5 ± 1.0 years) were included in the 22q11.2DS group. The control group consisted of 16 girls (mean age 9.6 ± 1.3 years). In both 22q11.2DS subjects and controls, a pre-existing vertebral rotation to the right was observed between T5 and T12 (mean 0.8-2.6°). There were no statistically significant differences. **Conclusions**: Before the adolescent growth spurt, vertebral rotation to the right in the transverse plane is already present in children with 22q11.2DS, largely comparable to a control population. Further longitudinal follow-up is required to determine whether increased thoracic vertebral rotation prior to the growth spurt is involved in the development of clinically relevant AIS.

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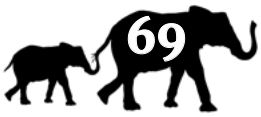
068: The role of orthopaedic conditions in lower extremity pain and exercise intolerance in children with 22q11.2 deletion syndrome *

Femke G.M. van den Helder[1], and Michiel L. Houben[1]

[1]*Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center, Utrecht, The Netherlands.*

Background: Throughout childhood and adolescence, many patients with 22q11.2 deletion syndrome (22q11DS) experience lower extremity pain and/or exercise intolerance, affecting daily activities and quality of life. Given the syndrome's somatic manifestations, several medical factors may be involved. In our previous study, we examined (i) the prevalence of lower extremity pain and exercise intolerance in youth with 22q11DS and (ii) associations between medical factors such as congenital heart defects, hypocalcaemia, and orthopaedic conditions and lower extremity pain. Building on these findings, the current study focuses on the association between lower extremity pain and orthopaedic conditions. **Methods:** Data were extracted from medical records at the Dutch national 22q11 reference center in Utrecht. In total, 177 participants aged 12–18 years were included; 51% were female, with a mean age of 15 years (SD 2.1). Patient and family reports on standardised routine care questions concerning the presence and severity of lower extremity pain and exercise intolerance have been recorded, as well as the presence of distinct orthopaedic problems (e.g. scoliosis, patellar luxation, pes planus). Descriptive, bivariate and multivariate analyses were performed. **Results:** Lower extremity pain is highly prevalent among adolescents aged 12–18 years with 22q11DS, with 50% reporting pain alongside orthopaedic problems. Pes planus was initially associated with leg pain in univariate and orthopaedic-only multivariate analyses (OR 1.9, p = 0.04), but not after adjustment for age, sex and education level (OR 1.6, p = 0.11). No significant associations were found for scoliosis, patellar luxation, or clubfeet. Education level emerged as a significant predictor, with children in special education more likely to report leg pain (OR 0.4, p = 0.02). **Conclusions:** Cognitive factors, reflected in education level, may contribute more to leg pain than orthopaedic conditions alone. The high prevalence highlights the need for routine assessment and further research into underlying mechanisms.



069: Incidental neuroradiological findings in 22q11DS: update in an expanded sample

J. Eric Schmitt[1,2], Simon Smerconish[1,2], David Roalf[1], T. Blaine Crowley[3,4], Victoria Giunta[3,4], Daniel E. McGinn[3,4], Elaine H. Zackai[3,4,6,7], Beverly S. Emanuel[3,4,6,7], Sarah Hopkins[3,5], Madeline Chadehumbe[3,7], Raquel E. Gur[1,3], Donna M. McDonald-McGinn[3,4,6], and Aaron Alexander-Bloch[1]

[1]Department of Psychiatry, Neurodevelopment & Psychosis Section, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [2]Division of Neuroradiology, Department of Radiology, University of Philadelphia, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [7]NeurAbilities, Voorhees, PA, USA.

Background: The 22q11.2 deletion syndrome (22q11DS) is the most commonly occurring microdeletion in humans with several neuroanatomical features observed with increased frequency relative to the typically-developing population. The current study aims to provide updated epidemiological information on neuroradiological findings in a large sample of individuals with 22q11DS. **Materials and Methods:** A systematic review of all available clinical brain MRI scans (N = 230) from individuals with 22q11DS performed at the Children's Hospital of Philadelphia was conducted by a board-certified neuroradiologist with expertise in 22q11DS. Qualitative and semi-quantitative neuroradiographic findings in the sample, aged newborn to young adults, were grouped into 10 tracked measures. **Results:** The vast majority of individuals with 22q11DS were found to have at least 1 atypical radiological finding (87.8%). The most frequent findings included cavum septum pellucidum (60.9%), white matter hyperintensities (43.0%), and chronic microhemorrhages (12.6%). Several rare findings including Chiari malformations (4.8%), polymicrogyria (4.8%), and underopercularization (10.4%), were overrepresented in the sample. Semi-quantitative measures included increased prevalence of cerebral volume deficits (29.6%), thicker cortex (36.5%), and smaller floccular volumes (34.3%). **Conclusions:** Numerous radiological findings are observed in 22q11DS at a significantly greater frequency than in the typically-developing population. These results are generally concordant with prior studies with smaller samples.

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070: Handgrip strength in adults with 22q11.2 deletion syndrome

Erik Boot[1,2,3], and Claudia Vingerhoets[1,2]

[1]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [2]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Institute (MHeNs), Maastricht University, Maastricht, The Netherlands; [3]The Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada.

Background: Clinical observations and preliminary data suggest diminished muscle strength in adults with 22q11.2 deletion syndrome (22q11.2DS). We explored handgrip strength in adults with 22q11.2DS as a simple, reliable proxy for overall muscle strength, a measure that is inversely associated with adverse health outcomes and frailty. **Methods:** Handgrip strength was measured in 40 adults (median age 30.0 years, range 18-65; 37.5% male) with a confirmed typical 22q11.2 deletion (including LCR22A to LCR22B) using a calibrated Jamar hydraulic dynamometer. All participants were capable of following standardized test instructions and were judged to have exerted maximal effort. From six attempts (three per hand), the maximum score was selected and compared with age- and sex-matched normative reference values. Subsequently, we determined the proportion of participants with scores below the 10th and 50th percentiles (p10 and p50), including 95% confidence intervals (CIs). We also calculated the median difference between the p50 value and the participants' maximum grip strength, expressed in relative (percentage) and absolute terms. **Results:** Overall, 7.5% of participants (3/40; 95% CI: 6.6-15.7%) scored below the p10, while 72.5% (29/40; 95% CI: 58.7-86.3%) scored below the p50. The median grip strength of the study cohort was 13.4% lower (range 69.0% higher to 51.3% lower; 4.1 kg, range 19.6 higher to 25.3 kg lower) than the age- and sex-matched p50 reference values. **Conclusions:** The results of this study support the hypothesis that reduced muscle strength affects a significant proportion of the adults with 22q11.2DS. As an easy-to-administer and quick assessment, handgrip strength shows promise for use at both the group and individual levels in 22q11.2DS as a potential predictor of age-related health outcomes and frailty.

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071: The cutaneous spectrum of 22q11.2 deletion syndrome: a retrospective cohort analysis across age groups

Hanadys Ale[1,2], Aditi Chokshi,[3], Lucia Martinez,[2], Victoria Rosali Gonzalez[2], Lucila Mesa[4], Victoria Griffith[5], Sarah Asbek[6], Camille Robinson[3], and Raul Escobar[7]

[1]Division of Immunology, Allergy and Rheumatology, Joe DiMaggio Children's Hospital, Memorial Healthcare System, Hollywood, FL, United States; [2]Florida International University Herbert Wertheim College of Medicine Miami, FL, United States; [3]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, Graduate Medical Education, University of Miami Miller School of Medicine, Miami, FL, United States; [4]Lincoln Memorial University – DeBusk College of Osteopathic Medicine, Harrogate, TN, United States; [5]Department of Internal Medicine, Graduate Medical Education, Memorial Healthcare System, Hollywood, FL, United States; [6]Department of Dermatology, Graduate Medical Education, Wake Forest Baptist Medical Center Winston-Salem, NC, United States; [7]Department of Internal Medicine, Graduate Medical Education, Larkin Hospital, Palm Springs, FL, United States.

Background: 22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion syndrome and is associated with wide-ranging systemic manifestations. However, dermatologic findings remain under-characterized. Cutaneous manifestations may provide early diagnostic clues or reflect underlying immune dysregulation. This study aimed to describe the prevalence and spectrum of dermatologic conditions in pediatric and adult patients with 22q11.2DS. **Methods:** A retrospective single-center chart review was conducted at Memorial Healthcare System in Hollywood, Florida. Patients with genetically confirmed 22q11.2DS were identified through an electronic medical record search using diagnostic keywords. Demographic and dermatologic data were obtained through manual chart review supplemented by a comprehensive keyword search using 57 dermatology-related terms. Frequencies of dermatologic diagnoses were compared between pediatric and adult cohorts. **Results:** Of 211 records screened, 191 met inclusion criteria (156 pediatric; 35 adult). Dermatologic conditions were documented in 62.2% of pediatric and 71.4% of adult patients. Pediatric patients demonstrated 33 distinct dermatologic diagnoses, most commonly atopic dermatitis/eczema (47%), acne (11%), seborrheic dermatitis (9%), thrush (8%), and abscesses (7%). Adults exhibited 52 dermatologic diagnoses, with acne (15.4%), atopic dermatitis (9.6%), seborrheic dermatitis (7.7%), abscesses (7.7%), and alopecia (7.7%) being most frequent. **Conclusions:** Dermatologic conditions are common and often persistent in individuals with 22q11.2DS, likely reflecting underlying immune dysregulation. These findings underscore dermatologic involvement as a clinically relevant yet underrecognized component of the 22q11.2DS phenotype. Early recognition and longitudinal dermatologic surveillance may improve multidisciplinary care across the lifespan. Prospective studies using standardized skin assessments are needed to better characterize disease progression and guide targeted management.

072: 22q through the back door *

Lily N. Elman[1,2], Audrey Green[1,2], T. Blaine Crowley[1,2], Daniel E. McGinn[1,2], Evie Andrewes[1,2], Lydia Rockart[1,2], Lydia Hamilton[1,2], Oanh Tran[1,2], Jennifer Borowka[2,3], Natalie Ginn[4], Abraham Haimed[3,5], Michele P. Lambert[1,3,5], Ethan Goldberg[4,6], Beverly S. Emanuel[1,2,5], Elaine H. Zackai[1,2,5], and Donna M. McDonald-McGinn[1,2,5]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Epilepsy Neurogenetics Initiative (ENGIN), Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [6]Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.

Background: Children with 22q11.2 deletion syndrome (22q11.2DS) generally come to diagnosis with common associated features, including congenital heart disease (CHD), immunodeficiency, palatal anomalies, hypocalcemia, and developmental/speech delay. Conversely, patients' sans cardinal features frequently traverse a protracted diagnostic odyssey. Here we report examples of those diagnosed "through the back door" with uncommon associated findings. **Methods:** Three patients with a laboratory confirmed 22q11.2 deletion, evaluated under an IRB protocol, were included from our 1880 patients with 22q11.2DS. **Results:** Patient 1 was diagnosed with 22q11.2DS by Hematology at 17 years following detection of a *TBX1* deletion on a primary immunodeficiency panel for idiopathic thrombocytopenia. Subsequent microarray identified a standard chromosome 22q11.2 deletion. Patient 2 presented to Genetics at 3 months with bilateral club feet. A standard chromosome 22q11.2 deletion was identified via MLPA. Patient 3 was diagnosed with a standard 22q11.2 deletion by Neurology at 17 years via whole exome sequencing due to adolescent onset idiopathic seizures. Following the 22q11.2DS diagnosis, all patients were noted to have additional actionable features and benefited from 22q11.2DS-specific multidisciplinary care. **Conclusions:** 22q11.2DS is common. It is the most common cause of syndromic palatal anomalies and schizophrenia and the second most common cause of CHD and developmental delay after Down syndrome. However, based on the reported prevalence (1:1000 pregnancies, 1:1500 miscarriages, 1:2148 livebirths) compared with the number of individuals with 22q11.2DS followed in large 22q Centers, such as our own, affected individuals may not be coming to attention ever, perhaps related to the absence of cardinal features. Thus, we endorse a lower index of suspicion in the presence of less common associated features. Moreover, we predict detection will increase with the use of broad-based comprehensive genomic studies by subspecialists without an elevated index of suspicion specific to 22q11.2DS, as well as the increasing uptake in 22q11.2-specific non-invasive-prenatal-testing (NIPT).

073: Outcomes in patients with 22q11.2 deletion syndrome following speech surgery

Oksana A. Jackson[1,2,3]

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA, [2]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA, [3]Division of Plastic, Reconstructive and Oral Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA,

Background: Velopharyngeal dysfunction is a common manifestation of 22q11.2DS, commonly treated with posterior pharyngeal flap (PPF) or Furlow palatoplasty. Staged strategy is used in select patients, however evidence is limited regarding its effect on speech or perioperative risks. This study compares speech outcomes, complications and their predictors among patients undergoing single or staged procedure. **Methods:** A retrospective review of 115 patients with 22q11.2DS treated for VPD by a single surgeon (2009-2024). Patients underwent Furlow (15), PPF (82), or staged Furlow with PPF (18). Demographics, comorbidities, imaging, and perioperative complications were abstracted from the EMR. Speech outcomes, including nasality, nasal emission, articulation, and total PWSS, were assessed preoperatively, at 1 year postoperatively and at most recent follow-up. **Results:** Furlow-only group exhibited the highest pre-operative VP closure (82.5%) compared to staged (60%) and PPF-only groups (40%). Baseline PWSS followed a similar pattern (median 11.5, 13.0, and 16.0). Speech improved in all groups postoperatively, with the PPF-only cohort showing reductions in PWSS of -11.0, articulation -6.0, and nasality -3.0 ($p<0.001$), and improvement in incompetent speech classification from 100% to 25.6% ($p<0.005$). Staged patients exhibited limited improvement after Furlow, with most gains occurring after PPF. Greater preoperative velopharyngeal closure predicted better postoperative articulation and total scores, while older age at surgery was associated with worse postoperative speech in all groups. Complication rates were low across groups. **Conclusions:** All surgical approaches improved speech. Primary PPF produced the greatest improvements, while staged Furlow followed by PPF provided a safe, anatomy-driven pathway to improvement in select patients.

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074: Timing of surgery for velopharyngeal insufficiency in patients with 22q11.2 deletion syndrome: a retrospective chart analysis *

Jette A Boxem[1,2], Cynthia B. Solot[3], Michiel L. Houben[4], T. Blaine Crowley[1], Donna M. McDonald-McGinn[1], Aebele B. Mink van der Molen[2], and Oksana A. Jackson[5]

[1]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Plastic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Speech-Language Pathology and Center for Childhood Communication, 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA; [4]Dept. of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [5]Division of Plastic, Reconstructive, and Oral Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: Managing velopharyngeal dysfunction (VPD) in children with 22q11.2 Deletion Syndrome (22q11DS) is complex due to associated speech–language delays, learning difficulties, and behavioral challenges. In addition, speech improvement following palatal surgery is often slower in this population compared to non-syndromic children. This study aimed to determine the optimal timing of speech surgery in children with 22q11DS and severe hypernasality by comparing early versus late intervention, and to evaluate the influence of preoperative factors on postoperative speech outcomes. **Methods:** Fifty patients with severe hypernasality and VPD undergoing speech-correcting surgery were included. Postoperative speech outcomes were assessed using the Pittsburgh Weighted Speech Scale (PWSS) and the CHOP-VPD scale. A generalized additive mixed-effects regression model was used to analyze differences in outcomes between early (<6 years) and late (≥6 years) surgery. Covariates including onset of speech and hearing loss were analyzed and adjusted for. **Results:** Patients operated on at ≥6 years demonstrated significantly later speech onset. Age at surgery (cutoff 6 years) did not significantly influence overall postoperative speech outcomes (PWSS, p = 0.2085). However, preoperative compensatory articulation errors were significantly associated with worse postoperative articulation subscores (estimate 2.1 points, p = 0.043) and showed a trend toward affecting total PWSS scores (p = 0.089). **Conclusion:** Determining the timing of palatal surgery in children with 22q11DS remains challenging due to anatomical variability and complex speech–language profiles. No significant difference in speech outcomes was observed between early and later surgical intervention. However, the absence of preoperative compensatory articulation errors was associated with significantly better postoperative articulation outcomes, highlighting the importance of early speech evaluation and targeted therapy.

075: Bilateral buccal myomucosal flap palatoplasty for the management of velopharyngeal dysfunction in children with 22q11.2 deletion syndrome: case series of 4 patients

Jill Arganbright[1], Meghan Tracy[1], Janelle Noel-MacDonnell[1], Kathryn Dent[1], Susan Parsons[1], and Nikita Raje[1]

[1]*Children's Mercy Hospital, Kansas City, MO, United States.*

Background: Velopharyngeal dysfunction (VPD) is one of the most common clinical features of 22q11.2 deletion syndrome (22q11.2DS) and often requires surgical intervention. Treating VPD is complex and prior studies have demonstrated poorer speech outcomes postoperatively in children with 22q11.2DS compared to those without. The use of the bilateral myomucosal buccal flap palatoplasty (BMBFP) is a relatively new surgical treatment of VPD and has growing popularity for non-syndromic patients; however, there are no current publications looking at BMBFP outcomes for children with 22q11.2DS. The purpose of this paper is to investigate the safety and utility of BMBFP for the correction of VPD in children with 22q11.2DS. **Methods:** Chart review of patients in our 22q Center's repository July 2020 to July 2025, and CPT codes were used to identify patients undergoing BMBFP. Data collected included genetic diagnosis, demographics, past medical history, surgical details, complications, and speech/resonance outcomes. **Results:** Four patients with 22q11.2DS underwent BMBFP (3 male, 1 female; ages 5-11 years). Average length of clinical follow-up 40 months (range 27-53). One patient had a prior Furlow palatoplasty. Postoperatively, all patients were admitted to the floor, none required PICU. The average length of postoperative hospital stay was 2.75 days (range 2.0-4.0). No patients had postoperative wound breakdown/dehiscence. Resonance speech outcomes showed 3 of the 4 patients had improved resonance, and no additional speech surgery. One patient showed no noticeable improvement, but behavior has limited postoperative speech assessment. **Conclusions:** The use of BMBFP for the management of pediatric VPD demonstrated successful speech outcomes in 3 of 4 patients. Patients with 22q11.2DS did well with this procedure, showing similar speech improvement compared to those without the syndrome and had minimal complications. Larger multisite studies are needed to better quantify the risks and expected outcomes for children with 22q11.2DS undergoing BMBFP for the treatment of VPD.

076: Presentations of congenital anterior glottic webs and laryngeal clefts in individuals with 22q11.2 deletion syndrome: patterns, outcomes, and clinical pathways

Lisa Elden[1], Karen Zur[1], Ian Jacobs[1], Luv Javia[1], Steve Sobol[1], Donna McDonald-McGinn[2], T. Blaine Crowley[2], Elaine Zackai[2], and Ryan Ruiz[1]

[1]Department of Pediatric Otolaryngology Children's Hospital of Philadelphia, Perelman School of Medicine Philadelphia, PA, USA; [2]Department of Pediatrics (Genetics), Children's Hospital of Philadelphia, Perelman School of Medicine Philadelphia, PA, USA.

Background: Airway anomalies occur in 14–17% of symptomatic individuals with 22q11.2 deletion syndrome (22q11.2DS), most commonly in association with conotruncal cardiac defects. Congenital anterior glottic webs and laryngeal clefts—reported in 21–29% and 5–25% of patients undergoing bronchoscopy, respectively—are likely underrecognized due to variable and subtle presentations. **Objective:** To characterize clinical features and outcomes of congenital anterior glottic webs and laryngeal clefts in 22q11.2DS across a spectrum of presentations. **Methods**: We conducted a retrospective review (1999–2025) of inpatient and outpatient records from the 22q and You Center at Children's Hospital of Philadelphia (IRB 07-005352). Patients with congenital anterior glottic webs or laryngeal clefts were included; those with isolated laryngomalacia were excluded. **Results:** Laryngeal clefts were frequently identified incidentally during airway evaluation. Symptomatic patients more often demonstrated oropharyngeal dysphagia with recurrent aspiration confirmed by swallow study and operative laryngoscopy.Anterior glottic webs presented more distinctly with high-pitched or weak cry, aphonia or dysphonia, and intermittent or severe stridor. Four neonates with known 22q11.2DS and associated vascular rings or interrupted aortic arch exhibited respiratory symptoms disproportionate to cardiac findings. Five additional patients presented with stridor as the sentinel symptom and were subsequently diagnosed with 22q11.2DS, most without cardiovascular anomalies.Eighty percent underwent laryngotracheoplasty or endoscopic web division for airway compromise. Persistent dysphonia was generally managed conservatively; voice quality improved with therapy in most cases, and some families declined further intervention. **Conclusions:** Congenital webs and clefts in 22q11.2DS have distinct but often subtle presentations. Early features include increased work of breathing disproportionate to stridor, dysphonia, and atypical cry. Later presentations may involve dysphonia or reduced exercise tolerance rather than stridor alone. Flexible laryngoscopy is warranted when these features are present, particularly in patients undergoing cardiac intervention. Newly identified webs should prompt genetic testing, as up to 30–65%.

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077: Altered Sleep Architecture and NREM Physiology in 22q11.2 Deletion Syndrome *

Kathleen P. O'Hora[1,2], Rune Bøen[3,4], Hoki Fung[3,4], Charles Schleifer[3,4], Leila Kushan-Wells[3,4], Jennifer Xu[3,4], Natasha Reddivalam[3,4], Jared M. Saletin[1,2], and Carrie E. Bearden[3,5]

[1]E.P. Bradley Hospital Sleep Laboratory, Providence, RI, USA; [2]Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA; [3]Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA; [4] Neuroscience Interdepartmental Program, University of California, Los Angeles, CA, USA; [5]Department of Psychology, University of California, Los Angeles, CA, USA.

Background: Sleep disturbances are prevalent and associated with psychiatric symptoms in individuals with 22q11.2 Deletion Syndrome (22q11.2DS). Prior work suggests that individuals with 22q11.2DS may experience non-restorative sleep, characterized by adequate sleep quantity without corresponding daytime benefits. However, the neurophysiological underpinnings of this inefficient sleep pattern remain poorly understood. **Methods:** We compared sleep macrostructure, architecture, and physiology between individuals with 22q11.2DS (n=30, M_{age}=20.9 years, Age range:13-33, 53% males) and typically developing (TD) controls (n=35; M_{age}=19.9 years, Age range: 10-28, 45.7% males). Participants completed multi-night sleep EEG recordings using a wearable headband (*Dreem 3*), yielding 250 total nights of data (22q11.2DS: range: 1-11, median: 3, TD: 1-11 nights, median: 4 nights). Power spectra were estimated using Welch's method across all NREM epochs (N2+N3) from the F7-F8 channel. Group differences in absolute and relative power (0.5-25 Hz) were tested at each frequency using linear mixed effects models. Age and sex were regressed out of each outcome and False Discovery Rate correction was applied. **Results:** Relative to controls, individuals with 22q11.2DS exhibited longer sleep duration (p=0.003) and greater wake after sleep onset (p<0.001). 22q11.2DS exhibited a shift towards lighter NREM sleep stages, with increased N2 (p<0.001), but decreased N3 sleep (p=0.002). Spectral analyses revealed globally increased NREM power in 22q11.2DS, with significantly elevated power in theta/alpha (5-10Hz), and sigma/beta (13-25 Hz) frequency ranges (all p_{adj}<0.049). In contrast, relative power differences were restricted to the alpha band (8-10 Hz, all p_{adj}<0.031). **Conclusions:** Individuals with 22q11.2DS exhibited longer sleep duration, reduced deep sleep and altered NREM spectral profiles, characterized by elevated absolute power and selective increases in relative alpha power. Together, these findings suggest a pattern of inefficient sleep marked by high NREM physiological arousal. Data collection is ongoing; future research will determine if inefficient sleep pattern is related to psychopathology risk in 22qDel carriers.

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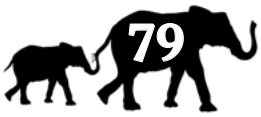
078: Gastrointestinal symptom burden is associated with anxiety, stress, and sleep disturbance in children with 22q11.2 deletion syndrome

Alain J. Benitez[1,2] Luc Santilli,[1] Kush Patel,[1] Audrey Olson,[3] Lydia Rockart,[3] Robin Miccio,[1] Lauren White,[2,4] Donna McDonald-McGinn,[2,3,5] and Maria Mascarenhas[1,2,3]

[1]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (22q11.2DS) is among the most common rare genetic conditions and carries elevated risk for neurodevelopmental and psychiatric disorders. Up to 91% of affected individuals report chronic gastrointestinal (GI) symptoms (abdominal pain, nausea/vomiting, dysphagia, gastroesophageal reflux, and constipation). In adults with 22q11.2DS, GI symptoms are strongly associated with depression, anxiety, and psychosis; however, pediatric data remain limited. Assessing the link between GI symptoms and psychosocial burden in children may guide comprehensive care to improve outcomes. **Methods:** Under an IRB approved study, children with 22q11.2DS and their caregivers were enrolled. Caregivers completed validated questionnaires assessing GI symptoms (PedsQL™ Gastrointestinal Symptoms Parent Module [PedsQL-GISPM] and Bristol Stool Form Scale [BSFS]), psychosocial functioning (Perceived Stress Scale [PSS-10], Generalized Anxiety Disorder-7 [GAD-7], Screen for Child Anxiety Related Disorders [SCARED]), and sleep disturbance (PROMIS™ Sleep Disturbance). **Results:** Twenty-five child–caregiver dyads were analyzed (mean child age, 10 years; 52% female; 80% White). Based on BSFS, 48% had constipation-type stools (Types 1–2), 44% normal stools (Types 3–4), and 8% diarrhea-type stools (Types 5–7). The mean PedsQL-GISPM total score was 79.9 ± 13.6 (range 40.5–98.1), with 16.7% demonstrating clinically meaningful impairment (score <70). Lowest subscale scores were in Communication (54.6 ± 23.3), Constipation (61.3 ± 22.9), and Stomach Pain (66.7 ± 25.8). Greater GI burden correlated significantly with higher perceived stress (PSS-10 $r = -0.44$, $p = 0.015$), anxiety (GAD-7 $r = -0.49$, $p = 0.007$; SCARED $r = -0.71$, $p < 0.0001$), and sleep disturbance ($r = -0.55$, $p = 0.003$). **Conclusions:** Children with 22q11.2DS experience substantial GI symptoms, particularly constipation and abdominal pain, which are significantly associated with stress, anxiety, and sleep disturbance. Integrated, multidisciplinary care addressing both GI and psychosocial health is essential to optimize well-being in this population.

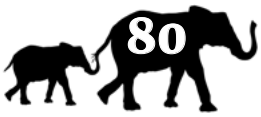


079: Speech and language in 22q11.2 deletion as a window into understanding long term outcome

Cynthia Solot[1]

[1]*Department of Speech-Language Pathology and Center for Childhood Communication, 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA*

Speech and language delays and disorders are hallmarks of the 22q11.2 Deletion Syndrome (22qDS) and affect nearly all individuals with 22qDS. Deficits range from mild to severe, simple to complex, and may affect the individual through their life span. Language is a fundamental neurocognitive domain. Early language delays can adversely affect communication, social development, behavior, learning and literacy, academic achievement and employment. What we know about language in 22qDS to date will be discussed, including associations of attainment of early milestones on language development, trajectories in language and factors influencing those trajectories, patterns of performance on language measures and impact of medical comorbidities. Research in language in 22qDS has focused on children and adolescents. There is a paucity of data on language in adults.Speech is also significantly affected in 22qDS by multiple factors, including developmental/phonological skills, motor speech disorders and the effects of palate abnormalities. Many children have unintelligible speech early on which can further limit their interactions and use of language. Speech disorders, which can reach into adolescence and adulthood, will be discussed. The significant role of speech and language in development highlights the importance of early identification, targeted intervention, parent counseling and close follow-up throughout childhood, adolescence and into adulthood.



080: Predictors of persistent expressive language impairment in 22q11.2 deletion syndrome *

Gracie Trulove[1,2], T. Blaine Crowley[3,4], Daniel E. McGinn[3,4], Audrey Olson[3,4], Sarah Hopkins[1,2,3], Donna M. McDonald-McGinn[1,3,4], Cynthia Solot[3,5], and Samuel Alperin[1,2,3]

[1]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [2]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Department of Speech-Language Pathology, the Center for Childhood Communication, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (22qDS) is frequently associated with language impairment, though expressive and receptive language outcomes vary widely. Identification of medical and developmental factors associated with persistent expressive language impairment may improve prognostication and early intervention planning. **Methods**: We conducted a retrospective chart review under IRB approval of individuals with a laboratory confirmed 22q11.2 deletion followed within the 22q and You Center at the Children's Hospital of Philadelphia. Inclusion criteria required completion of at least one Preschool Language Scale (PLS) or Clinical Evaluation of Language Fundamentals (CELF) assessment, with at least one evaluation obtained at ≥60 months of age. Participants were categorized by significant impairment (≥2SD) of most recent expressive language score (>70 vs ≤70). Demographic variables, genetic characteristics, gestational age, inheritance pattern, cardiac disease category, and comorbidities associated with 22qDS were compared. Parent-reported developmental milestones including age of first word, phrase, and sentence were also analyzed. **Results**: Of 624 individuals identified, 197 met inclusion criteria with complete language data. One hundred thirteen demonstrated expressive language scores >70, while 84 had scores ≤70. Gestational age, severity of cardiac disease and hearing loss status were significantly associated with expressive language outcome, with higher impairment rates observed among individuals born preterm and those with hearing loss. Later acquisition of first word (>36 mo), first phrase (>48 mo), and first sentence was significantly associated with persistent expressive language impairment. Race demonstrated an association in unadjusted analyses, but interpretation was limited by small subgroup sizes. Sex, ethnicity, inheritance pattern, genetic breakpoints, cleft lip/palate, velopharyngeal insufficiency, seizures, hypocalcemia, and autism diagnosis were not significantly associated with outcome. **Conclusions**: Persistent expressive language impairment affects a substantial proportion of individuals with 22qDS. Early developmental language milestones and selected medical factors may assist in risk stratification and guide anticipatory intervention planning.

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081: Language development in 22q11.2 deletion syndrome from preschool to school-age and in adolescence: evidence from two longitudinal studies

Tessel Boerma[1,2], Jantine Wignand[1,2], Manik Djelantik[3], Emma Everaert[1,2,4], Ania Fiksinski[2], Michiel Houben[2], Iris Selten[5], and Frank Wijnen[1]

[1]Institute for Language Sciences, Department of Languages, Literature and Communication, Utrecht University, Utrecht, The Netherlands; [2]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Institute of Education and Child Studies, Leiden University, Leiden, The Netherlands; [5]Brain and Cognition, University of Amsterdam, Amsterdam, The Netherlands.

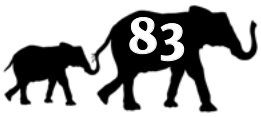
Background: Many children with 22q11.2 deletion syndrome (22q11DS) have difficulties learning language. Little is, however, known about the adolescent language profile and research about the course of language development over time in 22q11DS is scarce. For example, it is unknown if adolescents face similar problems as younger children, if early language skills are predictive of later abilities, and how trajectories in 22q11DS compare to typical development, making prognosis difficult. The current research therefore investigated language development in 22q11DS from preschool to school-age and in adolescence. **Methods:** The first study included 35 children with 22q11DS and 67 typically developing (TD) children who were between 3 and 6.5 years at the first test wave. The second test wave was 5.5 years later. The second study included 28 adolescents with 22q11DS between 14 and 19 years who were tested twice with an interval of 2 to 2.5 years. Standardized tests were used to measure the participants' language skills in different domains. **Results:** Preliminary analyses suggest that language skills of children with 22q11DS and TD peers diverge from preschool to school-age. Scores of children with 22q11DS increased at a slower rate than in TD children, pointing to a developmental lag. Additionally, results showed severe language deficits of adolescents across domains, which remained stable over time. While language comprehension skills were in line with intellectual ability, production skills were weaker. **Conclusions:** The current research provides a description of the course and stability of language development in 22q11DS throughout important periods in childhood and adolescence, improving prognoses for parents and their offspring. Language development from preschool to school-age particularly raises concerns, increasing the risk of overburdening and emphasizing the importance of early intervention. Furthermore, this research is the first to describe the language profile of adolescents with 22q11DS, enabling the formulation of guidelines for professionals.

082: Memory, attention and vocabulary in 22q11.2 deletion syndrome: a longitudinal study *

Jantine R. Wignand[1,2], Tessel D. Boerma[1,2], Emma Everaert[3], Iris S. Selten[4], Michiel L. Houben[2] and Frank N.K. Wijnen[1]

[1]Institute for Language Sciences, Utrecht University, Utrecht, The Netherlands; [2]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Institute of Education & Child Studies, Leiden University, Leiden, The Netherlands; [4]Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands.

Background: Many children with 22q11.2 deletion syndrome (22q11DS) have difficulties learning words, resulting in smaller vocabulary sizes relative to typically developing (TD) children. Vocabulary is essential for academic skills and success in life. It is, however, unknown what factors contribute to the vocabulary problems in children with 22q11DS. In TD children, vocabulary growth is known to depend on short-term and working memory and attention. As children with 22q11DS are reported to have (relatively) weak cognitive skills, we hypothesize that there is a similar relation for children with 22q11DS. The present research was the first to test this hypothesis in a longitudinal study. **Methods**: 44 children with 22q11DS and 81 TD children between the ages of 3 and 6,5 years participated in a first measurement wave approximately 6 years ago. About 75% of them participate in the current (2nd) wave. Age-appropriate (standardized) tests are used to measure short-term and working memory, selective attention and receptive and expressive vocabulary. **Results**: Data from the first measurement showed that children with 22q11DS have both weaker memory and attention skills and a smaller vocabulary than TD-children. Preliminary results from the current wave show a predictive relation between selective attention at wave 1 (preschool age) and expressive vocabulary at wave 2 (school age). At the conference, more elaborate data will be presented. **Conclusions**: The findings will contribute to a better understanding of the relation between vocabulary acquisition and cognitive prerequisites in both typical and atypical development, and are likely to have implications for diagnostics and treatment of language difficulties (in 22q11DS).



083: Additional diagnoses in selected patients with autism and 22q11.2 deletion syndrome: casting an even wider net

Jennifer Rodstein[1], Caroline Y. Kuo[2], Apisadaporn Thambundit[2], Reina Capati[2] and Sulagna C. Saitta[1,2,3]

Departments of Human Genetics, Pediatrics and Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.

Introduction: Autism spectrum disorder (ASD) is described in 1:31 children in the US. Recently, the American Academy of Pediatrics has endorsed exome or whole genome sequencing as a first tier genetic test for patients with neurodevelopmental disorders (NDD). While ~20-30% of patients with 22q11.2 deletions/duplications also display features of ASD, this is largely attributed to the deletion/duplication itself. We selected patients considered as phenotypic outliers, non-verbal with stereotypical behaviors and ordered clinical-grade comprehensive sequencing based on their autism phenotype. **Patient 1:** a 14 yo nonverbal male with a paternally inherited B-D deletion. Unlike his affected father who completed a graduate degree, he is nonverbal and has tics. Trio WGS identified a *de novo* heterozygous variant that is predicted to affect normal splicing of *SETD1A*, (c. 517+1 G>A) a known ASD/NDD gene in chr16p11.2. **Patient 2:** an unrelated 12 yo nonverbal male with self-injurious behaviors, coarser facial features and typical A-D 22q11.2 deletion. Duo WGS identified a heterozygous missense variant in *SMARCC2* that was not maternally inherited (c.3448 A>G; p.Thr1150Ala). *SMARCC2* (chr12q13) is associated with Coffin-Siris syndrome and our patient does show overlapping features of this known syndromic ASD/NDD presentation. Here we highlight cases that were selected based on "severe" ASD phenotypes. We utilized a comprehensive sequencing-based approach that is now indicated for ASD/NDD patients without known 22q11.2 deletions/duplications. These findings have impact on both patient medical management and implications for large-scale research initiatives. The molecular findings align with exciting new human neural organoid modeling studies describing how distinct genetic lesions, particularly those affecting chromatin remodeling, are found in convergent regulatory pathways affecting neurodevelopment. We anticipate that more 22q11.2 deletion patients with additional genetic diagnoses will be recognized by WES/WGS, raising consideration of using a trio WGS-first diagnostic approach moving forward.

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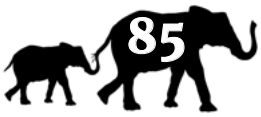
084: Cognitive and emotional profiles in young adults with chromosome 22q11.2 deletion syndrome

Kathleen Angkustsiri[1,2], Andrea Schneider[1,2], Hannah Culpepper[3], Marwa Zafarullah[3], and Flora Tassone[2,3]

[1]Department of Pediatrics, University of California Davis, Sacramento, CA, USA; [2]UC Davis MIND Institute, Sacramento, CA, USA; [3]Department of Biochemistry and Molecular Medicine, University of California Davis, Sacramento, CA, USA.

Background: Individuals with chromosome 22q11.2 deletion syndrome (22q) commonly display difficulties with cognitive and emotional function, including challenges with executive function and social/adaptive skills that persist into young adulthood, a period of higher psychiatric vulnerability. This study compares cognitive and emotional profiles in young 22q adults, ages 19-28, to typically developing (TD) peers in a study of metabolic markers of cognitive and psychiatric symptoms. **Methods:** Participants included 30 young adults (22q n=20; TD n=10) with a mean age of 22.8 yrs (SD=3). Males comprised 1/3 of the sample. Data was collected using a cognitive assessment (WASI-2) and standardized battery (NIH Toolbox: Cognition and Emotion). **Results:** Full-Scale IQ (FSIQ) scores for participants with 22q ranged from 60–127 (M = 84.7, SD = 21.7) and FSIQ in TD ranged from 97-143 (M = 120, SD = 24.6). Scores on the NIH-Toolbox Cognition Battery were significantly lower on all domains in 22q vs. TD. Emotion Battery was significant for lower scores in Psychological Well Being (22q: 46.82 vs. TD: 54.25, p=0.03), Friendship (22q: 42.55 vs. TD: 55.13, p=0.02), and Social Satisfaction (22q: 46.32 vs. TD: 54.44, p=0.02), but not sadness/depression. Fear/anxiety was mildly elevated in the 22q group (22q: 58.21 vs. TD: 48.58, p=0.02). Self-Efficacy was rated significantly lower in the 22q group (22q: 38.97 vs TD: 51.78, p=<0.001). **Conclusions:** Young adults with 22q demonstrate broad and clinically meaningful cognitive impairments relative to TD peers, particularly in executive functioning. Although emotional differences were less global, there were differences in psychological well-being, friendship, and social satisfaction alongside elevated anxiety, highlighting a dual vulnerability in cognitive control and social-emotional functioning during a critical developmental transition to adulthood. These results provide intervention targets, such as executive functioning and social skills, to improve long-term adaptive and psychiatric outcomes in young adults with 22q.

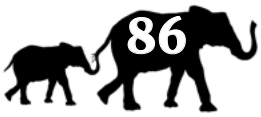


085: 30 years later: IQ profile among individuals with 22q11.2 deletion syndrome

Edward M. Moss[1], Katherine Baum[2], Michael F. Woodin[3], T. Blaine Crowley[4,5], Elaine H. Zackai[4,5,6], and Donna M. McDonald-McGinn[4,5,6]

[1]Edward Moss, PhD, PC, Bryn Mawr, PA, USA; [2]Comprehensive Neuropsychology Services, PLLC, Bryn Mawr, PA, USA; [3]Outpatient Behavioral Health, Reid Health Services, IN, USA; [4]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

Background: Over 30 years ago, we first reported IQ profiles among individuals with 22q11.2DS. Findings highlighted the presence of a nonverbal learning disability (NLD), first described in 1967. This was unexpected, as most children with 22q11.2DS experience developmental speech and language delays. Others have reported similar findings of this NLD profile. Nevertheless, controversy remains about both the NLD concept and its application to this population. Our original findings were based upon a small patient population. We now revisit this concept with a much larger patient population. **Methods:** An IRB-approved retrospective chart review yielded 747 evaluations of 471 unique patients with 22q11.2DS (49% female; mean age 8.7 years), performed between 1981-2024. From 1981-2024, the child and adult Wechsler IQ test batteries underwent at least seven major revisions, calling into question the relevance of the verbal/nonverbal NLD notion. To adjust for these changes, verbally-mediated subtests were compared to subtests assessing visual-spatial and/or visual-motor integration skills, using two-tailed t-tests. Verbal superiority of ≥10 points was required to define NLD. Verbally-mediated subtests were also compared to subtests assessing working memory skills, and assessing graphomotor skills. **Results:** The mean Full Scale IQ score of the entire population (747 IQ tests) was 77 (6th percentile; Borderline range. Comparing scores on verbal subtests to those requiring visual-spatial or visual-motor skills, 71% met criteria for NLD (p=0.01). There was a significant difference between verbally subtests and those assessing graphomotor skills (p=0.02), but no difference between verbally-mediated subtests and those requiring working memory skills (p=0.17). **Conclusions:** The mean IQ score of this sample was consistent with results of multiple previous studies. The finding of much stronger verbal than nonverbal intellectual abilities persist. Relatively strong working memory skills, but much weaker graphomotor skills were also found. These findings inform treatment and educational planning for this population.



086: Neurocognitive profiles of individuals with 22q11.2DS: effects of deletion size, intellectual disability, and overall psychopathology burden

Ruben C. Gur[1,2], Donna M. McDonald-McGinn[3,4], Kosha Ruparel[1,2], Carrie Bearden[5], Ann Swillen[6,7], Thérèse van Amelsvoort[8], Jonathan Sebat[9], Marianne van den Bree[10], Sébastien Jacquemont[11,12], Anne Bassett[13], Jacob Vorstman[14] and Raquel E. Gur[1,2]

[1]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Lifespan Brain Institute (LiBI) of the Children's Hospital of Pennsylvania (CHOP) and Penn Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]22q and You Center, Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [5]Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA; [6]Department of Human Genetics, KU Leuven, Leuven, Belgium; [7]Center for Human Genetics, University Hospital Leuven, Leuven, Belgium; [8]Department of Psychiatry & Neuropsychology, Maastricht University, Maastricht, The Netherlands; [9]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA; [10]Centre for Neuropsychiatric Genetics and Genomics Division of Psychological Medicine and Clinical Neurosciences Cardiff, Cardiff, UK; [11]CHU Sainte-Justine Azrieli Research Centre, Montréal, QC, Canada; [12]Department of Pediatrics, University of Montreal, Montreal, QC, Canada; [13]Dalglish Family 22q Clinic and Toronto General Hospital Research Institute, University Health Network; Clinical Genetics Research Program and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health; Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [14]Department of Psychiatry, Temerty Faculty of Medicine, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada.

Background: The 22q11.2 deletion (22q) is associated with neurocognitive deficits, but information is limited on how deletion size, intellectual disability (ID) and psychopathology burden (PB) groupings affect the severity and profile of the deficits. **Methods:** 582 individuals with 22q from a collaborative project were assessed using the same neurocognitive battery and with data available on these three factors. **Results:** Overall, the sample demonstrated deficits across all neurocognitive domains in both accuracy and speed of performance, which were most pronounced for nonverbal reasoning, face memory, and social cognition. Deletion size had a significant effect on overall severity of deficits (P<.001), with LCR22A-LCR22D deletions (84%) having the greatest impact while rarer LCR22A-LCR22B deletions (4.5%) had the least severe deficits. Individuals with moderate to severe ID had significantly poorer neurocognitive performance than those with mild or no ID (F=122.90, df=1,475.296, p<.001), with ID status particularly affecting abstraction/mental flexibility, and emotion identification domains (ID status x test F=5.23, df=9,3796.34, p<.001), and ID severity was mildly associated with greater PB (C^2=7.35, df = 2, p = .025). PB impacted performance linearly (F=3.13, df=2,475.07, p=.045) with higher burden associated with poorer performance on abstraction and mental flexibility, face memory, and age differentiation domains. Notably, the neurocognitive profiles were nearly identical across all of the deletion size, ID, and PB groups assessed. **Discussion**: The results overall indicate that each of the factors considered (deletion size, ID and PB) affects the severity of cognitive deficits in individuals with 22q. While these effects are evident across neurocognitive domains, some domains are more affected than others, notwithstanding a clear neurocognitive profile for 22q across groupings. The results suggest early targeted interventions for 22q, especially in the areas of abstraction and mental flexibility, nonverbal reasoning, face memory and social cognition.

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087: Educational best practices for school-age children with 22q11.2 deletion syndrome: recommendations for educators

Stephen R. Hooper[1], Edward M. Moss[2], Jane Summers[3], Katherine Baum[4], Ania M. Fiksinski[5], Maude Schneider[6], Cheryl Cytrynbaum[3], Donna M. McDonald-McGinn[7], Andrea Shugar[3] and Ann Swillen[8] on behalf of the International Brain Behavior Consortium Study Investigators

[1]Departments of Health Sciences and Psychiatry, School of Medicine, University of North Carolina at Chapel Hill, NC, USA; [2]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Psychiatry and Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada; [4]Comprehensive Neuropsychology Services, Bryn Mawr, PA, USA and 22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Departments of Pediatrics and Psychology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [6]Clinical Psychology Unit for Intellectual and Developmental Disabilities, Faculty of Psychology and Educational Sciences, University of Geneva, Geneva, Switzerland; [7]22q and You Center, Clinical Genetics Center, and Section of Genetic Counseling, Division of Genetic and Genomic Medicine, The Department of Pediatrics, The Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, Children's Hospital of Philadelphia, PA, Pennsylvania, USA; [8]Department of Human Genetics, KU Leuven, Centre for Human Genetics, University Hospitals Leuven, Leuven, Belgium.

Background: The recent publication of medical care recommendations for children with 22q11.2DS has promoted strategies for standards of care for this population; however, there are few educational counterparts. The primary purpose of this paper is to provide best practice recommendations for addressing the educational needs of school-age children with 22q11.2 DS. **Methods:** A subgroup of the 22q11.2DS International Brain and Behaviour Consortium (22q11.2DS IBBC) initiated the development of best practice educational recommendations for school-age children with 22q11.2DS. The core writing group comprised eight international experts/professionals with clinical expertise of at least 20 years in the cognition and educational needs of children with 22q11.2DS. Members represented Australia, Belgium, Canada, Ireland, the Netherlands, Switzerland, and the United States of America. Parent/family input also was solicited and incorporated into the recommendations. A systematic literature search over the past 30 years was performed and recommendations were developed through an evidence-informed consensus process. **Results:** In addition to enhancing awareness and symptom recognition for a wide array of professionals working with children with 22q11.2DS, we focus on the educational burden and classroom/learning needs across developmental time periods, addressing the challenges inherent in different school settings and providing strategies for serving students with 22q11.2DS. Consensus findings from our literature review yielded 10 best practice recommendations for teachers and other educators that range from early identification to addressing the comorbidity present in 22q11.2DS to transition-related challenges and advocacy to communication and associated documentation. **Conclusions:** These recommendations will serve to advance an array of evidence-based educational strategies that will facilitate learning while at the same time addressing the multiple co-morbidities associated with 22q11.2DS at different developmental epochs. International collaborative studies are desperately needed to assess the effectiveness of specific academic interventions, recommendations, and educational policies for this school-age population to advance this critically important area.

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088: Psychoeducation across the lifespan in 22q11.2 deletion syndrome: enhancing communication and tailored support in home, school, and work contexts

Ann Swillen[1,2], Marie Meuris[1], Robin De Croon[3, 4], Maxwell Szymanski[3, 4], and Katrien Verbert[3, 4]

[1]Center for Human Genetics, University Hospital Leuven, Leuven, Belgium; [2]Department of Human Genetics, KU Leuven, Leuven, Belgium; *[3]Department of Computer Science, KU Leuven, Leuven, Belgium*; *[4]Augment, imec research group at KU Leuven, Leuven, Belgium*.

Background: 22q11.2 deletion syndrome (22q11DS) is a complex neurogenetic condition characterized by heterogeneous medical, cognitive, behavioral, and psychiatric manifestations that evolve across development. These interrelated difficulties significantly affect learning, psychosocial functioning, and later vocational participation. Families and professionals frequently report limited awareness of syndrome specific educational and psychosocial needs (SEN), resulting in challenges in communication, inconsistent accommodations, and fragmented support across home, school, and work environments. This underscores the need for structured psychoeducational resources to enhance understanding and guide tailored interventions throughout the lifespan**. Methods:** To address these needs, we developed a set of psychoeducational tools, including *The Genetic Puzzle* and accompanying app, as well as infographics describing the educational and psychosocial needs of individuals with 22q11DS across preschool, primary, and secondary school. These materials were cocreated with parents, educators, clinicians, and individuals with 22q11DS. Their aims were to (1) increase knowledge among educators and employers, (2) facilitate communication between families, professionals, and workplace supervisors, and (3) support individualized accommodations in educational and vocational settings. **Results:** Since their introduction in Spring 2025, the infographics have been adopted by more than 200 families and school teams. Users report improved understanding of syndrome specific learning and psychosocial profiles, clearer communication, and more effective collaboration among educational staff. Parents describe enhanced dialogue with teachers, while educators note more coherent multidisciplinary coordination. Adults with 22q11DS and vocational coaches indicate that psychoeducation similarly benefits workplace functioning by supporting informed disclosure, guiding practical accommodations, and improving employer understanding of cognitive/ social challenges relevant to job performance. **Conclusions:** Psychoeducation is a critical component of comprehensive care for individuals with 22q11DS. Tools such as the Genetic Puzzle (App) and targeted infographics enhance shared understanding, strengthen communication across home, school, and work contexts, and contribute to more integrated, individualized educational and vocational support.

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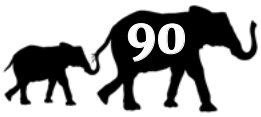
089: Interactive digital psychoeducation for 22q11.2 deletion syndrome: iterative, user-centred development of an app to support understanding of genetic complexity

Maxwell Szymanski[1,2], Robin De Croon[1,2], Ann Swillen[3,4], Marie Meuris[3,4], and Katrien Verbert[1,2]

[1]KU Leuven, Department of Computer Science, Leuven, Belgium; [2]Augment, imec research group at KU Leuven, Leuven, Belgium; [3]Center for Human Genetics, University Hospital Leuven, Leuven, Belgium; [4]KU Leuven, Department of Human Genetics, Leuven, Belgium.

Background: 22q11DS is a genetic condition whose medical and behavioural characteristics require accessible psychoeducation for affected individuals and their families. Our earlier developed Genetic Puzzle, a physical psychoeducational tool, has shown clinical value in supporting dialogue around diagnosis. However, as its reach as a physical resource remains constrained by availability and scalability, our co-designed digital application addresses these barriers. **Methods:** We developed a psychoeducational app enabling playful exploration of 22q11DS through interactive puzzle-building, with puzzle pieces representing syndrome-related symptoms. Phase 1 evaluated prototypes with clinical and human-centred design experts (n=5), after which we iteratively refined a functional proof of concept through semi-structured interviews, a logging-enabled trial period, and a second interview round with eight families of children with 22q11DS (aged 8–22). Thematic analysis distilled design goals informing phase 2, which explores support of clinical and informal dialogue, evaluated through an 8 month longitudinal usability trial at 43 families, and ongoing co-design studies with families and clinicians. **Results:** During phase 1, the families actively used the app, with sessions exceeding 30 minutes. Video content was strongly preferred over text (7/8), and personalization features (theme selection, avatars) positively affected intention-to-return (7/8). Importantly, five families used the app to initiate new conversations about syndrome-related topics, validating the app's role as a communication scaffold. Phase 2 usability evaluations affirmed videos as explanations as a valued resource, whilst suggesting navigation efficiency and emotional tone as refinement priorities. Co-design results suggest the need for additional dialogue-support through e.g. question logbooks and visualisations of changing symptom profiles. Detailed findings from this extensive trial and the resulting refined application will be demonstrated at the conference. **Conclusion:** A digitally-mediated approach to genetic psychoeducation is feasible and well-received. Our user-centred process helped understand the cognitive and social interaction needs, resulting in an accessible and clinically validated psychoeducational tool.

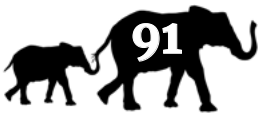


090: Development and evaluation of an evidence-based group-based psychoeducation program for families affected by 22q11.2 deletion syndrome

Ania Fiksinski[1], Lieke Reijn[1,2], and Michiel Houben[2]

[1]Department of Pediatric Psychology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.

Background: A novel diagnosis of the 22q11.2 deletion syndrome (22q11DS) leaves many parents in search of reliable information about the impact of the condition on their child, and of adequate access to (health care) services and support. This search occurs in the context of an emotionally turbulent phase, where parents are also trying to move towards acceptance of the presence of 22q11DS in their family. There is a pressing need for professional support, guidance and information at this stage. As of yet, evidence-based programs offering such psychoeducation to families affected by 22q11DS are largely lacking. **Methods:** In collaboration with the Dutch 22q11 Foundation, a project was initiated to develop, evaluate, and implement an evidence-based group-based psychoeducation program for parents whose child has recently (<two years) been diagnosed with 22q11DS. A face-to-face focus group was conducted, with six individual parents of children with 22q11DS (age 7-21 years; diagnosed >five years before). The discussion was semi-structured with predefined questions. The recorded conversation was transcribed and thematically analyzed. The results were compared with predefined themes based on literature and clinical experience. **Results:** Building-blocks of the developed psychoeducation program have been defined based upon these results. Key themes of the program, emerging from the focus group, were: 'Important information overview', 'Acknowledging the impact on parents', 'Providing support to cope with the diagnosis', 'Attention for impact on family and social circles', 'Tips for sharing the diagnosis', 'Help with handling healthcare and coordination', 'Tools for dealing with authorities', 'Setting future expectations (including variability)' and 'Tools for transition (>18yr)'. **Conclusions:** An evidence-based group-based psychoeducational program for parents of children with recent 22q11DS diagnoses has been developed and will be evaluated in a pilot, including assessment of several domains for parents (and children), including perceived agency and competency, quality of life and stress, and overall well-being.

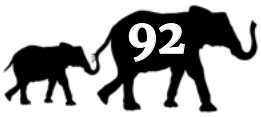


091: Rare mutations implicate CGE interneurons as a vulnerable axis of cognitive deficits across psychiatric disorders

Stephanie A. Herrlinger[1, 2], Jiayao Wang[3], Bovey Y Rao[1,2,4], Jonathan Chang[3], Joseph A. Gogos [1,2,5,6,7], Attila Losonczy[1,2] and Dennis Vitkup[3]

[1]Department of Neuroscience, Columbia University, New York, NY, USA; [2]Mortimer B. Zuckerman Mind Brain Behavior Institute, Columbia University, New York, NY, USA; [3]Department of Systems Biology and Department Biomedical Informatics, Columbia University, New York, NY, USA; [4]Doctoral Program in Neurobiology and Behavior, Columbia University, New York, NY, USA; [5]Department of Physiology, Columbia University, New York, NY, USA; [6]Department of Psychiatry, Columbia University, New York, NY, USA; [7]Stavros Niarchos Foundation Center for Precision Psychiatry and Mental Health, Columbia University, New York, NY, USA.

Background: Neuropsychiatric disorders such as autism spectrum disorder (ASD) and schizophrenia (SCZ) share genetic risk factors, including genes affected by rare high-penetrance single nucleotide variants (SNVs) and copy number variants (CNVs). ASD and SCZ exhibit both overlapping and distinct clinical phenotypes. Cognitive deficits and intellectual disability—critical predictors of long-term outcomes—are common to both conditions. **Methods:** To investigate shared and disorder-specific neurobiological impact of highly penetrant rare mutations in ASD and SCZ, we analyzed human single-nucleus whole-brain sequencing data to identify strongly affected brain cell types. We performed validation studies in a relevant rodent model to confirm our findings. **Results:** Our analysis revealed caudal ganglionic eminence (CGE)-derived GABAergic interneurons as a key nexus for cognitive deficits across these disorders. Notably, genes within 22q11.2 deletions, known to confer a high risk for SCZ, ASD, and cognitive impairment, showed a strong expression bias toward vasoactive intestinal peptide-expressing cells (VIP+) among CGE subtypes. To explore perturbations of VIP+ GABAergic interneurons in the 22q11.2 deletion syndrome *in vivo*, we examined their activity in the *Df(16)A*$^{+/-}$ mouse model during a spatial navigation task and observed reduced activity along with altered responses to random rewards. At the population level, VIP+ interneurons exhibited impaired spatial encoding and diminished subtype-specific activity suggesting deficient disinhibition in CA1 microcircuits in the hippocampus, a region essential for learning and memory. **Conclusions:** Overall, these results demonstrate the crucial role of CGE-derived interneurons in mediating cognitive processes that are disrupted across a range of psychiatric and neurodevelopmental disorders.

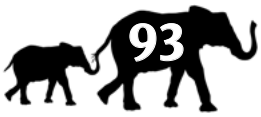


092: 22q11.2 deletion as a window into understanding the genomics of psychiatric illness

Anne Bassett[1,2]

[1]Department of Psychiatry, University of Toronto, and Division of Cardiology & Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada; [2]Dalglish Family 22q Clinic, University Health Network and Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON

The 22q11.2 deletion conveys the greatest known molecular genetic risk for schizophrenia. The combined effects of the reduced dosage of the multiple genes in the 22q11.2 deletion region must play a role. These genes have not been implicated in genetic studies of schizophrenia in the general population. Nonetheless, there is substantial evidence that the polygenic nature of causation of schizophrenia and related psychotic illnesses is highly comparable between 22q11.2 deletion syndrome and other forms of schizophrenia without the amplifying effects of this rare pathogenic copy number variation. We will discuss the many points of similarity in genomics, in genetic mechanisms, and in the guidance that genetic results are bringing to our understanding of the pathogenesis of schizophrenia. This will include the latest results on additional genetic factors - common and rare - that contribute to risk, and how these may be used for risk prediction.



093: Medical burden, psychopathology and neurocognition in 22q11.2 deletion syndrome

Raquel E. Gur[1, 2], Donna M. McDonald-McGinn[3,4], Ruben C. Gur[1,2], Arielle Ered[1,2], Austin T. Moran[1], Claudine B. Van Arman[1], Alyssa M. Neppach[1,2], Mia Schwartzberg[1], R Sean Gallagher[1], Simon Smerconish[1,2], Kosha Ruparel[1, 2], Scott Troyan [1, 2], Tyler M. Moore [1, 2], Amy Cassidy[1,2], Lauren K. White[2], T. Blaine Crowley[3], Daniel E. McGinn[3], Audrey Olson[3], Oanh Tran[3], Elaine H. Zackai[3,4], Beverly S. Emanuel[3,4], Yana Poltavets[5,6], Ronnie Weinberger[5], Michal Taler[6,7,8], and Doron Gothelf[5,6,7]

[1]Neurodevelopment & Psychosis Section, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Lifespan Brain Institute, Penn Medicine and Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]22q and You Center, Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, US; [5]Behavioral Neurogenetics Center, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [6]Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel; [7]The Gray Faculty of Medical & Health Sciences, Tel Aviv University, Israel; [8]Pediatric Molecular Psychiatry Laboratory, Sheba Medical Center, Tel-Aviv, Israel.

Background: Medical, psychiatric, and neurocognitive conditions impact outcomes in 22q11.2 deletion syndrome (22qDS), requiring a systematic approach to quantify medical burden. Notably, there are several chronic medical conditions affecting multiple organs for which an index of medical burden is available. In large phenotyped samples followed clinically, we applied validated tools allowing comprehensive measurement of medical burden effects on psychopathology, neurocognition, and functional outcome. **Methods:** We assessed 241 individuals with 22qDS (Philadelphia 155, 57% male; Tel Aviv 86, 50% male; ages 21.82 ± 8.62yrs) for medical burden, psychopathology, neurocognitive domains - executive, episodic memory, complex cognition, social cognition, sensorimotor speed, and global functioning. Medical burden was assessed using EHR, self and collateral-reports for eight systems commonly associated with 22qDS - ENT, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, neurological, endocrine, immunological. Each system was scored 0-4 and averaged for total score. Psychopathology was assessed in a standardized clinical interview and disorders were also scored 0-4 (0=None, 1=Past, 2=Mild, 3=Moderate, 4=Severe). Neurocognition was assessed with a computerized neurocognitive battery. **Results:** Across sites, burden was mild for medical (37.3%), psychiatric (46.9%), and neurocognitive (24.8%) domains. Medical burden was correlated with psychopathology, neurocognitive deficits and more strongly with worse functional outcome. No effects of age, sex, or site were significant. Severe medical burden was rare (<5%) except for endocrine (17.2%). Overall, these findings indicate individuals were predominantly impacted by symptoms ranging from mild to severe in endocrine (69.1%), ENT (58.4%), immunological (49.8%), musculoskeletal (48.1%), and gastrointestinal (44.6%) systems. **Conclusions:** Medical burden in this sample of adolescents to young adults is predominantly mild but multisystemic with modest associations with psychiatric severity, neurocognitive deficits and functional impairment. These findings support the importance of integrated medical and psychiatric care models and the incorporation of standardized medical, psychiatric and neurocognitive measures of burden to enhance outcome.

094: Developmental trajectories of irritability and associations with a psychosis-prone state in youth with 22q11.2 deletion syndrome and other neurodevelopmental copy number variants

Jessica H. Hall[1,2], Josephine E. Haddon[1,3], Samuel J. R. A. Chawner[1], Jeremy Hall[1,3], Peter Holmans[1,3], Michael J. Owen[1,3] and Marianne B. M. van den Bree[1,3]

[1]Division of Psychological Medicine and Clinical Neurosciences, Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK; [2]Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff University, Cardiff, UK; [3]Neuroscience and Mental Health Innovation Institute, Cardiff University, Cardiff, UK.

Background: Young people with 22q11.2DS and other neurodevelopmental copy number variants (ND-CNVs) show elevated irritability compared to unaffected siblings, even after accounting for co-occurring diagnoses, underscoring its relevance to the ND-CNV phenotype. Irritability is also central to psychosis-spectrum presentations, where heightened anger and reactivity reflect emotion-regulation difficulties. Examining irritability in youth at high genomic risk for psychosis may help identify behavioural markers of vulnerability to later psychopathology. **Methods:** At baseline, 654 youths with ND-CNVs (205 with 22q11.2DS; 60.7% male; mean age 10.3±3.2 years) and 278 sibling controls (50% male; mean age 11.2±3.0 years) were assessed. After a minimum 18-month interval, families were invited for up to five follow-ups, yielding 1,506 observations. Irritability and psychopathology were assessed using the Child and Adolescent Psychiatric Assessment (CAPA). At older ages (mean age 14.57±4.01 years), a subset of 378 youths with ND-CNVs completed the Structured Interview for Prodromal Symptoms (SIPS) to assess psychosis-proneness. Generalised mixed-effects models examined irritability trajectories in ND-CNV youths versus controls and differences between psychosis-prone and non-psychosis-prone ND-CNV groups, adjusting for co-occurring ADHD, anxiety, autism, and sleep disturbances. **Results:** Youths with 22q11.2DS showed higher irritability across development compared with controls (β=0.60, $p<0.001$); the same pattern emerged for other ND-CNVs (β=0.60, $p<0.001$). Although ADHD, anxiety, autism, and sleep disturbances were each associated with elevated irritability, ND-CNV status remained linked to persistently higher irritability after adjustment. Within 22q11.2DS, psychosis-prone youths showed higher irritability trajectories than those who were not (β=0.35, $p=0.023$).; this was also evident in other ND-CNVs (β=0.39, $p<0.001$). **Conclusions:** Youths with 22q11.2DS and other ND-CNVs display elevated irritability across development. Psychosis-prone youths showed elevated irritability compared to those who were not. Clinically, these findings highlight the importance of monitoring irritability in ND-CNV populations, as heightened irritability in genomically vulnerable young people may signal broader affective dysregulation relevant to emerging subthreshold psychosis.

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095: Exposure to trauma and post-traumatic stress disorder in 22q11.2 deletion syndrome

Adi Drapisz[1], Yana Poltavets[1], Ronnie Weinberg [1], Naama De La Fonataine[1], Nitza Nakash-Axelrod[1,3], Michal Taller [1], and Doron Gothelf [1,2,3]

[1]The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [2]Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel; [3]The Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel.

Background: Evidence regarding exposure to trauma and rates and characteristics of post-traumatic stress disorder (PTSD) in neurogenetic conditions, including 22q11DS is limited. **Aims**: To investigate trauma exposure and PTSD rates and characteristics in 22q11.2DS compared to Williams syndrome (WS) and to non-syndromal PTSD (NSPTSD). **Method**: Individuals with 22q11DS (n=47) and WS (n=26) and their parents were interviewed for trauma exposure and PTSD symptoms using the Trauma History Questionnaire (THQ) and the Child PTSD Symptom Scale (CPSS). Diagnosis of PTSD was determined by clinical evaluation. PTSD Symptom profiles were compared with 63 age and gender matched NSPTSD individuals. **Results**: Exposure to ≥5 traumatic events were reported by 51.1% of individuals with 22q11.2DS and 53.4% of individuals with WS. Painful or frightening medical procedures and bullying were the most frequently endorsed traumatic experiences in both groups. PTSD prevalence was elevated in both syndromes, affecting 20.0% of individuals with 22q11.2DS and 15.4% with WS. Significant differences in PTSD symptom clusters were observed across the 22q11.2DS, WS, and NSPTSD groups. 22q11DS compared to NSPTSD had significantly lower scores on the cognition and mood cluster (proband and parent report) and higher scores on hyperarousal symptoms (parent report). There was no correlation between IQ and CPSS scores. **Conclusions**: Individuals with 22q11.2DS and WS experience high cumulative rates of trauma exposure, particularly related to medical procedures and bullying, and exhibit elevated rates of PTSD. The PTSD symptom profile in 22q11.2DS appears to differ from non-syndromal PTSD. These findings highlight the need for routine trauma and PTSD screening in individuals with 22q11.2DS and suggest that PTSD manifestations in this population may be phenotypically distinct.

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096: Copy Number Variants in Spanish Psychiatric Care: Clinical Characteristics and Findings from a Multicenter Cohort

Damià Heine-Suñer[4,5], Maria Victoria Llull Albertí[4], Javier Labad[6], Jesús Herrera-Imbroda[7], Vicent Balanzá-Martínez[8], Amaya Hervas[9], Anna Maria Cueto-González[10], Antoni Ramos-Quiroga[11], Rosa Ayesa-Arriola[12], Iñaki Zorrilla[13], Ana García-Blanco[14], Paz García-Portilla[15], Edith Pomarol-Clotet[16], Bàrbara Arias[17], Covadonga Martínez[18], Olga Rivero[19], the CESPED group, and Elisabet Vilella[1,2.3]

[1]*Hospital Universitari Institut Pere Mata, Reus, Catalonia, Spain; Institut de Recerca Biomèdica Catalunya Sud (IRBCatSud), Reus, Catalonia, Spain;* [2]*Universitat Rovira i Virgili, Reus, Catalonia, Spain;* [3]*Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain;* [4]*Grup Genòmica de la Salut, Institut d'Investigació Sanitària de les Illes Balears (IdISBa), Palma, Illes Balears, Spain;* [5]*Unitat de Diagnòstic Mol•lecular i Genètica Clínica (UDMGC), Hospital Universitari de Son Espases, Palma, Illes Balears, Spain;* [6]*Department of Mental Health and Addictions, Consorci Sanitari del Maresme, Hospital Universitari de Mataró, Universitat Autònoma de Barcelona, Mataró, Spain;* [7]*Unidad de Gestión Clínica de Salud Mental, Hospital Regional Universitario de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA)-Plataforma Bionand, Plaza del Hospital Civil, s/n, Málaga, Spain;* [8]*Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Valencia, Spain;* [9]*Child and Adolescent Mental Health Service University Hospital Mutua Terrassa Barcelona Spain;* [10]*Clinical and Molecular Genetics Area, Vall d'Hebron Hospital Medicine Genetics Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain.*[11]*Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR);* [12] *Department of Psychiatry, Marqués de Valdecilla University Hospital, IDIVAL, CIBERSAM, School of Medicine, University of Cantabria, Santander, Spain;* [13]*BIORABA, Department of Psychiatry, Hospital Universitario de Alava; University of the Basque Country, UPV/EHU, Leioa, Spain;*[14]*Department of Psychiatry and Clinical Psychology, La Fe University and Polytechnic Hospital, Spain;* [15]*Area de Psiquiatría, Universidad de Oviedo, Oviedo, Spain; Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain;*[16]*FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain;* [17]*Department of Evolutionary Biology, Ecology and Environmental Sciences, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain;*[18]*Department of Child and Adolescent Psychiatry, Instituto de Investigación Sanitaria Gregorio Marañón, IiSGM, Hospital General Universitario Gregorio Marañón, Madrid, Spain;* [19]*Research Group on Psychiatry and Neurodegenerative Diseases, Biomedical Research Institute INCLIVA, Valencia, Spain.*

Background: Copy number variants (CNVs) contribute substantially to neurodevelopmental and psychiatric disorders, with neuropsychiatric CNVs (npCNVs) estimated to occur in 2–5% of affected individuals. Despite this, most patients in Spain with psychiatric diagnoses are not routinely offered genetic testing. **Objective:** To characterize CNVs in a large multicenter psychiatric cohort and to determine whether patients carrying npCNVs differ from non-carriers in their clinical characteristics based on systematic genetic testing and deep phenotyping. **Methods:** Patients aged 5–65 years with autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), bipolar disorder type I (BDI), or schizophrenia spectrum disorders (SSD), without severe intellectual disability and with no prior genetic testing, were recruited across 15 mental health centers. Sociodemographic, clinical, neurodevelopmental, and medical comorbidity variables were collected. CNV analysis was performed using the CytoScan XON array. A severity index incorporating psychiatric and non-psychiatric comorbidities, treatment resistance, perinatal complications, congenital malformations, mild intellectual disability, and epilepsy was categorized into mild, moderate, and severe. **Results:** Of 1,556 recruited participants, 31% were under 18 years. Severity differed significantly across diagnoses ($p = 2.8 \times 10^{-8}$), with the highest severity in SSD. Among 624 individuals with available CNV results, 20 (3.2%) carried an npCNV (1.1% ADHD, 3.9% ASD, 2.3% BDI, 4.4% SSD), consistent with published frequencies. npCNV carriers showed high severity scores, but differences were not statistically significant. In a first CNV analysis, we identified 1q21.1-q21.2, 3q29 (2 cases), 15q11.2 (2 cases), 15q13.2-q13.3, 16p11.2 (3 cases), 16p12.2-p12.1, and 22q11.21 (1 deletion and 1 duplication). The presence of npCNVs did not modify the association between CNV status and clinical severity. **Conclusions:** High clinical severity (12.9%) was most frequent in SSD. npCNV prevalence is significant in our cohort with 1/312 patients showing a 22q11 alteration. npCNVs were not found to be significantly associated with increased clinical severity. This study shows that genetic testing programs in psychiatry enable the systematic identification of clinically relevant CNVs.

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097: Association between sluggish cognitive tempo symptoms and psychiatric diagnosis in a cohort of children with 22q11.2 deletion syndrome

Veselina Gadancheva[1], and Fiona McNicholas[1,2,3]

[1]Department of Psychiatry, Children's Health Ireland, Dublin, Ireland; [2]School of Medicine, University College Dublin, Ireland; [3]St. John of God Community Services, Lucena CAMHS, Dublin, Ireland.

Background: Cognitive disengagement syndrome (CDS) also known as sluggish cognitive tempo is a behavioural phenotype characterised by excessive daydreaming, mental "fogginess," and slowed cognitive processing. While not a formal diagnostic category, SCT is a distinct, measurable cluster within the Child Behaviour Checklist 6-18 years (CBCL). Research indicates that SCT is associated with significant functional impairment, social withdrawal, and emotional dysregulation, and often overlaps with autism spectrum disorder (ASD) and attention deficit hyperreactivity disorder (ADHD). Given the high prevalence of neurodevelopmental disorders in 22q11.2 Deletion Syndrome (22q11.2DS), this preliminary study aims to explore the clinical symptomatology among youth with 22q11.2DS who exhibit clinically significant SCT scores based on CBCL reports. **Methods:** We are conducting a retrospective chart review of patients with 22q11.2DS (age 6–18 years) referred for psychiatric evaluation between 2022 and 2025. Data are extracted from clinical records and parent-reported CBCL. Descriptive and correlational statistical analyses are performed to examine the relationship between SCT scores and clinical psychiatric symptoms. **Results:** This is an ongoing exploratory study of a small sample size of approximately 30 individuals. Analysis will focus on demographic and diagnostic variables, with particular emphasis on the co-occurrence of ASD and ADHD, as well as parent-reported social difficulties, mood disturbances, and anxiety symptoms. Preliminary observations suggest that elevated SCT scores correlate with specific internalising symptoms and social-communication challenges within this cohort. **Conclusions:** Identifying SCT symptoms in 22q11.2DS provides critical insight into the syndrome's complex neurodevelopmental and behavioural impact. Systematically screening for SCT/CDS using the CBCL may enhance clinical formulation and lead to more targeted, personalised therapeutic and educational interventions for this population.

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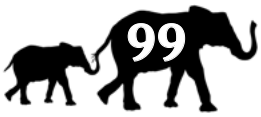
098: Emerging Discoveries on 22q11.2 and the Blood–Brain Barrier

Francesco Papaleo[1]

[1]*Genetics of Cognition Laboratory (GeCo), Neuroscience Area, Istituto Italiano di Tecnologia, Genova, Italy*

The 22q11.2 deletion syndrome (22q11.2DS) is a major genetic risk factor for neurodevelopmental and psychiatric disorders, yet the mechanisms linking this genetic condition to altered brain development and immune system remain poorly understood. In our recent work we identified blood–brain barrier (BBB) dysfunctions as a central and early driver of altered developmental trajectories in a mouse model of 22q11.2DS. Reduced expression of tight junction proteins in 22q11.2DS, particularly claudin-5, leads to increased BBB permeability, peripheral myeloid cell infiltration into the brain, neuroinflammation, and progressive social and cortical deficits emerging during adolescence. Remarkably, neonatal intranasal oxytocin administration produces a long-lasting rescue of these phenotypes by directly restoring endothelial tight junction integrity, sealing both the BBB and the blood–CSF barrier, and preventing immune cell entry—independently of secondary effects on microglia or regulatory T cells. Complementary evidence from Crockett et al. demonstrates that mitochondrial dysfunction within BBB endothelial cells also compromises barrier integrity in 22q11.2DS. Pharmacological enhancement of endothelial mitochondrial function with bezafibrate restores BBB integrity and rescues social memory deficits, further supporting a causal link between barrier dysfunction and behavior. Together, these studies position BBB dysfunction as a key mechanism in 22q11.2DS and highlight brain barrier stabilization as a promising, time-sensitive target for early therapeutic intervention.

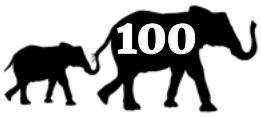


099: Biochemical alterations in tryptophan metabolism in 22q11.2 deletion syndrome

Cassandra J. Hatzipantelis[1,2,3], David E. Olson[1,2,3,4], Kathleen Angkustsiri[5,6], Andrea Schneider[5,6], and Flora Tassone[1,3,6]

[1]Department of Chemistry, University of California, Davis, Davis, CA, USA; [2]Department of Biochemistry & Molecular Medicine, School of Medicine, University of California, Davis, Sacramento, CA, USA; [3]Institute for Psychedelics and Neurotherapeutics, University of California, Davis, Davis, CA, USA; [4]Center for Neuroscience, University of California, Davis, Davis, USA; [5]Department of Pediatrics, University of California Davis, Davis, CA, USA; [6]UC Davis MIND Institute, University of California Davis, Sacramento, CA, USA.

Background: 22q11.2 deletion syndrome (22q), the most common microdeletion disorder in humans, is associated with phenotypic heterogeneity, including a high prevalence of neurocognitive impairment and psychotic disorders. While psychosis emerges in only a subset of affected individuals, reliable molecular biomarkers capable of identifying vulnerability prior to clinical onset remain largely undefined. Endogenous psychedelics have long been hypothesized to contribute to altered serotonergic signaling in psychosis-related disorders. Compounds such as N,N-dimethyltryptamine (DMT), 5-hydroxy-DMT (bufotenine), and 5-methoxy-DMT have been detected in human tissues and bodily fluids. However, efforts to link these molecules to psychotic symptoms have yielded inconsistent results, due to rapid metabolism, extensive peripheral degradation, and low steady-state concentrations that limit reliable detection in biospecimens. **Methods:** Measurements of endogenous psychedelics levels was carried out by targeted analysis using the Vanquish UHPLC system coupled to SCIEX QTRAP 6500+ LC-MS/MS system. **Results:** To address these limitations, we used a longitudinal study design and attempted to quantify a range of tryptophan metabolites in individuals with 22q and typically developing controls. While we did not observe any endogenous psychedelics, we did identify a previously unrecognized tryptophan metabolite (UTM) that appears to be dysregulated in patients with 22q. Preliminary analyses revealed significantly reduced plasma 5-HT levels and elevated UTM levels in 22q participants compared to controls, independent of sex. Notably, the 5-HT:UTM ratio favored serotonin in controls and UTM in 22q participants across visits, with no significant effect of age or gender. **Conclusions:** These findings indicate altered tryptophan metabolism in 22q, consistent with a shift away from serotonin production toward increased UTM-related pathway activity. Ongoing analyses are assessing whether elevated UTM levels are linked to greater psychosis risk. This work establishes a foundation for evaluating metabolic biomarkers relevant to 22q pathology and may inform early identification strategies and targeted interventions for psychosis risk in this population.

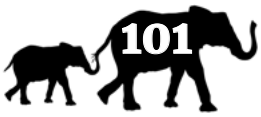


100: Systemic energy metabolism disruption as a biomarker of psychosis risk in 22q11.2 deletion syndrome

Marwa Zafarullah[1], Hannah Culpepper[1], Blythe Durbin-Johnson[2], Andrea Schneider[3,4], Kathleen Angkustsiri[3,4], and Flora Tassone[1,4]

[1]Department of Biochemistry & Molecular Medicine, School of Medicine, University of California, Davis, Sacramento, CA, USA; [2]Department of Biostatics, University of California Davis, Davis, Sacramento, CA, USA; [3]Department of Pediatrics, University of California Davis, Davis, CA, USA; [4]UC Davis MIND Institute, University of California Davis, Sacramento, CA, USA.

Background: 22q11.2 deletion syndrome (22q) confers markedly elevated risk for psychotic disorders, yet reliable biological predictors of symptom emergence remain unidentified. Psychosis onset in 22q is often preceded by subtle cognitive and behavioral changes, emphasizing the need for mechanistic biomarkers. We leveraged longitudinal biospecimens to determine whether systemic metabolic alterations are associated with psychosis-relevant symptom domains using untargeted metabolomics. **Methods:** Biological specimens from 26 participants (16 22q, 10 typically developing [TD] controls) were collected at baseline and follow-up. Global metabolomic profiling (UPLC-MS/MS) was performed. Two-way repeated-measures ANOVA with FDR correction identified significant metabolites, and PLS-DA characterized group separation. Associations with psychosis-relevant symptom domains (SIPS) and NIH Toolbox cognition were examined. **Results:** PLS-DA demonstrated robust metabolic separation between 22q and TD groups, with 22q exhibiting substantially greater longitudinal metabolic instability (183 vs. 53 metabolites), suggesting vulnerability to systemic metabolic perturbations. Core alterations involved mitochondrial bioenergetics, including elevated lactate, pyruvate, N-lactoyl amino acids, and α-ketoglutarate alongside reduced citrate, consistent with tricarboxylic acid cycle disruption and impaired oxidative phosphorylation. Lipid metabolism, inflammatory signaling, and oxidative stress-related metabolites were also altered, indicating convergent dysregulation of pathways implicated in psychosis. FDR-corrected associations were observed across SIPS symptom domains: Positive (n=41), Disorganization (n=43), Negative (n=8), and General (n=3). Recurrent metabolites included glycine and gamma-glutamylglycine (linking glutamatergic signaling and redox homeostasis), acylglycines (mitochondrial β-oxidation), and lipid species involved in inflammatory and membrane signaling. One lysophospholipid (1-nonadecenoyl-GPC [19:1]) was FDR-significantly associated with Flanker inhibitory control; no metabolites survived correction for crystallized cognition. **Conclusions:** Collectively, these findings identify convergent disturbances in bioenergetic, inflammatory, and oxidative pathways, mechanisms strongly implicated in psychosis, suggesting that systemic metabolic dysregulation may contribute to neurobiological vulnerability in 22q. Although preliminary, this study supports metabolomic profiling as a promising strategy to identify mechanistic biomarkers associated with psychosis risk and developmental trajectories in 22q.

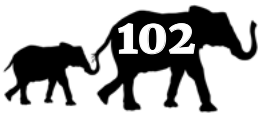


101: The making and un-making of association cortico-cortical connections in 22q11DS

Anthony -S. LaMantia[1,2], Thomas M. Maynard[1], Zachary D. Erwin[1], and Shah Rukh[1,3]

[1]*The Fralin Biomedical Research Institute at Virginia Tech-Carilion School of Medicine, Roanoke VA USA;* [2]*Deparment of Biological Sciences, Virginia Tech, Blacksburg VA, USA*, [3]*Translational Biology, Medicine and Health Graduate Program, Virginia Tech, Roanoke, VA, USA.*

Background: Association cortico-cortical connections—critical for complex behaviors—are selectively compromised in a broad range of neurodevelopmental disorders (NDDs) including 22q11.2 Deletion Syndrome (22q11DS). Despite the centrality of disrupted association cortical connectivity for behavioral pathology in nearly all NDDs including 22q11DS, there is no clear explanation for selective pathogenesis. This reflects the as-yet undefined genetic architecture and developmental programs that guide the construction of association cortico-cortical circuits. Indeed, it is still unclear whether—or how—mechanisms that account for association cortical development are distinct from those that underly development of primary sensory or motor cortices. **Methods:** Our work in mouse models of 22q11.2 Deletion Syndrome provides a framework for understanding critical genetic, cellular, and developmental mechanisms that ensure optimal association cortico-cortical connectivity based upon how 22q11-deletion disrupts these mechanisms. **Results:** We found that a distinct neuron class: upper layer association cortical projection neurons (L 2/3 PNs), is targeted by two sequential 22q11 deletion-dependent developmental pathogenic changes. First, fewer L 2/3 PN are generated in fetal association cortices due to 22q11 deletion-dependent transient disruption of the neurogenic capacity of rapidly dividing cortical intermediate progenitors. These progenitors amplify L 2/3 PN numbers in association cortices; they are maximally vulnerable to 22q11 deletion-dependent cell cycle dysregulation as their proliferative activity peaks—not before or after, and the L 2/3 PN progeny they generate are selectively compromised for subsequent association cortico-cortical circuit differentiation. Second, selectively altered 22q11-dependent mitochondrial and metabolic support of axonal, dendritic and synaptic differentiation during post-natal development diminishes connectivity of a subset of L 2/3 PNs. Thus, establishing optimal association cortico-cortical connectivity also requires distinctive bioenergetic support compromised by 22q11 deletion. **Conclusions:** We argue that two essential "nodes" in the developmental trajectory are "hit" by 22q11 deletion—conforming to a "two-hit" hypothesis of neurodevelopmental disorder pathogenesis.

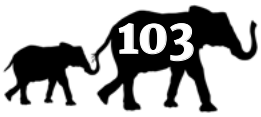


102: Neural circuit dysfunctions in animal and human models of schizophrenia risks

Stanislav S. Zakharenko[1]

[1]*Division of Neural Circuits and Behavior, Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN, USA*

Altered neural circuit function most likely underlies psychosis associated with schizophrenia (SCZ). One enigmatic symptom of SCZ is auditory hallucinations, which comprise approximately 85% of all hallucinations in this disorder. In this talk, I will discuss recent findings in the auditory cortex (ACx)—a region implicated in auditory hallucinations—using mouse models of 22q11 deletion syndrome (22q11DS) and 3q29 deletion syndrome (3q29DS), the two strongest known genetic risk factors for SCZ. Auditory hallucinations may arise from disruptions in auditory perception encoded by neural circuits converging onto the ACx. Normal perception requires the integration of incoming sensory information with interpretive processes derived from previously stored memories and experiences. When communication between these converging input pathways becomes unbalanced, internally generated signals may be perceived as real sensory events. Although such imbalances have been proposed to underlie hallucinations in SCZ, the specific circuit-level mechanisms remain poorly understood. I will describe suppressed neuronal activity in the ACx and its underlying mechanisms, driven by impaired bottom-up thalamocortical inputs, and a breakdown of cortical neuronal ensembles in 22q11DS and 3q29DS mice. We further find that the hallucinogen lysergic acid diethylamide (LSD) similarly suppresses activity in the ACx, while the antipsychotic haloperidol rescues these phenotypes in both genetic models. Thalamus-mediated cortical suppression is also observed in human thalamocortical assembloids carrying an isogenic 22q11.2 deletion. Additionally, I will introduce a novel top-down cerebellar input that projects to the ACx and is enhanced in 22q11DS mice. Together, abnormal activity in the ACx resulting from disrupted thalamocortical inputs, combined with enhanced top-down influences, may produce an input imbalance that contributes to abnormal perceptions such as auditory hallucinations. Our data also suggest that SCZ risk variants, including 22q11DS and 3q29DS, independently converge on and disrupt thalamocortical projections, leading to abnormal neuronal activity in the ACx.

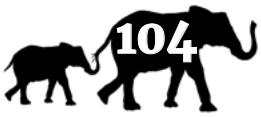


103: Cerebellar regulation of top-down auditory cortical circuits and its potential role in 22q11.2 deletion syndrome

Tae-Yeon Eom[1], Christopher M. Davenport[1], Jay Blundon[1], Feng Feng[1], Troy A. Hackett[2], and Stanislav S. Zakharenko[1]

[1]St. Jude Children's Research Hospital, Memphis, TN, USA; [2]Vanderbilt University Medical Center, Nashville, TN, USA.

Background: 22q11.2 deletion syndrome (22q11DS), also known as DiGeorge or velocardiofacial syndrome, is the most common microdeletion disorder in humans and is associated with multiple physical and neuropsychiatric morbidities. We previously identified local cerebellar dysplasia in both mouse models and individuals with 22q11DS. While these structural alterations may lead to pathological and functional dysconnectivity, the underlying circuit-level mechanisms remain poorly understood. Here, we used murine models of 22q11DS to delineate cerebellar output pathways that polysynaptically connect to auditory information-processing regions and to determine how these connections are altered in 22q11DS. **Methods:** We employed complementary anatomical and functional approaches to dissect connectivity between the cerebellar paraflocculus (PF) and the auditory cortex (ACx), including anatomical tracing, slice electrophysiology, chemogenetics, two-photon optogenetics and imaging, histological analysis, and immunohistochemistry. **Results:** Anatomical tracing revealed polysynaptic connectivity from the PF to the ACx via three intermediate nodes: the deep cerebellar nuclei, dentate nucleus (DN), and subthalamic nuclei, including the zona incerta (ZI) and ventromedial thalamus (VM). Functional assays confirmed the activity of this circuit. Notably, projections to the ACx were preferentially enriched in layer 1, suggesting that the DN-ZI/VM-ACx pathway may support top-down modulation of auditory cortical processing. Chemogenetic inhibition of PF Purkinje cells altered layer 1 neuronal activity in the ACx, further supporting cerebellar regulation of auditory cortical circuits. In 22q11DS mouse models, spontaneous activity was altered in both the PF and DN. **Conclusions:** These findings indicate that cerebellar abnormalities contribute to functional circuit disruptions in schizophrenia-associated 22q11DS. Cerebellar dysplasia impairs cerebellar output, leading to altered functional connectivity among forebrain regions, including the ZI/VM and the ACx, and may underlie sensory-processing deficits observed in 22q11DS.

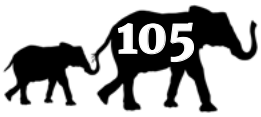


104: Associations between psychotic symptoms and subthalamic nuclei volumes in the 22.11.2 deletion syndrome (22q11DS) using Ultra High Field (UHF) MRI

J. Eric Schmitt[1,2], Simon Smerconish[2], David Roalf[1,3], Sarah Hopkins[4,6,7], Aaron Alexander-Bloch[1], T. Blaine Crowley[4], R. Sean Gallagher[1,3], Daniel E. McGinn[3], Kosha Ruparel[1,3], Lauren K. White[1,3], Elaine H. Zackai[3,4,6], Anne Bassett[9], Ruben C. Gur[1,3], Raquel. E. Gur[1,3], Stanislav Zakharenko[10], and Donna M. McDonald-McGinn[4,5,7,8]

[1]Department of Psychiatry, Neurodevelopment & Psychosis Section, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Radiology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]Lifespan Brain Institute (LiBI) at Penn & CHOP Philadelphia, PA, USA; [4]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [7]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [8]NeurAbilities, Voorhees, NJ, USA; [9]Department of Psychiatry, University of Toronto, Toronto, Canada; [10]St. Jude Children's Hospital, Memphis, TN, USA.

Background: The thalamus is a critical relay station, with a well-established role in sensory modulation and has regionally-specific connectivity with both the cortex and cerebellum. The thalamus has been implicated in the pathophysiology of schizophrenia in non-deleted populations. Prior neuroimaging studies have additionally shown that the thalamus is associated with the 22q11.2DS endophenotype, and suggest that it may be involved in the development of auditory hallucinations. However, the thalamus has complex internal architecture composed of numerous subnuclei that are difficult to measure accurately at conventional field strengths. **Methods**: Sagittal MP2RAGE MRI data was acquired at 7.0 Tesla on N=45 individuals with 22q11DS, including 8 individuals with either a clinical diagnosis of schizophrenia or other psychotic disorder. Subjects also completed the Structured Interview of Psychosis-risk Symptoms (SIPS). Total thalamic and subthalamic nuclei volumes were calculated using THOMAS segmentation, resulting in 12 regions of interest (ROIs) per thalamic hemisphere. Regression models were used to quantify associations between measures of psychosis and thalamic volumes after adjusting for sex, age, and total brain volume. **Results**: Global thalamic volumes were 5.9% smaller in the group with clinical psychosis (10.0 versus 10.7 cm^3), but differences were not statistically significant. However, SIPS sum scores were significantly associated with smaller total thalamic volumes (p-value = 0.0017), left and right hemispheric volumes (respective p-values 0.0030 and 0.0015), and with 10 thalamic subnuclei including bilateral medial geniculate nuclei (MGN), pulvinar, centromedian nuclei, and medial dorsal nuclei. Similar patterns were seen when examining positive and negative SIPS items separately. **Conclusions**: Several thalamic subnuclei volumes are associated with psychotic symptoms in 22q11DS. UHF complements conventional MRI by providing improved spatial resolution and increased signal to noise ratio (SNR), which may be particularly useful for investigating small structures and subtle neuroanatomic pathways.

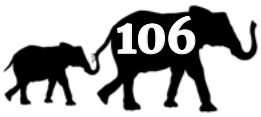


105: Cerebellar differences in 22q11.2 duplication syndrome *

Samuel Alperin[1,2,3], Madeline Chadehumbe[4], T. Blaine Crowley[3,5], Donna M. McDonald-McGinn[3,5,6] and Sarah Hopkins[1,2,3]

[1]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Neurology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]NeurAbilities Healthcare, Voorhees, New Jersey, USA; [5]Division of Human Genetic and Genomic Medicine, Children's Hospital of Philadelphia; [6]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

Background: We previously reported neuroradiologic findings in individuals with 22q11.2 duplication syndrome (22q11.2DupS). We sought to further review those with cerebellar abnormalities and differences, which represented approximately 10% of those with available MRIs. **Methods:** Under IRB approval, we retrospectively reviewed the medical records and MRI reports of patients with a diagnosis of 22q11.2DupS followed in the 22q and You Center at the Children's Hospital of Philadelphia. **Results:** We identified nine individuals with cerebellar differences. Seven are male, and seven are Caucasian. Seven had the standard LCR22A-LCR22D duplication, one has a nested LCR22B-LCR22D duplication, and one has a distal LCR22E-LCR22H duplication not overlapping with the standard LCR22A-LCR22D region. Five had Chiari I malformations, including 2 who underwent decompression surgery. Three had cerebellar ectopia (considered a normal variant), and one had vermian dysgenesis. None had seizures, but 5 had headaches, including both individuals with Chiari I malformations requiring decompression. **Conclusion:** Cerebellar abnormalities, particularly Chiari I, appear more common in this cohort of individuals with 22q11.2DupS as compared to our patients with the reciprocal 22q11.2 deletion. Additional analyses will include evaluation of secondary genetic diagnoses and associated comorbidities, including tethered cord or other spinal cord malformations.

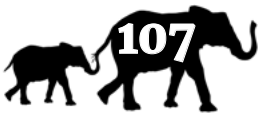


106: Neurodevelopmental perturbations in 22q11.2DS by mouse and human functional genomic approaches*

Wenna Chen[1], Lijie Shi[1], Elisha J. Fogel[1], Bernice E. Morrow[1], and Deyou Zheng[1,2,3]

[1]Department of Genetics, Albert Einstein College of Medicine, NY, USA; [2] Department of Neurology, Albert Einstein College of Medicine, NY, USA ; [3] Department of Neuroscience, Albert Einstein College of Medicine, NY, USA

Background: The neurodevelopmental origin and cause for variable psychiatric presentations in 22q11.2DS are not completely understood. Previously, many studies have used mouse models with a nested 1.5Mb A-B deletion (Lgdel/+ or Df1/+). Recently, a 3Mb A-D deletion mouse model (Del(3Mb)/+) was generated with characteristic schizophrenia-associated behavioral phenotypes (PMID32066675). There is also single-cell human brain data from the first trimester to adolescence (PMID39779846) that can be analyzed to map the normal expression and regulation of 22q11.2 genes. Combining mouse and human data, we aim to identify molecular mechanisms underlying perturbed neurodevelopment and psychiatric vulnerability in 22q11.2DS. **Methods:** To better address potential variations in Del(3Mb)/+ mice, the forebrain (FB), midbrain (MB) and hindbrain (HB) from 47 individual E15.5 embryos (31 Del(3Mb)/+ and 16 wildtype) underwent RNA-seq. We characterized the differentially expressed genes (DEGs) and scored per-sample enrichment for psychiatric risk genes via gene set variation analysis (GSVA), using gene-sets curated in our prior work (PMID35501678). Statistical significance of GSVA scores was characterized by linear mixed-effects model. **Results:** RNA-seq data revealed uniform downregulation of 22q11.2 genes, but the DEGs outside the deleted region (non-22q DEGs) showed variable changes among the Del(3Mb)/+ samples. We found 467, 456, 658 non-22q DEGs in FB, MB, and HB, respectively, with 115 shared. The non-22q DEGs are enriched for neuronal differentiation, synaptic transmission, and mitochondrial function. GSVA highlighted significant downregulation of schizophrenia and intellectual disability risk genes in the Del(3Mb)/+ FB, but not in the MB or HB. The human brain dataset showed many 22q11.2 genes broadly expressed across cell types throughout development, except *CLDN5*, which displays vascular cell-specific expression. **Conclusions:** Our findings indicate early molecular alterations during peak neurogenesis in 22q11.2DS embryos. We plan to perform further analysis with larger sample sizes and single-cell approaches to characterize perturbed pathways linked to psychiatric vulnerability.

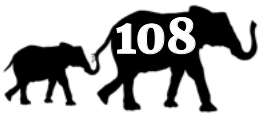


107: Disorganized inhibitory dynamics in hippocampal area CA1 of 22q11.2 deletion mutant mice

Stephanie A. Herrlinger[1,2,3], Bovey Y Rao[1,2,4], Margaret E. Conde Paredes[1,2,4,5], Anna L. Tuttman[1,2], Haroon Arain[1], Erdem Varol[5], Joseph A. Gogos[1,2,3,6,7], and Attila Losonczy[1,2]

[1]Department of Neuroscience, Columbia University, New York, NY, USA; [2]Mortimer B. Zuckerman Mind Brain Behavior Institute, Columbia University, New York, NY, USA; [3]Stavros Niarchos Foundation Center for Precision Psychiatry and Mental Health, Columbia University, New York, NY, USA; [4]Doctoral Program in Neurobiology and Behavior, Columbia University, New York, NY, USA; [5]Department of Computer Science & Engineering, Tandon School of Engineering, New York University, New York, NY, USA; [6]Department of Physiology, Columbia University, New York, NY, USA; [7]Department of Psychiatry, Columbia University, New York, NY, USA.

Background: Individuals with the 22q11.2 deletion syndrome, one of the strongest genetic risk factors for schizophrenia, demonstrate cognitive impairments, including episodic memory dysfunction. Place cell activity of excitatory pyramidal neurons in the hippocampus supporting episodic memory is impaired in a mouse model for the 22q11.2 deletion (*Df(16)A$^{+/-}$*). While excitatory dynamics are under tight inhibitory control by multiple subtypes of GABAergic interneurons, previous studies have predominantly focused on a single subtype of PV-expressing interneurons; there have not yet been studies describing the functional relationships between molecularly identified inhibitory types in *Df(16)A$^{+/-}$* mice. **Methods:** Here, we examined interneuron subtype-specific activity dynamics in the dorsal hippocampal area CA1 of *Df(16)A$^{+/-}$* mice during random foraging and spatial reward navigation tasks. We used 3D acousto-optical deflector two-photon microscopy with *post hoc* immunohistochemical identification to describe 5 distinct GABAergic interneuron cell types simultaneously in behaving animals. **Results:** We found that multiple interneuron types exhibit aberrant responses to reward locations and delayed reward enrichment extinction. *Df(16)A$^{+/-}$* inhibitory interneurons also carry markedly reduced spatial information in a subtype-dependent manner. We observed task-dependent changes in the correlation structure and coactivity among multiple GABAergic subtypes, suggesting a broadly disorganized microcircuit functionality in mutant mice. **Conclusions:** Overall, we identify widespread and heterogeneous subtype-specific alterations in interneuron dynamics during spatial reward navigation, reflecting impaired flexibility and organization in CA1 inhibitory microcircuits. Our study provides critical insights into how schizophrenia-risk mutations affect local-circuit interactions among diverse cell types in the mouse hippocampus during learning and spatial navigation.

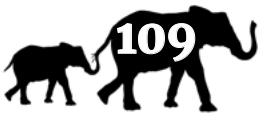


108: Olfactory deficits and structural anomalies of the olfactory system in 22q11.2 deletion syndrome

David R. Roalf[1,4], Donna M. McDonald-McGinn[2,3], Bruce I. Turetsky[1], Paul J. Moberg[1], T. Blaine Crowley[2], Phoebe Freedman[1,4], Monica E. Calkins[1,4], R. Sean Gallagher[1,4], Audrey Olson[2], Daniel E. McGinn[2], Lydia Rockart[2], Oanh Tran[2], Elaine H. Zackai[2,3], Beverly S. Emanuel[2,3], Kosha Ruparel[1,4], Russell T. Shinohara[3], Lauren White[4], and Raquel E. Gur[1,4]

[1]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; [2]22q and You Center and Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, PA, USA; [5]Lifespan Brain Institute at Penn and CHOP, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (22qDS) confers approximately 25% risk for schizophrenia-spectrum disorders and shares key neurodevelopmental features with idiopathic psychosis. The olfactory system develops early in utero and provides a unique window into gestational brain anomalies relevant to psychosis. We hypothesized that individuals with 22qDS would show olfactory function impairments and structural anomalies of the olfactory system, similar to deficits seen with psychosis. **Methods:** Participants included 22qDS (n=101) and typically developing (TD) controls (n=52). Sinonasal symptoms (SNOT), odor identification, and odor discrimination (Sniffin' Sticks) were assessed behaviorally. Structural 3T MRI measured olfactory bulb volume, sulcus depth and length. Subsets completed each measure; sample sizes are reported per analysis. **Results:** 22qDS compared to TD, showed elevated SNOT scores ($p<0.001$), indicating greater sinonasal symptom burden. Olfactory identification scores ($p<0.001$) and odor discrimination scores ($p<0.001$) were lower in 22qDS relative to TD. Olfactory bulb volume was significantly smaller in 22q11DS compared to TD ($p=0.003$). In contrast, olfactory sulcus depth ($p=0.937$) and sulcus length ($p=0.501$) did not differ significantly between groups. These dissociable findings suggest that functional olfactory deficits and structural reductions in primary olfactory sense organ (bulb volume) are prominent in 22q11DS, whereas cortical olfactory morphology may be preserved. **Conclusions:** 22qDS is associated with elevated sinonasal symptom burden, robust deficits in olfactory identification and discrimination, and smaller olfactory bulb volume relative to TD controls. The profile of olfactory deficits in 22qDS mirrors that reported in idiopathic schizophrenia and psychosis spectrum youth, supporting shared neurodevelopmental mechanisms and the utility of 22qDS as a genetic model for psychosis risk. However, the co-occurrence of functional deficits and reduced bulb volume in the absence of sulcal anomalies may distinguish the olfactory phenotype of 22qDS from idiopathic psychosis, where sulcal depth reductions are more prominent, and warrants further investigation as a marker of differential psychosis risk mechanisms.



109: Impact of the 22q11.2 Deletion on Brain Structure and Function: Insights from the ENIGMA Consortium

Carrie E. Bearden[1]

[1]*Department of Psychiatry and Behavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA, USA, Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA*

22q11.2 deletion syndrome (22q11DS) is associated with a markedly increased risk for neuropsychiatric disorders, yet the neurobiological mechanisms linking this genetic variant to brain alterations remain incompletely understood. Leveraging the Enhancing NeuroImaging Genetics through Meta Analysis 22q11.2 (ENIGMA-22q) Working Group—the largest international cohort of molecularly confirmed 22q11DS carriers to date (470 individuals with 22q11DS and 380 matched controls across 15 sites/scanners)—we investigated the structural and functional brain signatures of this high-impact genetic condition. We first characterized large-scale cortical alterations, identifying widespread reductions in cortical surface area (average Cohen's d = -1.04), with differential effects in midline posterior and lateral association regions, alongside increased mean cortical thickness (average Cohen's d =0.62), with regionally specific thinning in temporal and cingulate cortices. Structural deviations in 22q11.2-associated psychosis showed convergence with those observed in idiopathic psychotic disorder, particularly in frontotemporal regions, and scaled with deletion size, highlighting dose-dependent effects. Parallel analyses of subcortical structures revealed similar patterns of deviation. To probe underlying mechanisms, we integrated neuroimaging maps with molecular data. Cortical thickness alterations spatially overlapped with maps of glutamatergic and GABAergic receptor density, implicating disruption of excitatory–inhibitory signaling in cortical development. Imaging-transcriptomic analyses further identified DGCR8 haploinsufficiency as a potential contributor to altered corticogenesis via dysregulation of cell cycle processes. Finally, cross-species and longitudinal analyses revealed an anomalous developmental trajectory of functional brain connectivity. In the LgDel mouse model, early-life hyperconnectivity transitions to hippocampal hypoconnectivity during adolescence, paralleling patterns observed in human 22q11DS. These changes are associated with developmental alterations in dendritic spine density, suggesting synaptic mechanisms underlying evolving network dysfunction. Together, these findings provide a multiscale framework linking 22q11.2 gene dosage to brain development, circuit dynamics, and psychosis risk in 22q11DS.

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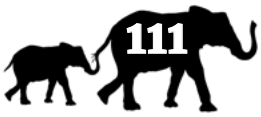
110: Network-specific deviations in functional brain development in 22q11.2DS linked to psychosis

Kaustubh Supekar[1], Leila Kushan[2], Charles Schleifer[3], Gabriela Repetto[4], Nicolas A Crossley[5], and Carrie Bearden[6]

[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA; [2]Department of Psychiatry and Behavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA, USA, Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA; [3]Department of Psychiatry and Behavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA, USA, Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA; [4]Center for Genetics and Genomics, Facultad de Medicina, Clinica Alemana Universidad del Desarrollo, Santiago, Chile; [5]Department of Psychiatry, Pontificia Universidad Católica de Chile, Santiago, Chile, Department of Psychiatry, University of Oxford, Oxford, UK;[6]Department of Psychiatry and Behavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA, USA, Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA

Background: 22q11.2DS is a genetic neurodevelopmental condition characterized by substantial individual variability in psychiatric outcomes, most prominently psychosis. However, the neurodevelopmental mechanisms underlying this variability remain unclear, as prior studies have relied on modest samples and group-level analyses. Here, we assemble one of the largest neurodevelopmental datasets (N=2,484) and apply a novel normative modeling approach to test the hypothesis that 22q11.2DS is associated with altered functional brain development and variability in psychosis outcomes is driven by network-specific developmental deviations. To evaluate whether similar developmental deviations are present outside a genetic risk context, we additionally examined individuals at clinical high risk (CHR) for psychosis. **Methods:** Multi-cohort fMRI and phenotypic data from 1,810 neurotypical individuals were used to develop a normative model of functional brain development describing how functional brain dynamics typically change from childhood to early adulthood. This model was applied to 81 individuals with 22q11.2DS and 75 neurotypical controls (ages 8-25years) from two independent cohorts, and to 518 CHR individuals. Individual deviations from typical developmental trajectories were estimated using attribution-derived regional brain dynamics. **Results:** The normative model learned reproducible latent representations of typical functional brain development across independent neurotypical cohorts. Individuals with 22q11.2DS showed consistent deviations from typical functional brain development, with reproducible alterations localized to the insula and MTL. Within the 22q11.2DS group, variability in psychosis outcomes was characterized by distinct network-specific developmental deviations across salience, limbic, and temporal systems, including prominent insula alterations. In CHR individuals, pre-conversion insula alterations were observed among those who later developed psychosis. **Conclusions:** Functional brain development in 22q11.2DS is characterized by network-specific neurodevelopmental alterations and not a uniform brain-wide disruption, highlighting the key role of developmental imbalance across salience, limbic, and temporal system dynamics in psychosis. Convergent insular involvement across genetic and clinical pathways suggests a shared salience-network developmental mechanism underlying psychosis.

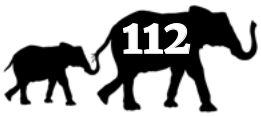


111: Striatal dopamine transporter binding in adults with 22q11.2 copy number variants: an [^{123}I]FP-CIT SPECT study *

Jeltje C.C. Spapens[1], Carmen F. M. van Hooijdonk[1], Rik Schalbroeck[2,3], Amy L. Sylvester[1], Erik Boot[1,4,5], Therese A.M.J. van Amelsvoort[1], Claudia Vingerhoets [1,4], and Jan Booij[3]

[1]Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands; [2]Institute of Education and Child Studies, Leiden University, Leiden, The Netherlands; [3]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [4]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [5]The Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada.

Background: Copy number variants (CNVs) at the 22q11.2 chromosomal locus, hemizygous 22q11.2 deletions or duplications, are associated with a broad spectrum of neuropsychiatric and other medical conditions. 22q11.2 deletion syndrome is linked to an increased risk for schizophrenia, with ~25% of patients developing psychosis. Individuals with a 22q11.2 deletion are also at increased risk for developing early-onset Parkinson's disease. The COMT (catechol-*O*-methyltransferase) gene at 22q11.2 is involved in dopamine metabolism. While previous studies have examined aspects of dopamine function in 22q11.2 CNV cases, striatal dopamine transporter (DAT) availability, a regulator of synaptic dopamine, has not yet been systematically investigated. **Methods:** Therefore, DAT availability was quantified using [^{123}I]FP-CIT single-photon emission computed tomography (SPECT) in 9 individuals with a 22q11.2 deletion, 9 with a 22q11.2 duplication (n = 9), and 8 controls on a brain-dedicated SPECT system. Specific binding ratios were calculated for the striatum, and images were processed using BRASS software with the occipital lobe as reference. **Results:** Permutation ANCOVA (controlling for age and sex) showed significantly higher striatal DAT availability in individuals with 22q11.2 deletions compared with those with duplications (p_{perm} = 0.026, η^2_p = 0.30), with no significant differences between individuals with 22q11.2 CNVs and controls. **Conclusions:** These findings suggest distinct nigrostriatal dopaminergic profiles associated with 22q11.2 CNV status, which may play a role in shaping frequently occurring neurological and psychiatric phenotypes in these individuals.

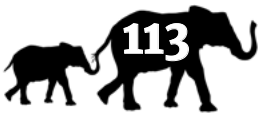


112: Cortical myoclonus as a distinct motor phenotype of 22q11.2 deletion syndrome

Nikolai Gil D. Reyes[1,2,3,4], Talyta Grippe[2], Benedetta Angeloni[2], Victor Lira[5], Connie Marras[2], Erik Boot[3,6,7], Ryan K.C. Yuen[8,9], Anthony E. Lang[2,10], Danielle M. Andrade[5], Robert Chen[1,2,10], and Anne S. Bassett[1,3,4,11]

[1]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [2]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada; [3]Dalglish Family 22q Clinic, Toronto General Hospital, Toronto, ON, Canada; [4]Clinical Genetics Research Program, Centre for Addiction & Mental Health, Toronto, ON, Canada; [5]Adult Genetic Epilepsy Program, Division of Neurology, Krembil Neurosciences Institute, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada; [6]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [7]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Institute (MHeNs), Maastricht University, Maastricht, The Netherlands; [8]Genetics and Genome Biology, The Hospital for Sick Children; Toronto, ON, Canada; [9]Department of Molecular Genetics, University of Toronto; Toronto, ON, Canada; [10]Krembil Research Institute, Toronto Western Hospital, Toronto, ON, Canada; [11]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada.

Background: Beyond Parkinson's disease, hyperkinetic movement disorders, including myoclonus, are increasingly recognized as neurologic manifestations associated with 22q11.2 microdeletion, yet neurophysiological and clinical characterization remains limited. **Methods:** We describe findings in adults with a typical 22q11.2 microdeletion who underwent expert neurologic evaluations for myoclonus between 1996 and 2025. Data were obtained through retrospective review, collecting relevant information regarding demographics, genetics, and available electro-clinical data (phenomenology, electromyography, EMG and/ or electroencephalography, EEG). **Results:** Among 290 adults, 15 (5.2%; 53.3% female) were identified with myoclonus based on clinical and neurophysiologic evaluation. Median age at neurological assessment was 29.2 (IQR: 21.7) years, and median age at onset was 24.0 (IQR: 11.4) years. Epilepsy was present in only 4/15 (28.6%) and clozapine-requiring psychotic disorder in 5/15 (33.3%), in addition to the myoclonus diagnosis. Clinically, myoclonus was most often observed at rest (13/15, 86.7%), and predominantly affected the distal upper extremities (12/15, 80.0%), followed by the face (6/15, 40.0%), and proximal upper extremities and trunk (4/15, 26.7% each). Neurophysiologic evidence supported cortical localization and physiology in all cases: short EMG burst duration (15/15, 100%; median 40, IQR: 5.0 ms), and presence of giant somatosensory evoked potentials (6/15, 40.0%), short-latency EEG discharge preceding myoclonic jerks (5/15, 33.3%), and negative myoclonus (2/15, 13.3%). **Conclusions:** This study extends prior findings of cortical myoclonus as a distinct movement disorder entity associated with 22q11.2DS, which may occur independently of epilepsy or clozapine exposure. These findings may support 22q11.2 microdeletion as a genetic etiology of cortical myoclonus. Neurologic assessment is essential for accurate diagnosis, localization, and clinical decision-making, and should include neurophysiologic evaluation.



113: Early-onset parkinson's disease with 22q11.2 microdeletion and pathogenic *GBA1* variant

Nikolai Gil D. Reyes,[1,2,3,4], Daniel G. Di Luca[2,5], Ivan Martinez-Valbuena[2,10,11], Erik Boot[3,6,7], Maria Corral[2], Ryan K.C. Yuen[8,9], Connie Marras[2], Anthony E. Lang[2,10], and Anne S. Bassett[1,3,4,12]

[1]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada; [3]Dalglish Family 22q Clinic, Toronto General Hospital, Toronto, Ontario, Canada; [4]Clinical Genetics Research Program, Centre for Addiction & Mental Health, Toronto, Ontario, Canada; [5]Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA; [6]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [7]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Institute (MHeN)s, Maastricht University, Maastricht, The Netherlands; [8]Genetics and Genome Biology, The Hospital for Sick Children; Toronto, Ontario, Canada; [9]Department of Molecular Genetics, University of Toronto; Toronto, Ontario, Canada; [10]Krembil Research Institute, Toronto Western Hospital, Toronto, Ontario, Canada; [11]Tanz Centre for Research in Neurodegenerative Diseases. University of Toronto, Toronto, Ontario, Canada; [12]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada.

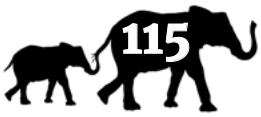
Background: It is well recognized that early-onset Parkinson's disease (EOPD) is strongly influenced by genetic factors. Oligogenic cases—where co-occurring variants jointly influence risk and expression—may exhibit phenotypic differences compared to typical sporadic and monogenic PD. However, reports describing combined effects of distinct high-risk variants remain limited. **Methods:** We present a case of oligogenic EOPD associated with 22q11.2 microdeletion and a severe pathogenic *GBA1* variant, and discuss potential implications. **Results:** A 27-year-old male with a *de novo* 2.5 Mb LCR22A-LCR22D 22q11.2 microdeletion developed new-onset parkinsonian motor features. Other neuropsychiatric features common in 22q11.2 deletion syndrome were present, including mild intellectual disability and anxiety/mood disorders treated with standard SSRI therapy. Short-term low-dose risperidone had been discontinued long before motor symptom onset. Neurologic examination demonstrated asymmetric parkinsonism. Brain MRI and laboratory investigations were unremarkable. Skin-based α-synuclein seed amplification assay was negative and serum neurofilament light chain was low (8.8 pg/mL). Levodopa/carbidopa therapy resulted in significant symptomatic improvement (MDS-UPDRS III: 26→17). Given the EOPD, and family history of PD and consanguinity, we pursued targeted genetic testing, which identified a severe, pathogenic heterozygous *GBA1* c.1448T>C (p.Leu483Pro) variant. **Conclusion:** This case highlights the potential additive, or possibly synergistic, effects of co-occurring high-risk genetic variants on PD penetrance and expression. The very early age at presentation relative to expectations for either 22q11.2 microdeletion or the *GBA1* variant alone supports an oligogenic model of disease expression in EOPD. For clinicians, these findings underscore the crucial role of comprehensive genetic evaluation—including both single-nucleotide and copy number variations—for individuals with EOPD and/or multisystem presentations. Further studies are needed to clarify how overall rare, high-risk variant burden modifies PD risk, clinical trajectory, and underlying mechanisms.

114: Assessing a polygenic risk score for Parkinson's disease in 22q11.2 deletion syndrome

Nikolai Gil D. Reyes[1,2,3,4], Shengjie Ying[2,3], Adrian I. Espiritu[5], Tracy Heung[2,3], Yue Yin[6], Erik Boot[7,8], Anthony E. Lang[4,9], Connie Marras[4], Ryan K.C. Yuen[6,10], Anne S. Bassett[1,2,3,11]

[1]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [2]Dalglish Family 22q Clinic, Toronto General Hospital, Toronto, ON, Canada; [3]Clinical Genetics Research Program, Centre for Addiction & Mental Health, Toronto, ON, Canada; [4]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada; [5]Department of Neurosciences, University of the Philippines-Philippine General Hospital, Manila, Philippines; [6]Genetics and Genome Biology, The Hospital for Sick Children; Toronto, ON, Canada; [7]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [8]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Institute (MHeN)s, Maastricht University, Maastricht, The Netherlands; [9]Krembil Research Institute, Toronto Western Hospital, Toronto, ON, Canada; [10]Department of Molecular Genetics, University of Toronto; Toronto, ON, Canada; [11]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada.

Background: The 22q11.2 microdeletion confers an elevated risk of parkinsonism, particularly early-onset Parkinson's disease (PD). The extent to which common genetic variation associated with idiopathic PD modifies parkinsonism risk in 22q11.2 deletion syndrome (22q11.2DS) remains unclear. **Methods:** We performed an out-of-sample PD polygenic risk score (PD-PRS) analysis in 205 unrelated adults with a typical 22q11.2 microdeletion (31 parkinsonism-cases, 174 controls) with available genome sequencing and movement disorder phenotype data. Allele-weighted risk scores were calculated in PLINK using a previously validated PD-PRS (PGS000903) comprising 1,392 single nucleotide polymorphisms (SNPs). Between-group comparisons were conducted in the full sample and in an age-adjusted subsample (controls $\geq$ 30 years). Association between PD-PRS and parkinsonism status was evaluated using logistic regression models adjusting for age, ancestry, and psychotic illness. Sensitivity analyses were performed using a genome-wide significant 90-variant PD-PRS (PGS000902; 37 overlapping SNPs). **Results:** Standardized PD-PRS did not differ significantly between individuals with and without parkinsonism in the full sample ($p = 0.85$) or age-adjusted sample ($p = 0.96$). Logistic regression revealed no significant association between PD-PRS and parkinsonism (unadjusted OR 0.96, 95% CI 0.66–1.41; adjusted OR 0.90, 95% CI 0.53–1.53; p for both models >0.5). Inclusion of PD-PRS in the full model increased explained variance by <2% (ΔNagelkerke $R^2 \leq 0.002$). Findings were consistent using the 90-variant PD-PRS. **Conclusions:** Interim analyses suggest the possibility that PD-PRS derived from a large population-based GWAS does not significantly modify parkinsonism risk in adults with a typical 22q11.2 microdeletion. These preliminary findings may indicate that PD-associated common genetic variation contribute minimally to motor expression in the presence of a high-impact variant such as 22q11.2 microdeletion. The genetic architecture of 22q11.2DS-associated (early-onset) parkinsonism may differ from that of idiopathic (late-onset) PD. Our findings support investigation of alternative genetic risk modifiers, including additional rare variants.



115: Biomarkers in tear fluid: examining dopamine and p-tau in participants with 22q11.2 deletion syndrome

Thérèse van Amelsvoort[1,2], Emma von Scheibler[1,2], Rianne van Roij[1], Erik Boot[1,3,4], Claudia Vingerhoets[1,3], David Linden[1], and Marlies Gijs[4]

[1]Mental Health & Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands; [2]Koraal, Institution for people with Intellectual Disability, Sittard, The Netherlands; [3]sHeerenloo, Institution for people with Intellectual Disability, Amersfoort, The Netherlands; [4]The Dalglish Family 22q Clinic, University Health Network, Toronto, OT, Canada; [5]Maastricht University Eye Clinic, Maastricht, The Netherlands.

Background: 22q11.2 deletion syndrome (22q11.2DS) increases the risk of developing neuropsychiatric disorders in adulthood particularly schizophrenia and Parkinson's disease. Nonetheless, timely diagnosis remains difficult since adequate screening methods are burdensome or expensive. Neurodegenerative biomarkers were recently detected in tears of healthy individuals and possibly correlated to age, suggesting their potential for earlier diagnosis and intervention measures. Since then, this method has been explored in individuals with Alzheimer's and Huntington's disease. Here we aim to investigate detectability of relevant biomarkers in tear samples of individuals with 22q11.2DS. **Methods:** A total of 30 (median age 24, 42 % male) participants with 22q11.2DS syndrome were included since September 2022 through the outpatient clinic of the Maastricht University Medical Centre and residential setting for people with intellectual disabilities Koraal. Tear samples were retrieved from participants older than 16 years without an ocular surface disorder using Schirmer strips. Levels of p-tau (general biomarker of neurodegeneration) and dopamine (relevant for schizophrenia and Parkinson's disease) were measured using an ELISA multiplex-immunoassay. Comparisons were made with data from healthy controls that were available at the tear biobank of Maastricht University Eye Clinic. **Results:** Interim analysis showed median dopamine concentrations were 183.4 (pg/ml) in people with 22q11.2DS, and almost twice as high (376pg/nl) in controls. Median p-tau levels were 367.9 (pg/ml), and undetectable in controls. Tear fluid detectability was 100% for p-tau and 96.6% for dopamine. There were no significant differences between median tear dopamine concentrations between participants with 22q11.2DS compared to healthy individuals. Data collection is still ongoing. **Conclusions:** In this study in participants with 22q11.2DS there biomarker detectability was high, and this method seems promising as an alternative for the more invasive blood sampling method. However, further research is needed, evaluating larger participant groups and age ranges.

116: Dopamine-associated oxidative stress differentially compromises cortical and striatal neurons and circuits in the *LgDel* 22q11DS mouse model

Anthony-S. LaMantia[1,2], Zachary D. Erwin[1], Thomas M. Maynard[1], Seth R. Batten[1], Terrence M. Lohrenz[1], Leonardo Barbosa[1], Paul Sands III[1], and P. Read Montague[1,3]

[1]The Fralin Biomedical Research Institute at Virginia Tech-Carilion School of Medicine, Roanoke, VA, USA; [2]Department of Biological Sciences, Virginia Tech, Blacksburg, VA, USA; [3]Department of Physics, Virginia Tech, Blacksburg, VA, USA.

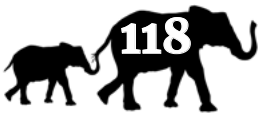
Background: Dysregulated dopamine (DA) signaling accompanies two brain diseases frequently associated with 22q11.2 Deletion Syndrome (22q11DS): Schizophrenia (Scz) and Parkinson's Disease (PD). DA release in forebrain regions targeted by Scz and PD pathology—association cortices and striatum—is accompanied by local generation of reactive oxygen species (ROS). This DA-associated ROS may generate acute oxidative stress—reflecting highly oxidative DA catabolism—that must be managed by cortical and striatal DA target neuron antioxidant defense (*a-OxD*) mechanisms. **Methods:** Using the *LgDel* 22q11DS mouse model, we asked whether DA-associated oxidative stress targets 22q11-deleted cortical or striatal DA-target neurons. **Results:** Transcriptomic analysis of cortico-cortical projection neurons (ccPNs), inter-telencephalic cortical projection neurons (itPNs) and striatal medium spiny neurons (MSNs) suggests each has distinct *a-OxD* signatures. Furthermore, the *a-OxD* signature of 22q11-deleted ccPNs differs more from control than those of 22q1-deleted itPNs or MSNs. In parallel, DA innervation for 22q11-deleted DA-target ccPNs increases 5-fold, while that of itPNs and MSNs is indistinguishable from control. DA release and ROS generation in the 22q11-deleted cortex vs. striatum is also divergent. A relatively modest level of DA release in the 22q11-deleted cortex elicits disproportionate ROS generation. In contrast, DA release and ROS increase in parallel—but substantially more than control in response to equivalent stimulus levels—in the 22q11-deleted striatum. Finally, DA-associated ROS generation may reflect distinct capacities of 22q11-deleted ccPN, itPN and MSN mitochondria to support DA catabolism via monoamine oxidases. **Conclusions:** Diminished *a-OxD* resilience of 22q11-deleted ccPNs to DA-associated oxidative stress may accelerate oxidative damage to cortico-cortical circuits and exacerbate association cortical dysfunction underlying Scz in 22q11DS. In contrast, chronically increased DA and ROS in more *a-OxD* resilient 22q11-deleted MSNs may lead to slower oxidative damage for striatal circuits, resulting in later onset PD motor deficits in 22q11DS.

117: Stem cell-based drug discovery for neurological disorders

Spyros Petrakis[1]

[1]*Institute of Applied Biosciences, Centre for Research and Technology, Thessaloniki, Greece*

Neurological disorders including 22q11.2 deletion syndrome (22q11.2 DS) present significant challenges for therapeutic development due to their complex genetic architecture, phenotypic variability, and limited access to disease-relevant human neural tissue. Stem cell–based models, particularly those derived from induced pluripotent stem cells (iPSCs) represent excellent tools for understanding disease mechanisms and accelerating drug discovery. Here, we present recent advances in the use of patient-derived iPSCs to model neurological disorders. By differentiating iPSCs into specific neuronal cell types we may recapitulate key pathological cellular and molecular features in vitro, enabling the identification of disease-relevant biological pathways. Importantly, stem cell–based systems provide a scalable platform for phenotypic drug screening. We indicatively present their use for the identification of repurposed drugs protecting from neurodevelopmental defects in the human brain. Extending to 22q11.2 DS, we have previously identified genes as potential disease determinants and computationally predicted chemical compounds which might reverse the hyperactive metabolic phenotype of 22q11.2DS neuronal cells. Together, these advances position stem cell–based drug discovery as a powerful strategy for developing targeted therapies for 22q11.2 DS or other associated neurological disorders.

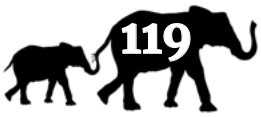


118: Aberrant glutamatergic transmission and homeostatic plasticity in a human neuronal model of 22q11.2 deletion syndrome

Weibo Niu[1], Jidong Guo[1], Ximing Ran[2,3], David Parker[4], Xiangru Li[5], Shaojun Yu[3], Sidney Imes[1,6], Ryan Purcell[7], Eric Guo[1], Sophia Y. Jiang[8], Gary J Bassell[9], Jennifer G Mulle[10], Opal Y. Ousley[1], Bradley Pearce[11], Yue Feng[12], Elaine F. Walker[4], Joseph F. Cubells[1,13], Zhaohui Qin[2,3], Erica Duncan[1,6], and Zhexing Wen[1,9,13,14]

[1]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA; [2]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, USA; [3]Department of Computer Science, Emory University, Atlanta, GA, USA; [4]Department of Psychology, Emory University, Atlanta, GA, USA; [5]College of Arts and Sciences, Emory University, Atlanta, GA, USA; [6]Atlanta Veterans Administration Health Care System, Decatur, GA, USA; [7]School of Neuroscience, Fralin Biomedical Research Institute at VTC, Virginia Tech, Roanoke, VA, USA; [8]Decatur High School, Decatur, GA, USA; [9]Department of Cell Biology, Emory University School of Medicine, Atlanta, GA, USA. [10]Department of Psychiatry, Rutgers University, New Brunswick, NJ, USA; [11]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA; [12]Department of Pharmacology and Chemical Biology, Emory University School of Medicine, Atlanta, GA, USA; [13]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA; [14]Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA.

Background: 22q11.2 Deletion Syndrome (22q11DS), the most prevalent chromosomal microdeletion disorder in humans, arises from hemizygous deletions of a 1.5-3.0 Mb region on chromosome 22. Notably, 20-30% of individuals with 22q11DS develop schizophrenia (SCZ) by early adulthood, making 22q11DS one of the strongest genetic risk factors for SCZ. However, the mechanisms by which the 22q11.2 deletion perturbs neuronal function and drives psychotic manifestations in 22q11DS remain poorly defined. **Methods:** We generated multiple iPSC lines from clinically well-characterized individuals with 22q11DS and age and sex-matched healthy controls. These iPSCs were then differentiated into 2D cortical neurons or 3D cortical organoids. Whole-cell patch clamp recordings were performed on neurons from 2 to 8 weeks after differentiation to assess the intrinsic membrane properties, excitatory synaptic transmission and homeostatic plasticity, followed by the spearman correlation analysis of neuronal phenotypes and psychosis-related clinical and psychophysiological measures. Furthermore, synaptosomes were extracted from both control and 22q11DS cortical organoids for integrative analysis of the mRNA and microRNA profiling, and a microRNA-gene regulatory network was then constructed at the pathway level. **Results:** Cellular and electrophysiological analyses revealed that 22q11DS neurons exhibit hyperexcitability, reduced glutamatergic synaptic transmission, and impaired homeostatic synaptic plasticity, which are pathophysiological hallmarks that align with the clinical, cognitive, and psychophysiological profiles of patients. Transcriptomic profiling of neurons and synaptosomes from 22q11DS cortical organoids uncovered dysregulated immune pathways and synaptic gene networks. Integrative microRNA analysis identified synergistic downregulation of hsa-miR-185-5p and hsa-miR-128-3p at synapses, driving aberrant regulation of immune and synaptic transcripts. Experimental knockdown of these microRNAs in control neurons recapitulated the molecular and functional phenotypes of 22q11DS neurons, thereby establishing a mechanistic link to synaptic dysfunction and impaired plasticity. **Conclusions:** Our findings demonstrated aberrant synaptic transmission and impaired homeostatic plasticity in 22q11DS neurons and revealed microRNA-driven gene regulatory networks contributing to the synaptic pathology.

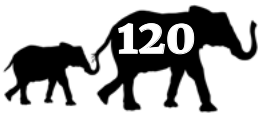


119: Altered neurophysiological activity of iPSC-derived neurons of 22q11.2 deletion syndrome

Adrian J Harwood[1,2], Jeremy Hall[2], and Gemma Wilkinson[2]

[1]Mental Health and Neuroscience Research Institute (MHENS), Maastricht University, Maastricht, The Netherlands; [2]Second Neuroscience and Mental Health Innovation Institute (NMHII), Cardiff University, Cardiff, UK.

Background: The CONVERGE research programme aims to compare the biology of three recurrent Copy Number Variants (CNVs), 22q11.2 deletions, 1q21.1 deletions and 16p11.2 duplications, to seek common mechanisms that increase their risk for mental health conditions. The research programme cross-correlates multi-modal analyses, spanning from patient deep phenotyping, brain imaging, mouse model electrophysiology and cellular studies of patient derived induced Pluripotent Stem Cells (iPSC). Here, we report our recent analysis of 22q11.2DS patient iPSC. **Methods:** We analysed patient-derived induced pluripotent stem cells (iPSCs) and CRISPR-engineered isogenic 22q11.2 deletion lines differentiated into functional neurons. Neuronal activity was assessed using multi-electrode arrays and high-throughput calcium imaging. **Results:** Patient-derived neurons exhibited reduced spontaneous neuronal activity and altered network synchrony. At the cellular level, calcium responses were attenuated, and neurons showed altered dose-dependent sensitivity to drugs that target both NMDA and AMPA Glutamate receptor sub-types. **Conclusions:** These findings indicate disrupted glutamatergic and calcium signalling in 22q11.2DS neurons. Our current work focuses on identifying the molecular mechanisms underlying these functional changes, with the aim of pinpointing pathway components that may offer targets for pharmacological rescue.



120: Mapping genes differentially expressed in 22q deletion syndrome to sub-populations of control cells defined using scRNA-seq at developmental timepoints during neuro-differentiation

Janet C. Harwood[1], Karolina Dec[2], Jamie Wood[2], David Linden[1], Thérèse van Amelsvoort[1], and Adrian J. Harwood[1,2]

[1]*Mental Health and Neuroscience Research Institute (MHeNs), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands;* [2]*Neuroscience & Mental Health Innovation Institute, Hadyn Ellis Building, Cardiff University, Cardiff, UK.*

Background: A key question in mental health is how genes identified as risk genes for psychiatric disorders affect the developing brain. The next step towards elucidating the mechanisms involved in the etiology of neuro-psychiatric conditions is to characterise cells at intermediate timepoints during neuro-differentiation, specifically where and when the risk genes are expressed. 22q11.2 deletion carriers have debilitating variable phenotypes and carry a high risk for neuro-psychiatric disorders, the condition is known as 22q deletion syndrome (22qDS). Haploinsufficiency of genes within the 22qDS CNV region have been well studied but this does not fully explain how neurodevelopment is affected. Bulk differential gene expression (DEG) analysis in 22qDS patient populations has shown that 89% of the DEGs in 22qDS are located outside of the 22qDS region and their differential expression is dependent on the developmental stage. **Methods:** We have generated a single cell RNA-seq (scRNA) time course from induced pluripotent stem cells (iPSC) developed to neural progenitor cells (NPC). We clustered the gene expression profiles and used manual cell - type annotation to characterise sub-populations of cells at each timepoint. We used published protein coding genes differentially expressed in 22qDS iPSC cells and followed their expression through sub-populations of control cells in our scRNA time course to establish when and where they are expressed in normal development. **Results:** We show that the expression of a subset of the DEGs in 22qDS iPS cells, some of which are known risk genes for neurodevelopmental disorders (NDDs), occurs early in normal development, in specific populations of cells and at specific developmental timepoints. **Conclusions:** We can map the expression of neuro-psychiatric risk genes to specific cell populations during early neural development. These molecular signatures of cell subpopulations in early neurodevelopment will define neuro-psychiatric conditions associated with 22qDS in terms of developmental time and place.

121: Transcriptomic signature of iPSC-derived neural progenitor cells from 22q11.2 microduplication carriers

Natasa Kovacevic-Grujicic[1], Jovana Kostic[1], Mina Peric[1], Luka Bojic[1], Ivana Hadzi Makuncevic[1], Goran Cuturilo[2,3], Adrian J. Harwood[4,5], Danijela Drakulic[1], and Milena Stevanovic[1,6]

[1]Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia; [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [3]University Children's Hospital, Belgrade, Serbia; [4]Mental Health and Neuroscience Research Institute, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; [5]Neuroscience and Mental Health Innovation Institute, Cardiff University, Cardiff, UK; [6] Serbian Academy of Sciences and Arts, Belgrade, Serbia.

Background: 22q11.2 Duplication Syndrome (22q11.2DupS) is associated with an elevated risk of developing neurodevelopmental disorders. To date, transcriptomic profiling of neural cells derived from individuals with 22q11.2DupS remains limited, restricting insight into the molecular mechanisms underlying its neurobiological effects. **Methods:** We performed bioinformatics analysis on transcriptomic data obtained from iPSCs-derived neural progenitor cells (NPCs) of three patients with an inherited form of 22q11.2DupS, their asymptomatic mothers that carry the microduplication, and three healthy individuals. **Results:** Differential gene expression analysis identified 54 upregulated and 58 downregulated genes in NPCs from all microduplication carriers compared with controls. Gene Ontology (GO) enrichment analysis showed that upregulated genes were significantly enriched in terms related to neuronal and synaptic components, vesicle-mediated secretion, and ion channel complexes. Downregulated genes were enriched in GO terms associated with structural extracellular matrix organization, endoplasmic reticulum lumen, growth factor/Wnt signaling, and RNA polymerase II-mediated transcriptional regulation and repression. Weighted gene co-expression network analysis identified a module that was significantly negatively correlated with controls showing enrichment in the 22q11.2 CNV syndrome, impaired T cell function, and hypoparathyroidism. Within this module, 14 of 25 genes associated with 22q11.2 CNV syndrome pathway are regulated by hsa-miR-7-5p. These genes were significantly enriched in symptomatic 22q11.2 microduplication carriers compared with controls, whereas asymptomatic carriers showed a statistical trend toward enrichment. Expression analysis revealed significantly decreased levels of hsa-miR-7-5p in NPCs from affected carriers compared with controls, with a trend toward reduced expression compared with asymptomatic carriers. **Conclusions:** NPCs from 22q11.2 microduplication carriers exhibit a distinct transcriptomic signature relative to healthy controls, providing preliminary insight into the molecular impact of this microduplication on neural differentiation.

122: Neural lineage–specific transcriptomic signatures of intrafamilial clinical variability in a mother–child pair with 22q11.2 microdeletion

Danijela Drakulic[1], Ivana Hadzi Makuncevic[1], Natasa Kovacevic-Grujicic[1], Mina Peric[1], Friederike Ehrhart[2], Jovana Kostic[1], Stefan Lazic[1], Goran Cuturilo[3,4], Spyros Petrakis[5], David E. J. Linden[2], Adrian J. Harwood[2,6], and Milena Stevanovic[1,7]

[1]Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia; [2]Mental Health and Neuroscience Research Institute, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; [3]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [4]University Children's Hospital, Belgrade, Serbia; [5]Centre for Research and Technology Hellas (CERTH), Thessaloniki, Greece; [6]Neuroscience and Mental Health Innovation Institute, Cardiff University, Cardiff, UK; [7]Serbian Academy of Sciences and Arts, Belgrade, Serbia (current affiliation).

Background: In 22q11.2DS, the deletion arises *de novo* in over 90% of affected individuals, whereas in approximately 10% of cases is inherited from a heterozygous parent. Although the majority of patients (85–90%) carry the 2.5–3.0 Mb 22q11.2 microdeletion, 5–10% harbor the smaller 1.5 Mb (LCR22A–B) or 2 Mb (LCR22A–C) deletions. Clinical presentation is highly variable, with individuals in the second generation often exhibiting a greater number of clinical features and more severe phenotype compared to their transmitting parents. Individuals with 22q11.2DS are shown to be at increased risk for neurodevelopmental, cognitive, psychiatric, and social–emotional difficulties, with the literature suggesting association of smaller deletion size with a significantly higher risk of development of mental and behavioral abnormalities. **Methods:** To investigate intrafamilial neurodevelopmental differences that may influence clinical presentation, we analyzed the transcriptomic profiles of neural progenitor cells, neurons, and astrocytes differentiated from induced pluripotent stem cells derived from a mother and her child carrying a 1.5 Mb 22q11.2 microdeletion. **Results:** At the neural progenitor cell stage, differential expression analysis identified 204 downregulated and 165 upregulated genes in the symptomatic child relative to the asymptomatic mother. GO analysis revealed enrichment of immune-related, cell adhesion and synaptic pathways among downregulated genes, whereas no significant enrichment was observed for upregulated genes. In neurons, 2405 downregulated and 2294 upregulated DEGs were identified. GO analysis for upregulated genes revealed enrichment of pathways related to cholesterol biosynthesis and metabolism. In astrocytes, 178 genes were downregulated and 205 upregulated in the symptomatic child; however, GO analysis did not identify biological pathways that are enriched in DEG lists more than would be expected by chance. **Conclusions:** Transcriptomic analysis revealed cell type–specific molecular dysregulation underlying the symptomatic phenotype, with prominent alterations in immune, synaptic, and cholesterol-related pathways.

123: The effectiveness and safety of psychopharmacotherapy in 22q11.2 deletion syndrome

Doron Gothelf[1,2,3]

[1]The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [2]Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel; [3]The Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel.

The 22q11.2 deletion syndrome (22q11DS) is associated with high rates of psychiatric disorders across the lifespan, including ADHD, anxiety, mood disorders, and psychotic spectrum disorders, affecting most individuals with the syndrome. Despite this substantial burden, pharmacological treatment in 22q11DS remains challenging, and clinical decision-making has largely relied on evidence derived from the general population rather than syndrome-specific data. This lecture provides a comprehensive review of the evidence for the effectiveness and side effects of traditional psychiatric treatments in 22q11DS, covering antipsychotics, stimulants, and antidepressants. While these medications are generally effective, individuals with 22q11DS may be particularly vulnerable to certain adverse effects owing to the syndrome's medical comorbidities. Relevant safety considerations and practical monitoring recommendations will be discussed, with attention to cardiac, metabolic, and neurological risks that are of clinical importance in this population. The lecture will also review recent publications on medications affecting the glutamatergic system, an area of growing interest given the haploinsufficiency of the *PRODH* gene and alteration of glutamatergic signalling in 22q11.2DS mouse models. Overall, the aim of this lecture is to offer clinicians and researchers an up-to-date perspective on what is currently known about psychiatric pharmacotherapy in 22q11DS, and to highlight future directions for improving treatment outcomes in this population.

124: Targeting prefrontal chloride transport for cognitive remediation in 22q11.2 deletion syndrome and substance use disorders

Arghya Mukherjee[1,2]

[1]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]University of Pennsylvania, Philadelphia, PA, USA.

Background: Cognitive deficits are strong predictors of functional outcomes in schizophrenia and addiction. These deficits are associated with dysfunctional GABAergic inhibition and excitatory-inhibitory (E-I) imbalance in the prefrontal cortex (PFC). However, a targetable molecular mechanism of PFC E-I imbalance remains elusive. Postsynaptic potassium-chloride cotransporters (KCC2) mediate chloride homeostasis in adult neurons. Specifically, KCC2 maintains chloride levels required for inhibitory GABA-A receptor signaling. Using the 22q11.2 deletion (22q11DS) mouse model and a chronic methamphetamine use model we tested whether chloride dysregulation is a shared, targetable pathology underlying cognitive deficits. **Methods:** We measured PFC KCC2 expression and function in post-mortem human brains and animal models using snRNA sequencing, immunohistochemistry and slice physiology. Optogenetic perturbations, multi-electrode electrophysiology and chloride photometry was used to characterize the fidelity of PFC networks *in vivo*. To establish causality, we targeted KCC2 knockdown to the PFC of wild type animals and assessed working memory and behavioral flexibility on an attention control task. Finally, we used this pipeline to evaluate the therapeutic effects of a novel small molecule KCC2 activator. **Results:** KCC2 expression was reduced in the PFC of patients and animal models. *Ex vivo* recordings revealed depolarized GABA reversal potentials in the PFC, consistent with increased intracellular chloride. *In vivo*, KCC2 dysfunction was associated with reduced chloride dynamics, increased noise in PFC networks. These circuit dysfunctions were accompanied by deficits in working memory and cognitive flexibility, which were recapitulated through knockdown of KCC2 in PFC excitatory neurons, thus establishing causality. Systemic administration of a first-in-class KCC2 agonist rescued both physiological and cognitive deficits across animal models. **Conclusions:** Our study establishes KCC2 dysfunction as a conserved, therapeutically addressable contributor to cognitive deficits in psychosis and addiction. KCC2 agonism restores E-I balance through chloride normalization, offering a mechanistically distinct strategy from current antipsychotics for treating cognitive impairments across mental disorders.

125: Effects of riluzole on psychiatric symptoms, excitation-inhibition balance and functional connectivity in 22q11.2 deletion syndrome

Claudia Vingerhoets[1,2], Amy Sylvester[1], Desmond Tse[3], Jeltje Spapens[1], Sophie Kappert[1], Nele Soons[1], David Linden[1], Dimo Ivanov[3,4] and Therese van Amelsvoort[1]

[1]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands; [2]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [3]Max Planck Institute for Empirical Aesthetics, Frankfurt, Germany; [4]Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands.

Background: Imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) neural transmission is commonly implicated in the aetiology of psychiatric and cognitive dysfunction. Moreover, excitation-inhibition imbalance appears to correlate with functional connectivity in healthy populations. Genetically mediated disruption of neural excitation-inhibition balance is thought to contribute to the psychiatric profile of 22q11DS. Therefore, riluzole, a glutamate and GABA modulating FDA-approved drug, has the potential to reduce psychiatric symptoms. Here we examined the effect of riluzole treatment on psychiatric symptoms, excitation/inhibition balance and functional connectivity. **Methods:** 29 participants (19 females, mean age = 30.6, SD = 12.5) with a molecular confirmed diagnosis of 22q11DS were included in this placebo-controlled, fixed-order crossover trial. Eight participants also underwent MRI-scanning. All participants received placebo for 8 weeks, followed by 8 weeks of 100mg/day riluzole. 7-Tesla proton magnetic resonance spectroscopy (^{1}H-MRS) in the anterior cingulate cortex (ACC) and resting-state functional MRI data were acquired after the placebo and riluzole intervention periods. **Results:** Riluzole had no significant effect on psychotic symptoms. However, exploratory analyses indicated that riluzole reduced anxiety (p = 0.001) and impairments in abstract thinking (p = 0.039) compared to baseline. Riluzole administration was associated with a non-significant reduction in glutamate concentration and increase in GABA concentration. After placebo, activity in the ACC seed region was significantly correlated with primary nodes of the salience network (insula) and the cortico-striatal-thalamic loop (putamen, caudate, thalamus). There was no significant change in functional connectivity between the ACC seed and any of these voxels after riluzole administration. **Conclusions:** Our results suggest riluzole may have beneficial effects on anxiety and cognition. However, given the limited sample size and high levels of individual variability, these findings must be taken with caution. Future studies should aim to replicate these findings in a larger sample and attempt to stratify participants by baseline excitation-inhibition imbalance.

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126: Ten-year retrospective review of psychotropic medication use in individuals with 22q11.2 deletion syndrome *

Samuel Alperin[1,2,3], Sarah Hopkins[1,2,3], Madeline Chadehumbe[4], T. Blaine Crowley[3,5], Daniel E. McGinn[3,5], Audrey Olson[3,5], Oanh Tran[3,5], R. Sean Gallagher[7,8], Kosha Ruparel[7,8], Ruben Gur[7,8], Elaine H. Zackai[3,5,6], Beverly S. Emanuel[3,5,6], Raquel Gur[7,8], and Donna M. McDonald-McGinn[3,5,6]

[1]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Neurology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]NeurAbilities Healthcare, Voorhees, NJ, USA; [5]Division of Human Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [7]Lifespan Brain Institute (LiBI) of the Children's Hospital of Pennsylvania (CHOP) and Penn Medicine Philadelphia, PA, USA; [8]Department of Psychiatry, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

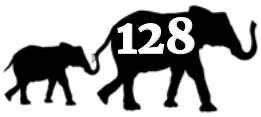
Background: 22q11.2 deletion syndrome (22qDS) is associated with a variety of behavioral and psychiatric disorders. Attention-deficit/hyperactivity disorder (ADHD) is one of the most common and frequently requires pharmacologic intervention. However, real-world prescribing patterns is poorly characterized and there is frequently a question of which of the options available for ADHD is most likely to be successful. This study examined medication utilization and treatment duration over a ten-year period within the 22q and You Center at the Children's Hospital of Philadelphia (CHOP). **Methods:** We conducted a retrospective chart review under IRB approval of individuals with a laboratory confirmed 22q11.2 deletion treated at CHOP between January 2016 and January 2026. Prescription data were extracted via the electronic medical record and consolidated to determine continuous treatment intervals. Medications were categorized as methylphenidate, amphetamine, alpha agonist (guanfacine or clonidine), SNRI (atomoxetine or viloxazine), or other. Outcomes included total number of patients, total prescriptions, most common medications and categories, and longest observed duration of use by category. **Results:** The final cohort included 93 patients with a total of 2,365 prescriptions recorded during the study period. The most commonly used individual medication was guanfacine hydrochloride extended-release. However, the most frequently utilized drug category overall was methylphenidate. The longest observed duration of use by category was 3,484 days for amphetamines, 3,455 days for methylphenidate, 2,654 days for alpha agonists, and 1,714 days for SNRIs. Stimulant medications demonstrated the greatest overall treatment persistence. **Conclusions**: In this ten-year retrospective review of individuals with 22qDS, stimulant medications were both the most prescribed and associated with the longest duration of use. Additional analyses will include subsequent diagnosis of additional neuropsychiatric conditions to provide real-world evidence to inform pharmacologic management strategies in this complex population.

127: Exploring the relationship between ADHD medication and psychotic symptoms in 22q11.2 deletion syndrome

Claudine B. Van Arman[1], Arielle Ered[1,2], Tyler M. Moore[1,2], Austin T. Moran[1], Alyssa M. Neppach[1,2], Mia Schwartzberg[1], R Sean Gallagher[1], Simon Smerconish[1,2], Kosha Ruparel[1, 2], Scott Troyan [1, 2], Amy Cassidy[1,2], Lauren K. White[2], T. Blaine Crowley[3], Daniel E. McGinn[3], Audrey Olson[3], Oanh Tran[3], Elaine H. Zackai[3,4], Beverly S. Emanuel[3,4], Ruben C. Gur[1,2], Donna M. McDonald-McGinn[3,4], and Raquel E. Gur[1,2]

[1]Neurodevelopment & Psychosis Section, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA USA; [2]Lifespan Brain Institute, Penn Medicine and Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]22q and You Center, Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

Objective: 22q11.2 Deletion Syndrome (22qDS) is associated with increased risk for neuropsychiatric disorders, including Attention Deficit/Hyperactivity Disorder (ADHD) in childhood and psychosis spectrum disorders in adolescence and early adulthood. In non-deleted individuals, stimulant medication has been associated with later onset psychosis symptoms. Many individuals with 22qDS utilize medications as part of treatment for ADHD, categorized into methylphenidate-based stimulants, amphetamine-based stimulants, and non-stimulant medications, providing an opportunity to examine potential mechanisms linking ADHD and its treatment to later onset psychosis. **Methods**: Data from three CHOP-Penn NIMH funded studies will be used to explore psychosis-spectrum symptoms in individuals with 22qDS with an ADHD diagnosis and compare psychosis symptoms between 1) methylphenidate, 2) amphetamine and 3) non-stimulant ADHD medication users. Next, the treated 22qDS cohort will be compared to deleted individuals with ADHD on no medication. Dosage will be harmonized by converting to dextroamphetamine equivalents, stratified by low to high dose. Psychosis spectrum symptoms were assessed using the Scale of Prodromal Symptoms positive symptom items, and medication dose and duration was collected by self-report and CHOP Electronic Medical Record. **Analysis:** An ANOVA comparing severity of positive symptom by medication group (methylphenidate, amphetamine, and non-stimulant) within the 22qDS with ADHD sample will be used, further investigated by adding medication dose level (low vs. high). Covariates will additionally be investigated. **Hypothesis:** We hypothesize that amphetamines will be associated with the highest psychosis symptoms, followed by methylphenidate, and non-stimulants will be associated with the lowest psychosis symptoms. **Implications**: These findings will help to uncover the influence of ADHD medication on positive psychotic symptoms in groups at high-risk for developing psychosis due to a rare copy number variant. The findings will help inform medication options for individuals with 22qDS and ADHD, who are at an increased risk of developing psychosis.

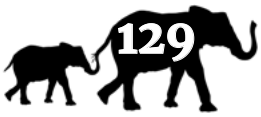


128: Patients with 22q11.2 deletion syndrome - Too challenging to treat?

Anne S. Bassett[1]

[1]*Department of Psychiatry, University of Toronto, Dalglish Family 22q Clinic, University Health Network, and Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada.*

Background: The complexity of individuals with 22q11.2 deletion syndrome (22q11.2DS) may be daunting to many health care professionals, and to caregivers. This may especially be the case with respect to the psychiatric features of this genetic condition. **Methods:** Using a narrative (qualitative) study method, we reflected on the wisdom of clinicians with over 100 collective years of experience with 500+ adult patients with 22q11.2DS at a single dedicated centre. **Results:** While undoubtedly recognizing the multi-system nature of the genetic condition, most clinical specialists and general practitioners accepted the challenge of caring for patients with 22q11.2DS. Disproportionately, however, psychiatric specialists and clinical teams in the community were exceptions in this regard. Many early psychosis intervention programs routinely exclude patients with developmental delay and/or intellectual disability, and many psychiatrists turn away patients with 22q11.2DS patients, citing complexity. Attributing signs and symptoms of serious but treatable psychiatric illness to "behaviour" often led to years of multiple therapy trials before accurate diagnosis and implementation of standard treatment. From the family/caregiver perspective, fears of psychiatric diagnostic labels and/or of evidence-based medications hindered or delayed delivery of standard-of-care, in contrast to usually immediate acceptance of comparable neurologic, endocrinologic, or cardiac diagnoses and treatment recommendations. Help-seeking in alternatives such as non-evidence-based therapies, or self-treatment with actively harmful alternatives such as cannabis, was common. **Conclusions:** If individuals with 22q11.2DS were known to be at a 1 in 4 risk of developing a severe yet treatable form of non-psychiatric illness (e.g., cancer), optimizing diagnosis and providing standard-of-care management would likely be a matter of urgency to healthcare systems, clinicians, and caregivers. Mechanisms to address systemic issues in clinical practice, and in the general population, related to recognizing psychotic illness and considering individuals with serious but treatable psychiatric illness worthy of care, are needed.

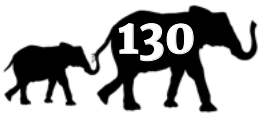


129: Resolution of dysautonomic "seizure-like" episodes following antipsychotic withdrawal in an adult with 22q11.2 deletion syndrome and prior scoliosis surgery

Madeline A Chadehumbe[1,2], Donna M. McDonald-McGinn[3,4,5], and Raquel E Gur[1,2]

[1]Department of Neurology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [2]NeurAbilities Healthcare, Voorhees, NJ, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Division of Human Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA; [5]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [6]Lifespan Brain Institute (LiBI) of the Children's Hospital of Pennsylvania (CHOP) and Penn Medicine, Philadelphia, PA, USA; [7]Department of Psychiatry, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (22q11.2DS) is associated with high rates of neuropsychiatric illness, epilepsy, and movement disorders such as early-onset parkinsonism. Up to 30% of adults develop psychotic disorders requiring antipsychotics, which can induce autonomic dysfunction through dopamine D2 receptor blockade. Additionally, scoliosis surgery - especially anterior approaches or instrumentation extending to lumbar levels - may injure the sympathetic chain, causing dysautonomia. These overlapping vulnerabilities can produce paroxysmal non-epileptic events (PNEE) mimicking seizures. **Case Description:** A 45-year-old man with confirmed 22q11.2DS, prior scoliosis surgery, and a Vagal Nerve Stimulator (VNS) for epilepsy (in remission since 2023) experienced frequent brief episodes of altered awareness, preceded by a white light, tachypnea, diaphoresis, and transient unresponsiveness. Episodes occurred mainly while seated and sometimes responded to VNS magnet activation. Prolonged video-EEG and Holter monitoring showed no epileptiform or cardiac abnormalities, confirming PNEE. He had chronic psychosis with auditory hallucinations and prior exposure to multiple antipsychotics (risperidone, quetiapine, aripiprazole, lurasidone, clozapine, ziprasidone, olanzapine), with parkinsonism and postural tachycardia on exam. After gradual antipsychotic discontinuation under close supervision, episodes resolved without psychotic relapse, and parkinsonian features improved. This suggests a multifactorial dysautonomic mechanism from chronic antipsychotic exposure compounded by possible sympathetic chain disruption from scoliosis surgery. **Discussion:** This case highlights the convergence of autonomic vulnerabilities in 22q11.2DS. Chronic antipsychotic use disrupts dopaminergic regulation of autonomic tone, while prior scoliosis surgery can cause lasting sympathetic dysfunction. Combined with the intrinsic autonomic instability of 22q11.2DS, these factors likely triggered the observed paroxysmal episodes. Awareness of these interacting mechanisms may prevent misdiagnosis and unnecessary antiseizure therapy escalation. **Conclusion:** Antipsychotic-induced dysautonomia, amplified by prior surgical sympathetic injury, can manifest as seizure-like events in 22q11.2DS. Clinicians should balance psychiatric management with vigilance for autonomic effects and tailor treatment to minimize compounded side effects.



130: Psychiatric management concerns in the transition from pediatrics to adult 22q providers

Kerry D. Conant[4], Ashmita Banerjee[1, 4, 6], Matt Blessing[1, 2], Gary Stobbe[1, 5, 6], and Emily Gallagher[1, 2, 3, 4]

[1]University of Washington, Seattle, WA, USA [2]Department of Pediatrics, University of Washington, Seattle, WA, USA; [3]Department of Global Health, University of Washington, Seattle, WA, USA; [4]Seattle Children's Hospital, Seattle, WA, USA; [5]Department of Neurology, University of Washington, Seattle, WA, USA; [6]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA.

Background: Psychiatry as an embedded service within a pediatric interdisciplinary 22q11.2-related disorders (22q) clinic has unique challenges affecting the transition of care to adult providers. Even with availability of qualified adult providers, transitioning psychiatric care is complicated by young adulthood being a vulnerable time for emerging mental health concerns. The purpose of this case review was to understand the factors that lead to a successful transition and identify barriers to transitioning psychiatric care. **Methods:** We reviewed records for 22q adult patients seen by Psychiatry from 2019-2025 and identified thirty-five unique patients. Of these thirty-five, only thirteen had successfully completed the referral process to establish care with adult 22q providers. Of these thirteen, 10 patients received overlapping care with a pediatric psychiatry provider while establishing care with the adult 22q provider. We will discuss salient cases, identify important lessons learned, and provide recommendations for successfully transitioning psychiatric care during early adulthood. **Results:** Barriers to transitioning care ranged from patient factors to clinic factors. Patient factors included active mental health concerns, emerging catatonia, active medical comorbidities, history of early psychosis or previous transient psychiatric symptoms, and difficulty participating in the interview due to intellectual disability. We also review the reasons for the referrals or transfers not completed. **Conclusions:** Transition of psychiatric care in 22q requires considerable preparation and overlap of care for a successful bridge to adult care. There is a rationale for continuing with the same psychiatric provider beyond the transition to adulthood as it may not be an appropriate time to transfer depending on the acute needs of the patients at this critical time for emergent mental health concerns. We highlight the need for overlapping care and close collaboration during an overlapping transition of care for greater comfort for the patient/family and better mental health outcomes overall.

131: Feasibility and acceptability of BE-WEHL-22q: a virtual wellness program for children with 22q11.2 deletion syndrome and their families

Luc Santilli[1], Alain J. Benitez[1,2], Audrey Olson[3], Lydia Rockart[3], Robin Miccio[1], Lauren White[2,4], Donna McDonald-McGinn[2,3,5], and Maria Mascarenhas[1,2,3]

[1]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia; [4]Department of Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, [4]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

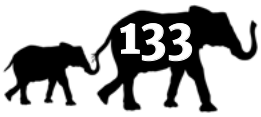
Background: Anxiety in association with 22q11.2 deletion syndrome (22q11.2DS) is well described and may precede psychosis onset, yet few interventions have been developed. We established "BE-WEHL-22q," an 8-week virtual wellness education program incorporating mindfulness, yoga, caring touch, sleep hygiene, and nutrition education, adapted for children with 22q11.2DS and their families. This pilot study evaluated the program's feasibility and acceptability. **Methods:** Children aged 7–14 years with a laboratory confirmed 22q11.2 deletion and at least one caregiver were recruited into this IRB-approved study consisting of eight virtual sessions including Coping and Resilience, Mindful Movement Yoga, Healthy Eating, and a 22q11.2DS-specific parenting session. Feasibility was assessed by enrollment, retention, and attendance rates. Acceptability was evaluated through satisfaction surveys, caregiver feedback, and practice log completion. Stool samples for microbiome analysis with accompanying diet records were obtained. **Results:** Forty-three families enrolled; 14 completed the full program (88% retention among families who began classes). Participants had a median age of 11 years (52.2% female; 79.5% white). Average session attendance was 8 of 8 sessions. Feedback was overwhelmingly positive, with one family noting the program "changed [their] family's health substantially." Families frequently engaged additional household members, demonstrating reach beyond the enrolled dyad. Caregivers described sessions as relaxing, informative, and engaging. The 22q11.2DS-specific parenting session received particularly strong feedback, described as "great" and "VERY helpful." Beyond the wellness program, need for contributing biological samples and diet history impacted participation in the program for a subset of families. **Conclusions:** BE-WEHL-22q is a feasible, well-received virtual wellness program for families affected by 22q11.2DS. Strong retention, high satisfaction, and family engagement beyond the enrolled dyad support its acceptability. The virtual format enabled participation across geographic barriers, important for rare disease populations. These findings support advancement to a larger efficacy trial examining BE-WEHL-22q's impact on anxiety, resilience, and brain-gut axis biomarkers.

132: Current findings and future directions from the IBBC-G2MH

Raquel E. Gur[1, 2]

[1]Neurodevelopment & Psychosis Section, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [2]Lifespan Brain Institute, Penn Medicine and Children's Hospital of Philadelphia, Philadelphia, PA, USA

The presentation of 22q11.2 deletion is complex and challenging requiring large sample sizes in a rare disorder. Global and ongoing collaborations have provided unique opportunities for attaining sufficiently powered samples through efforts from investigators and trainees with converging expertise to push forward a scientific agenda in partnership with individuals and families. The presentation will highlight the initiatives of the IBBC, building on foundations set by leaders in the 22q11.2 society. Major findings will be summarized to provide examples of the contributions to the field. These efforts have stimulated grant support and led to expanding the collaborations to other CNVs in the G2MH network. Initial findings from this effort will be summarized. The ongoing collaborations have expanded to multiple domains that have been supported by different granting agencies and provide the multilevel approach necessary to elucidate underlying mechanisms and advance treatment. Examples from neuroimaging, preclinical and sleep studies illustrate progress made. Will conclude by discussing future directions that capitalize on what we have learned, advances in technology and the gaps we wish to address between scientific discoveries and clinical applications that can benefit affected individuals and their families.



133: Seeing the Whole Elephant: AI-Powered Discovery Across a Referral Center's 22q Experience

Ian Campbell[1,2]

[1]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

A child with 22q11.2 deletion syndrome may see cardiology, immunology, endocrinology, plastic surgery, behavioral health, and genetics over the course of two decades. Each clinician documents their piece. Experienced providers develop remarkable intuition for these patterns, but translating that intuition into systematic, reproducible evidence across hundreds of patients has traditionally required months of manual chart review--if it happens at all. We describe an AI system that accepts clinical questions in plain language and returns structured case series by searching the complete medical record of a large pediatric referral center. The system can search every document written over the past twenty years for over 1.6 million patients. An automated pipeline identifies candidate patients through multi-stage review, confirms each case against user-specified criteria with citations to source documentation, extracts structured answers, and generates a report. Because the system reads the clinical narrative rather than relying on billing codes, it can discover patients and findings that were never formally coded. We demonstrate the system applied to our institution's 22q11.2 deletion syndrome population and discuss how the same approach could be used by any 22q center to systematically investigate clinical questions across their own cohort, from treatment outcomes and complication rates to pre-diagnosis phenotypic patterns. The framework is designed to put institutional experience at researchers' fingertips: any clinician or researcher with a question can go from hypothesis to structured case series in minutes rather than months. We discuss the accuracy and limitations of computationally derived case series, the biases inherent in retrospective clinical data, and the potential for extending this approach across 22q centers, where each institution searches its own records locally and de-identified results aggregate across sites without protected health information leaving any building.

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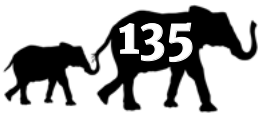
134: An exploratory study using machine learning to detect clinical patterns for 22q11.2 deletion syndrome *

Lais A. Soares[1], Guilherme P. Coelho[1], Vera L. Gil-da-Silva-Lopes[2], João Pedro Moretti[2], and Ana E. A. Silva[1]

[1]Faculty of Technology, University of Campinas (Unicamp), Limeira, São Paulo, Brazil; [2]Department of Medical Genetics and Genomic Medicine, School of Medical Sciences, University of Campinas (Unicamp), Campinas, São Paulo, Brazil.

Background: 22q11.2 deletion syndrome (22q11.2DS) is a congenital disorder that affects approximately 1 in 2,000–6,000 live births. Its suspicion is complicated by clinical heterogeneity. Approximately 66% of clinically suspected cases are confirmed through genetic testing. Given that over 180 clinical features have been described for 22q11.2DS, traditional pairwise correlation analyses are insufficient to fully capture the complexity of its phenotype. Association rule mining provides a multivariate framework for identifying complex relationships among phenotypic characteristics and may help improve current screening protocols. **Methods:** This study analysed data from 276 Brazilian individuals with confirmed 22q11.2DS, collected under standardised medical protocols via the CranFlow application. From an initial set of 733 attributes, 48 clinically relevant variables were selected according to established diagnostic suspicion criteria. Variables with ≥50% missing values and low variance (<0.01) were excluded, leaving 36 attributes for analysis. Missing data were treated as a separate category to avoid bias from imputation. Variables were transformed using one-hot encoding, and the Apriori algorithm was applied with a minimum support of 0.05 and confidence of 0.70. **Results:** Association rules were generated with confirmed 22q11.2 deletion status specified as the consequent. Analysis across different support thresholds (0.3, 0.4, and 0.5) revealed a consistent hierarchical phenotypic structure. Three features, hooded eyelids, hypernasal speech, and labiopalatal abnormalities, remained stable across all levels, representing the core phenotypic cluster. At intermediate support (0.4), additional features, including generalised cardiac malformations and elongated face, emerged, defining an expanded phenotype. Lower support (0.3) identified rarer manifestations, including alar hypoplasia, atrial septal defect, and ventricular septal defect. **Conclusions:** These findings suggest that association rule mining may help identify both core and less frequent phenotypic patterns, potentially contributing to refining diagnostic strategies and improving screening for 22q11.2DS.



135: Multisystem medical burden in 22q11.2 deletion syndrome - managing associated complex care

T. Blaine Crowley[1,2], Evie Andrewes[1,2], Audrey Green[1,2], Daniel E. McGinn[1,2], Lily Elman[1,2], Lydia Rockart[1,2], Lydia Hamilton[1,2], Elaine H. Zackai[1,2,3], and Donna M. McDonald-McGinn[1,2,3]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

Background: 22q11.2 deletion syndrome (22q11.2DS) is a common condition characterized by marked phenotypic variability and multisystem involvement, often requiring complex and lifelong medical management. While the clinical manifestations of 22q11.2DS are well documented, less attention has been given to the cumulative care burden placed on families responsible for coordinating multidisciplinary care. Methods: Accounting for changes in healthcare delivery following the COVID-19 pandemic, under IRB approval, we retrospectively examined 762 completed outpatient visits occurring within the 22q & You Center at the Children's Hospital of Philadelphia between 2022 and 2025. All provider recommendations for follow-up with subspecialty practices were tracked. Patient demographics, payor type, visit type, and social histories were also collected. Results: Five-hundred-and thirteen unique children had 762 visits, and 247 visits were categorized as new patient visits (32% of all visits, 48% of all children). Across all visit types, the mean number of subspecialty recommendations was 9. Mean number of recommendations for new patient visits was 13 and follow-up visits was 7. Follow-through on all recommendations occurred 34% of the time. New patients evaluated at one year of age or younger were much more likely to complete all recommendations (86%). Follow-up patients, regardless of age, were far less likely to complete recommendations (28%). Families with private health insurance and government insurance were equally likely to follow-through on recommendations. No singular diagnosis (i.e. CHD) impacted hospital-wide recommendation follow-through. While all follow-through declined with patient age. Conclusions: The extensive medical and developmental needs associated with 22q11.2DS create a substantial coordination burden for caregivers, who often function as primary managers of complex care systems. Emerging evidence suggests that caregiver stress and burnout are common in this population. Multidisciplinary clinical models and integrated care pathways may help reduce fragmentation of services, improve health outcomes, and mitigate caregiver burden in families affected by 22q11.2DS.

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136: Stakeholder survey in 240 members of and other relevant parties related to the Dutch 22q11 foundation

Kim van Bekkum[1], Erik Boot[2-4], Sasja Duijff[5], Ania Fiksinski[6,7], Michiel Houben[8], Petra Oostema[1], and Claudia Vingerhoets[2,3]

[1]Stichting Steun 22Q11, Uden, The Netherlands; [2]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Institute (MHeNS), Maastricht University, Maastricht, The Netherlands; [3]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [4]The Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada; [5]22qMinded, The Netherlands; [6]Department of Psychiatry and Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; [7]Department of Psychology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [8]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Background: Stichting Steun 22Q11, the Dutch Foundation supporting individuals with a 22q11.2 deletion or duplication and their families, in 2025 conducted an online survey among its members and other relevant parties to assess the experiences, needs and priorities of its stakeholders. **Methods:** A survey with 43 open-ended and closed-ended questions was distributed via direct emails to the Foundation's members, sponsors, and other direct stakeholders (n=300), and via social media (n=1.517 facebook group members, and n>6.400 followers).
Results:
A total of 240 (80%) respondents (mostly family members/caregivers) reported on (i) experiences with current and (ii) suggestions for future Foundation services and activities, (iii) societal impact of 22q11DS, (iv) membership, and (v) social media/visibility. Most of the Foundation's services (e.g. knowledge transfer, parental contact, research promotion) are well known to the respondents and the majority is also considered very important. Some services are less known and valued lower. Several activities have been attended at least once by approximately 50% of the respondents (family, zoo, and study day). The most important reasons to attend were peer support (32%), family-orientation (31%) and experience exchange (16%). Reasons for non-attendance were travel distance (22%), time impact (10%) and health issues (6%). Future Foundation services and activities were suggested for several domains: organization & partnerships, professional education, media awareness, age-specific (e.g. adult) programs, and novel activities & support care. The overall societal impact of 22q11DS was reported large: adequate medical care was reported in 48%, suitable education in 33%, and sufficient societal and financial support in 27% and 25%. Respondents' remarks (36%) often included limited (professional) understanding and support, and limited capacity after transition into adult care. **Conclusions:** The key findings from these analyses, and those on Foundation membership and on social media/visibility will be presented during the conference.

137: Caregiver burden and support needs in caregivers of adults with 22q11.2 deletion syndrome

Lisa Palmer[1], Tracy Heung[1,2], Nikolai Reyes[1, 2, 4,5], Samantha D'Arcy[1], and Anne S. Bassett[1,2,3]

[1]The Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada; *[2]Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada*; *[3]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada*; [4]*Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada;* [5]*Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada.*

Background: Adults with 22q11.2 deletion syndrome (22q11.2DS) often require lifelong support due to complex medical, cognitive, and psychosocial challenges. Caregivers play a critical role in managing these needs, yet the burden they experience, and their support needs, remain underexplored. **Methods:** We assessed caregiver burden using the standardized Zarit Burden Interview (ZBI) and examined current supports and anticipated future support needs using a brief survey created by clinical staff at our clinic for adults with 22q11.2DS. We assessed burden for unaffected caregivers (n=14, all relatives living with the adult with 22q) of 11 adults (median age 23.3, range 19.4-33.6 years; n=8 male) with a typical 22q11.2 deletion consecutively assessed at the clinic. We examined the relationship between caregiver burden and major features of 22q, including moderate-severe congenital heart defect (CHD, n=4), moderate-severe intellectual disability (ID, n=3) and psychotic illness (n=4) and explored common themes related to caregiver support needs. **Results:** Overall, ZBI scores indicated experience mild-moderate levels of caregiver burden (median score 37.5, range 14-61). There was no significant effect of ID or CHD on burden; however, caregivers of adults with 22q11.2DS and psychotic illness reported significantly higher burden (median score 51.5, range 35-61, vs 28.0, range 14-48 p=0.02). The most common current supports reported were family, friends, and the Adult 22q Clinic. The most frequently identified future support needs were related to housing and future planning for the adult with 22q. **Conclusions:** Caregivers of adults with 22q11.2DS experience substantial burden, particularly when psychotic illness is present. Although identifying many current informal supports, caregivers expressed significant concern about housing options and long-term care planning. These findings highlight the need for specialized support for caregivers and for targeted supports related to housing and long-term care planning for adults with 22q.11.2DS.

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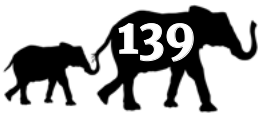
138: Optimizing 22q care: the impact of a single-day multidisciplinary clinic model

Jessica Goldberg[1], Valerie J Allegretti[2], Kelly Regan-Fendt[2,3], Jalen Clemmons[2], Sylvie Render[4], Mitch Bastillo[4], Elizabeth Lippner[5,3], Jennifer Miller[6,3], Naiomi Gunaratne[6,3], Margaret Ryan[6], Edward Jones[7,3], Chanel Howard[1], Ryan Cyzman[1], and Laura Swibel Rosenthal[1,3]

[1]Division of Otolaryngology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA; [2]Edwards Family Division of Genetics & Rare Diseases, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA; [3]Northwestern University Feinberg School of Medicine, Chicago, Illinois; [4]Department of Speech Language Pathology, Division of Rehabilitative Services, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA; [5]Division of Immunology, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA,[6]Division of Endocrinology, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA; [7]Division of Cardiology, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA.

Background: Traditionally, care for patients with 22q chromosomal abnormalities is fragmented across multiple specialties. In 2017, a "one stop" model of care was implemented. By 2025, the 22q Center was well-established to address challenges in diagnosis, workup, and adherence to established clinic care guidelines. **Methods:** A retrospective review of 180 pediatric patients, 0-21 years old, who opted to enrolled in the multidisciplinary clinic was conducted between 2015 and 2025. A core team of specialists evaluated patients during each monthly morning clinic session. Post-clinic conferences, with an expanded care team, were held to synthesize recommendations and develop the clinical program. Data were analyzed to assess the experience for patients, caregivers, and providers. **Results:** Patients completed a mean of 7.8 encounters (ranging from 1-10) per clinic visit in 2025, a significant increase from 1.4 encounters (ranging from 1-2) in 2015. By 2025, all patients were seen by genetics, social work, and child life, 90% by immunology and endocrinology, 80% by otolaryngology and phlebotomy, 75% by speech language pathology, and 60% by audiology. Patient/caregiver feedback was overall-positive, noting travel time reductions and improved communication between providers. Data shows improved time to completion and adherence to screening guidelines, increased patient/caregiver preparedness, and increased compliance with procedures. Volumes grew from 5 to a capacity-limited 52 patients per year, with data showing patient retention and reduced wait times. Providers reported successful implementation of clinical programs, educational programs, quality improvement projects, and improved adherence to clinical practice recommendations. **Conclusions:** The collaborative team culture created by combining expertise in this centralized care model resulted in streamlining the management of 22q chromosomal abnormalities. As clinic capacity and programmatic initiatives continue to grow, this model demonstrates a sustainable and effective approach for delivering complex, multidisciplinary care, while also serving as a robust platform for ongoing medical education and professional development.



139: Improving efficiency in the 22q deletion clinic *

Eme Ani[1], Felmy Ajayi[1], Hui Yann, Hui Yann Yap[1], Chayanuch O. Charoenrat[1], and Alice Roueche[1,2]

[1]King's College London, London, UK; [2]Guy's & St Thomas' Hospital NHS Foundation Trust, London, UK.

Background: The 22q11.2 paediatric specialist service at Evelina Hospital manages complex patients, which leads to prolonged outpatient appointments due to a lack of specialists in the country. This Quality Improvement (QI) project aimed to streamline the service by implementing a pre-clinic questionnaire, with the primary goals of reducing in-person clinic duration and improving patient satisfaction. **Methods:** Between October 2024 and February 2025, carers of patients scheduled for the 22q11.2 clinic were contacted by telephone before their appointments to identify and triage key concerns. We compared the clinic durations of this intervention group (n=13) against retrospective baseline data from pre-intervention patients (n=23) using an independent t-test. Additionally, carer satisfaction was assessed via an in-person post-clinic questionnaire. **Results:** The intervention significantly reduced mean clinic duration by nearly half, dropping from 61.83 minutes (SD = 15.32) pre-intervention to 33.55 minutes (SD = 6.41) post-intervention ($p < 0.001$). A Spearman's rank analysis showed a weak negative correlation between pre-clinic call length and in-person clinic duration ($rs = -0.25$, $p = 0.21$). Post-clinic feedback was overwhelmingly positive: 100% of carers felt their clinical concerns were fully addressed, and 54% specifically reported that the pre-clinic call improved their overall hospital experience. **Conclusion:** Implementing a pre-clinic questionnaire significantly reduced face-to-face clinic duration ($p < 0.001$) while maintaining high satisfaction and care standards. The weak correlation between call length and clinic duration suggests that efficiency gains stem from proactive pre-visit preparation rather than simply shifting consultation time to the phone. Future PDSA cycles will focus on optimising call scheduling and exploring digital questionnaire alternatives to improve sustainability.

140: Geographic impacts of healthcare utilization for patients with 22q11.2 deletion/duplication in the pacific northwest

Emily R. Gallagher[1, 2], Jade Singleton[2], and Kristy Carlin[2]

[1]University of Washington, Seattle, WA, USA; [2]Seattle Children's Research Institute, Seattle, WA, USA.

Background: Our 22q Program provides multidisciplinary care for >700 patients with 22q11.2-related disorders (22q), most of whom have complex medical needs and high healthcare utilization. Although most patients live in-state, many come from surrounding states or beyond. Our state is vast, and patients living in-state often have large geographic areas and natural barriers (i.e., mountain passes or bodies of water) that complicate access to care. We conducted a descriptive study to evaluate healthcare utilization by geographic location and travel barriers. **Methods:** We queried our EMR for diagnoses, zip codes, and billing and procedure codes. We calculated visit rate per patient-year Incidence Rate Ratios (IRRs) for patients <50 versus ≥50 miles from our center, as well as for those with natural barriers and from out-of-state. Primary outcomes were visits in 22q Clinic and other subspecialty clinics. Secondary outcomes included telemedicine visits, no-shows, ED visits, hospitalizations, and procedures. **Results:** There were no significant differences in utilization between patients living ≥50 versus <50 miles from our center for visits in 22q Clinic or most subspecialty clinics. However, patients living ≥50 miles away or across a mountain pass had higher IRRs for immunology visits and lower IRRs for ED visits. Patients traveling from out-of-state were less likely to have no-show visits and to use telemedicine. Both local and non-local in-state patients used telemedicine. **Conclusions:** Patients with geographic barriers accessed care at comparable rates to local patients. Telemedicine was used regardless of distance. Lower no-show rates likely reflect advance planning between families and the care team for patients who travel. Lower ED visits likely reflect access to local services. Increased immunology utilization may reflect regional workforce limitations or greater clinical complexity among patients living farther away from our center.

141: Shorter distance to main academic center associated with better longitudinal care and follow up in adult patients with 22q11.2 deletion syndrome *

Jasmyn Atalla[1], Blaine Crowley[2,3], Kathleen Sullivan[1,2,4], Jennifer Heimall[1,4], Donna M. McDonald-McGinn[2,3,4], and Timothy Buckey[1,4]

[1]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (DS) is the most common chromosomal microdeletion syndrome and a leading cause of developmental delay, congenital heart disease, and T cell immunodeficiency. While research centers on diagnosis and childhood outcomes, understanding of adult complications and access to care remains limited. We examined how geographic proximity vs other socio-economic factors affect specialty care utilization and survival in adults. **Methods:** We conducted a retrospective chart review of adults (≥18 years) with confirmed 22q11.2DS seen at the 22q and You Center at Children's Hospital of Philadelphia (CHOP) between 2001-2025. Exclusions included 22q11.2 duplication, residence >100 miles from CHOP, and no documented visit between 2001-2025. **Results:** Of 419 adults with 22q11.2DS, patients averaged 105 clinical visits and 36 unique diagnoses over the 24-year study period. Most followed specialties (% of cohort, mean # visits) were Cardiology (57%, 14), Genetics (49%, 4), Endocrinology (43%, 11), Orthopedics (43%, 11), Allergy/Immunology (38%, 6), Gastroenterology (26%, 13), Pulmonology (14%, 11), and Hematology/Oncology (12%, 10). Over 60% of patients underwent diagnostic procedures, averaging 22 per patient. Food allergy (21%, n=86) and asthma (20%, n=82) rates exceeded national averages, while allergic rhinitis was similar (27%, n=112) and eczema lower (3%, n=11). Patients living within 25 miles of CHOP (n=187) averaged 138 visits, compared with 79 visits among those 26-100 miles (n=232; $p<0.001$). Shorter distance to CHOP was associated with more visits, diagnoses, specialties, and diagnostic procedures, while socioeconomic status, measured by median household income for zip code, was not associated with diagnostic burden or visit frequency. **Conclusions:** Access to a tertiary 22q center is associated with increased healthcare access and specialty longitudinal care, along with a lower mortality rate in our 22q11.2DS cohort (2%, n=8) compared to the estimated 24% for inborn errors of immunity. Further study is needed to define adult disease burden in 22q11.2DS.

142: Where do we go from here? Strategies to support successful transition to adult interdisciplinary care from a pediatric 22q center

Matthew Blessing[1,2], Kerry Conant[2], Gary Stobbe[2,3], and Emily Gallagher[1,2]

[1]*Division of Craniofacial Medicine, University of Washington, Seattle, WA, USA;* [2]*Seattle Children's Hospital, Seattle, WA, USA;* [3]*Adult Autism Center, University of Washington, Seattle, WA, USA.*

Background: Patients with 22q11.2-related disorders require interdisciplinary care long-term. Historically, our team has struggled to transition our adult patients to a comparable specialty medical home. Consequently, we have continued to care for many young adult patients in our pediatric program. **Methods:** As part of a transition program, we have collaborated with a clinic that provides interdisciplinary care to adults with neurodevelopmental disabilities. They have developed an Adult 22q Program (AP). Over the past 2+ years, we have begun to introduce this option to patients and families. At our inaugural 22q Parent & Caregiver Education Day, a didactic with representatives of both programs was shared. We have well-integrated electronic medical records, allowing efficient sharing of information between programs. A chart review was conducted of all patients 19+ years old followed in our center, reviewing number of visits with providers of any specialty, whether a referral was placed to the AP, how many visits have been completed at the AP, and patients' distance from the AP. **Results:** 49 of 56 patients were seen in our center within the past 5 years, with 28 referrals placed to the AP. 3 families declined referral. In some cases, the AP has been introduced, but referral not yet placed, primarily in teenagers who have not reached adulthood. 6 patients have completed in-person and 13 have completed telemedicine visits with the AP. There is a direct relationship between number of visits in our program and likelihood to transition successfully. **Conclusions:** Trusting, long-term relationships with providers in an interdisciplinary pediatric center increase the likelihood of transition to an Adult 22q Program. Successful transition ensures ongoing holistic health care for adults with 22q11.2-related disorders. Telemedicine improves access; multiple-state licensing in the AP would, as well. Improved outreach and follow-up with adults who have not transitioned is needed.

143: Family voices

What do families/caregivers/individuals with 22q want you to know?

- 22q is common but the diagnostic odyssey is real
- Most people have never heard of 22q
    - What can we do to create change?
- Early childhood is difficult
    - Especially feeding and swallowing problems because the parent who is unable to feed their child feels like a failure; nasal regurgitation is not normal
- Transition to adolescence and adulthood is harder still
- Coordinated multidisciplinary care is limited
    - By geography
    - By healthcare systems
    - By internet providers
        - How do we gain access and how do we choose?
- Waiting for the other shoe to drop in the form of psychiatric illness is the most challenging
    - Behavioral health specialists are few and far between
    - Formal neuropsychological testing is necessary to help with short- and long-term planning
        - But it can be expensive or nonexistent
    - Treatments are confusing
- A diagnosis in an adult is both welcome and perplexing
    - Causing some people to spiral
- We are exhausted – mentally and physically
- We want to help – with research and fundraising but we are not sure how
- We are a global community willing to work together, with the power to unlock many doors
    - But our goals differ by the age of our children & there are many groups with divergent agendas
        - Including families with the duplication; distal deletions and duplications; dual diagnoses such as TANGO2 – who all need and deserve our help
            - How do we serve everyone?
            - How do we keep up?
    - If we can develop a common goal and the resources to tap into that potential, we can be successful
        - HELP US TO HELP YOU

144: 22q11.2DS - towards restoration of the lost folio

Peter Scambler[1]

[1]*Developmental Biology of Birth Defects, Great Ormond Street Hospital UCL Institute of Child Health, London, UK*

By definition, 22q11.2 deletion (and duplication) is caused by alterations of gene dosage during development. Treatments currently involve targeting specific issues such as congenital heart defect, learning and behavioral difficulty, and palatal insufficiency. Continuing my approach at previous meetings, I will draw from recent research advances suggesting, in principle at least, how these might be relevant to 22q11.2 gene dosage disorders. In particular, emphasis will be placed on model systems that are being developed that would improve our understanding of underlying developmental pathways affected and whether it might be feasible to “rewire” these in various ways.

145: Implementation of digital 22q care plan in electronic medical record to improve interdisciplinary coordination and visibility

Lindsey H. Benedict[1], Hannah Berntson[1], Matthew Blessing[1,2], Laura Cline[1], Leslie Cronk[1], and Emily Gallagher[1,2], Suzanne Siegel

[1]Seattle Children's Hospital, Seattle, WA, USA; [2]University of Washington, Seattle, WA, USA.

Background: Patients with 22q11.2 related disorders require lifelong interdisciplinary care across specialties. This level of care management is challenging to families and can prove difficult to coordinate. Our institution found that a failure to track patients' clinical and psychosocial needs in the electronic medical record (EMR) leads to duplicate work and a lack of visibility across subspeciality teams. This impacted clinician ability to assess patient needs during different clinical encounters across the organization. These missed opportunities lead to delays in care and increased burden for families. **Methods:** Our 22q Center has improved visibility and coordination by moving the collaborative 22q tracker, previously in Excel, used to coordinate care for over 300 patients, into the EMR. A comprehensive patient list and a digital care plan for each patient can be edited by anyone on the interdisciplinary 22q team and accessed across the organization. Each provider updates the digital care plan with follow-up recommendations during clinic. The 22q clinic RN reviews and updates other specialty clinic recommendations. This creates a visible, coordinated follow-up plan, increasing scheduling efficiency, team communication, and family compliance. **Results:** A diverse team of stakeholders created a digital tool for care coordination in the EMR. Patient information was transferred from the Excel tracking tool to the EMR. The digital care plan improved interdisciplinary efficacy by making clinical recommendations and relevant psychosocial information easily accessible. This decreased the time required for clinic prep and identified gaps in care. The team updates recommendations, in real time, and leave notes for nursing and other disciplines. **Conclusions:** Implementation of an interdisciplinary digital care plan, within the EMR, has increased visibility of patient care needs, optimized coordinated scheduling, and improved provider communication across disciplines. Our future goal is to better leverage the EMR to improve patient access to timely, coordinated care.

146: Engaging children with 22q11.2-related disorders in their interdisciplinary care

Hannah Berntson[2], Skyler Leonard[2,3], Maria Mills[2], Lex Powers[2], Cindy Trevino[4,5], Matthew Blessing[1,2]

[1]Division of Craniofacial Medicine, University of Washington, Seattle, WA, USA; [2]Seattle Children's Hospital, Seattle, WA, USA; [3]Department of Neurology, University of Washington, Seattle, WA, USA; [4]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA; [5]Center for Child Health, Behavior and Development, Seattle Children's Hospital, Seattle, WA, USA.

Background: Patients with 22q11.2-related disorders (22qRD) require interdisciplinary care throughout their lives. This often leads to long clinic days, involving multiple specialists. While this model helps to reduce travel time and cost, it can be challenging for patients and their caregivers. Our educational materials have been limited and directed towards caregivers. We have identified that our younger patients would benefit from developmentally appropriate, engaging, educational materials about 22qRD. **Methods:** Within our 22q center, we determined which health topics to develop into handouts, written at 2nd grade reading level. For some topics, a pediatrician wrote the first draft and then asked an expert in that field to edit. In other cases, specialists wrote the material. A nurse then integrated the medical information into comic book-style handouts using Canva. We also met with Child Life experts to determine what topics to include beyond 22q11.2-specific materials. **Results:** "All About Me" sections were developed, including preferred forms of communication, how the child copes during times of stress, and information about their family. Lots of space for drawing and coloring are included. 22q11.2-specific handouts were developed for cardiology, genetics, immunology, feeding, speech, endocrinology, otolaryngology, nephrology, neurodevelopment, education, mental and behavioral health, and dentistry. Relevant handouts are added to customizable binders for each patient, along with clinic passports to make clinic visits interactive and fun. **Conclusions:** Interdisciplinary clinic visits can be stressful for children with 22qRD. Providing our patients with fun and educational materials will involve them in their healthcare and comfort them. Next steps include asking for feedback via our Parent Advisory Committee, surveys of families' experiences in clinic, and at the 2026 International 22q11.2 Conference. We plan to collaborate with 22q foundations to share our materials beyond our center and in multiple languages.

147: Nonword repetition skills of both preschoolers with 22q11.2 deletion syndrome and peers with developmental language disorder are weak, but differently associated with vocabulary

Tessel Boerma[1], Marieke Huls[3], Emma Everaert[1,2,4], Iris Selten[5], Ellen Gerrits[1,6], Frank Wijnen[1]

[1]Institute for Language Sciences, Department of Languages, Literature and Communication, Utrecht University, Utrecht, The Netherlands; [2]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Pento, Ede, The Netherlands; [4]Institute of Education and Child Studies, Leiden University, Leiden, The Netherlands; [5]Brain and Cognition, University of Amsterdam, Amsterdam, The Netherlands; [6]Research group Speech and Language Therapy – Participation is Communication, HU University of Applied Sciences, Utrecht, The Netherlands.

Background: Weak nonword repetition has been frequently reported in groups of children at risk for atypical speech and/or language development, such as children with Developmental Language Disorder (DLD). In contrast, research on children with 22q11.2 Deletion Syndrome (22q11DS) points to relatively strong nonword repetition skills, suggesting a unique profile. As research is scarce and absent in preschool children, firm conclusions about possible strengths cannot be drawn. The current study therefore examined nonword repetition skills in preschoolers with 22q11DS, comparing them to typically developing (TD) peers and peers with DLD. **Methods:** A total of 180 children, aged 3 to 6.5 years old, participated (22q11DS: *n*=40, DLD: *n*=63, TD: *n*=77). Instruments included a nonword repetition task and four standardized language measures, testing vocabulary and grammar in both receptive and expressive modality. We analyzed children's repetitions of mono-, di-, and trisyllabic nonwords, and correlated performance with their language skills. **Results:** Children with 22q11DS repeated the nonwords less accurately than TD peers. They performed on par with peers with DLD, except for monosyllabic nonwords for which the children with 22q11DS obtained lower scores. In the 22q11DS and TD groups, nonword repetition performance was positively correlated with children's language skills in all domains, whereas expressive grammar was the only correlated domain in the DLD group. Moderation analyses indicated that associations between nonword repetition and vocabulary skills were stronger in the 22q11DS and TD groups in comparison with the DLD group. **Conclusions:** The results from the current study showed weak nonword repetition performance of both children with 22q11DS and children with DLD. While nonword repetition accuracy of children in these groups was broadly comparable, associations with language abilities were not. These findings indicate that phenotypic similarities between these groups may only be superficial and may be associated with different paths leading to these phenotypic expressions.

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148: Oxycephaly associated with 22q11.2 deletion syndrome: a first reported case *

Jette A. Boxem[1,2], Aebele B. Mink van der Molen[2], Elaine H. Zackai[1, 3], T. Blaine Crowley[1], Donna M. McDonald-McGinn[1,3], Scott P. Bartlett[4]

[1]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Plastic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Paediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [4]Division of Plastic, Reconstructive, and Oral Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

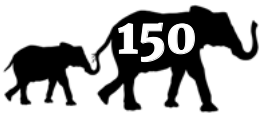
Background: Oxycephaly is a rare form of multi-suture craniosynostosis and has no known genetic etiology to date. We describe a late-onset case of craniosynostosis in a patient with a confirmed heterozygous 22q11.2 deletion and no pathogenic variants in *CDC45* or other known craniosynostosis-associated genes. **Results**: Our patient presented with elongated head shape indicative for oxycephaly, along with clinical and radiological evidence of increased intracranial pressure at 20 years of age. Surgical intervention was required to alleviate symptoms. **Conclusion:** This case expands the craniofacial phenotype of 22q11.2DS, highlights the potential for clinically significant complications such as symptomatic increased intracranial pressure, and underscores the importance of considering craniosynostosis in the differential diagnosis of atypical head shape even beyond infancy in patients with 22q11DS. Moreover, to our knowledge we report a first case of oxycephaly in a patient with 22q11.2DS.

149: Sleep disruption in a mouse model of 22q11.2 deletion syndrome *

Lara M. Boyle[1], Srdjan Joksimovic[2], Christopher M. Cielo[3], Donna M. McDonald-McGinn[4], Raquel E. Gur[1], Ashlea Choi[5], Shinjae Chung[5]

[1]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Pulmonary and Sleep Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Clinical Genetics Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Department of Neuroscience, University of Pennsylvania, Philadelphia, PA, USA.

Background: 22q11.2 deletion syndrome (22q11.2DS) confers elevated psychiatric risk, including a 20–25-fold increase in schizophrenia. Sleep disturbances are common in 22q11.2DS and correlate with psychosis and cognitive symptoms, yet their biological basis remains unclear. We used a mouse model of 22q11.2DS to characterize alterations in sleep and circadian regulation and compared findings to human polysomnography. **Methods:** Male and female Taconic Df(h22q11)/+ mice and wildtype littermates (C57BL/6NTac background) were studied at 2–6 months of age. For EEG sleep analysis, 6 male/3 female Df(h22q11)/+, 6 male/3 female wildtype mice were implanted with frontal and parietal electrodes to assess sleep structure. Circadian function in a wheel-running paradigm (9 female Df(h22q11)/+, 8 female wildtype). Human overnight polysomnography from adolescents with 22q11.2DS (age ≥13 years, n=30) was additionally analyzed. **Results:** Sleep macrostructure did not significantly differ between Df(h22q11)/+ mice and wildtype littermates. However, Df(h22q11)/+ mice had altered microstructure, including significantly increased frequency and reduced duration of wake and NREM bouts, as well as elevated microarousals. In circadian testing, Df(h22q11)/+ mice showed no significant differences in period or phase shifting but demonstrated increased intradaily variation. In adolescents with 22q11.2DS, polysomnography revealed reduced total sleep time (6.5±0.2 h), increased wake after sleep onset (58.9±6.8 min), reduced sleep efficiency (79.0±1.9%), as well as long sleep latency (43.5±7.1 min) and decreased REM percentage (15.9±1.0%). **Conclusions:** Although Df(h22q11)/+ mice did not show significant differences in sleep macrostructure, they demonstrated changes in microstructure consistent with sleep fragmentation. Similarly, while Df(h22q11)/+ mice did not have circadian changes in a wheel running paradigm, they showed activity fragmentation. Preliminary analysis of 22q11.2 adolescent sleep studies is also consistent with a pattern of sleep fragmentation, with additional changes in REM sleep percentage and sleep onset latency. Ongoing studies aim to determine mechanisms of sleep fragmentation and connect these mechanisms with hippocampal-dependent cognitive dysfunction.



150: Importance of timely screening for mental health concerns within a multidisciplinary 22q clinic setting and the barriers surrounding identification

Jalen D. Clemmons[1,2,3], Carter A. Puckett[1,2,3,4]

[1]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [2]Edwards Family Division of Genetics and Rare Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; *[3]Department of Family Services, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA*; *[4]University of Chicago, Crown Family School of Social Work, Policy, and Practice, Chicago, IL, USA.*

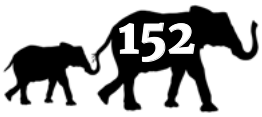
Background: Individuals diagnosed with 22q11.2 Deletion Syndrome (22q11.2DS) show high, persistent, and developmentally shifting mental health concerns and psychiatric risk, beginning in childhood and intensifying through adolescence and adulthood. Early mental health concerns for this population include anxiety, ADHD, and autism-related traits, while mood disorders and psychosis-spectrum symptoms increase with age. However, psychiatric conditions in 22q11.2DS are frequently under-identified and undertreated, highlighting gaps in routine screening and follow-up care. Without timely and effective interventions for these concerns, patients and their families experience compounding stressors resulting from increased mental health concerns and difficulty navigating barriers to accessing complex mental healthcare systems. Meanwhile, there are no recommended implementation and follow-up processes for psychiatric screening tools to address these pressing concerns. The purpose of this literature review is to assess implementation procedures for evidence-informed psychiatric screening tools in a 22q11.2DS multidisciplinary clinic setting. **Methods**: A narrative review was conducted by searching relevant databases for peer-reviewed qualitative and quantitative studies addressing 22q11.2DS, psychiatric conditions, mental health and Social Determinants of Health screening tools, and caregiver perceptions of mental healthcare access. A total of 18 studies were analyzed and coded inductively for common findings. **Results**: Screening tools are most effective in reducing patient and caregiver stressors when paired with family-centered implementation strategies. Specifically, approaches include allocating time during the appointment to complete screenings, having a relationally focused provider administer the screenings, and engaging families in conversation about risks and needs associated with positive screens. **Conclusions**: These findings convey the need to support the integration of care coordination staff, such as social workers, into 22q11.2DS clinics. Additionally, to promote care coordination efforts, cultural and structural shifts to clinic operations are necessary to ensure appropriate space and time for family-centered conversations.

151: Altered germ layer specification during gastrulation in 22q11.2 deletion syndrome *

Aidan Douglas[1], Eleonora Stronati[1], Elizabeth Abraham[1], Emily Megill[1], Olivia Mae Pericak[1], Conchi Estarás[1]

[1]*Department of Cardiovascular Sciences, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA.*

Background: Gastrulation is a fundamental developmental process that generates the three germ layers—ectoderm, mesoderm, and endoderm—which give rise to all tissues and organs. While severe defects in gastrulation often lead to early embryonic lethality, subtler perturbations may contribute to congenital disorders. We investigated whether the 22q11.2 microdeletion affects early germ layer specification during gastrulation, potentially contributing to defect in organs, including the heart. **Methods:** We modeled early human gastrulation using 2D micropatterned gastruloids generated from induced pluripotent stem cells (iPSCs) derived from individuals with 22q11.2DS and healthy controls. Germ layer patterning was assessed using immunofluorescence for lineage markers including Brachyury (mesoderm) and SOX2 (ectoderm). To determine whether similar alterations occur in vivo, we analyzed gastrulating embryos from the LgDel mouse model, which carries a large hemizygous deletion of the genomic region homologous to human 22q11.2. **Results:** Micropattern gastruloids derived from 22q11.2DS iPSCs displayed a significant expansion of the mesodermal domain (Brachyury$^+$) accompanied by a reduction of the ectodermal region (SOX2$^+$) compared with controls. Quantitative analysis showed that the enlarged mesodermal domain reflects an increased number of Brachyury-positive cells and a reduced number of SOX2-positive cells. Consistent with these findings, E7.5 LgDel mouse embryos exhibited increased expression of BMP4 and the pan-mesodermal marker Brachyury. Moreover, the primitive streak was expanded toward the anterior pole and showed increased Brachyury signal intensity compared with wild-type littermates. **Conclusions:** Our results indicate that early germ layer patterning is altered in 22q11.2 deletion syndrome, with a bias toward mesodermal specification. These findings suggest that defects during gastrulation may contribute to developmental phenotypes observed in 22q11.2DS.

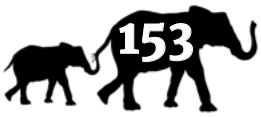


152: Establishing novel partnerships to create a comprehensive program for adults with 22q

Emily R. Gallagher[1, 2, 3, 4], Matt Blessing[1, 2], Kerry Conant[4], Gary Stobbe[1, 5, 6]

[1]University of Washington, Seattle, WA, USA; [2]Department of Pediatrics, University of Washington, Seattle, WA, USA; [3]Department of Global Health, University of Washington, Seattle, WA, USA; [4]Seattle Children's Hospital, Seattle, WA, USA; [5]Department of Neurology, University of Washington, Seattle, WA, USA; [6]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA.

Background: Our 22q Program cares for >700 patients with 22q11.2-related disorders (22q) who require multidisciplinary care from infancy through adolescence. Though we begin discussing transition to adult care during early adolescence, transition is usually delayed, typically because of inadequate access to a comprehensive program and experienced providers. Since 2020, we have tried 2 methods to improve transition options for adult patients with 22q, one of which was successful. We will discuss these approaches, elaborate on challenges and successes, and provide recommendations. **Methods:** From 2020-2023, we employed Method 1: direct outreach to providers in the community. Collaborating with an academic clinic focusing on transitioning complex patients to adult care, we created provider lists and referral plans. In 2024, we changed to Method 2: collaboration directly with providers in the Adult Neurodevelopmental Wellness Center (ANeW) at our adult academic hospital. **Results:** Method 1 resulted in a list of area providers caring for patients with complex issues. Providers were in primary care or subspecialties often needed by our patients (e.g., cardiology, endocrinology). The provider list was difficult to maintain. Parents/caregivers reported numerous phone calls, long wait times to establish care, and fragmented care. Method 2 resulted in an Adult 22q Program within ANeW for coordinated care. Transition now requires minimal work from parents/caregivers, facilitates provider hand-off, and results in comprehensive care. **Conclusions:** Partnering with providers caring for adults with neurodevelopmental differences has facilitated transition care for our patients with 22q. Benefits include frequent direct provider communication across programs, ease of transition, and access to comprehensive care with providers specializing in care for patients with complex needs. We now offer a transition overlap period where patients see providers in both clinics for up to a year until they fully transition. We believe this model can be duplicated in other regions.



153: Impact of chromosome 22q11.2 CNVs on height in two unrelated patients with achondroplasia *

Audrey Olson[1,2], T. Blaine Crowley[1,2], Lydia Hamilton[1,2], Evie Andrewes[1,2], Lily Elman[1,2], Lydia Rockart[1,2], Oanh Tran[1,2], Daniel E. McGinn[1,2], Beverly S. Emanuel[1,2,3], Elaine H. Zackai[1,2,3], Vaneeta Bamba[1,3,4], Lorraine L. Katz[1,3,4], and Donna M. McDonald-McGinn[1,2,3]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [4]Division of Endocrinology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

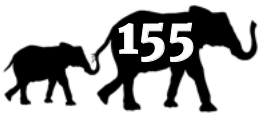
Background: Short stature has been observed in patients with chromosome 22q11.2 copy number variants (CNVs), with growth curves developed and available for patients with 22q11.2DS. Achondroplasia, the most common form of skeletal dysplasia, caused by a gain-of-function mutation in *FGFR3* (fibroblast growth factor receptor 3) results in overactive signaling, inhibiting chondrocyte proliferation and maturation in the growth plate, leading to severely restricted bone growth, characteristic disproportionate short stature, and macrocephaly. The Pediatric Endocrine Society has developed growth curves for Achondroplasia. Here we examined growth in two female patients with Achondroplasia and CNVs involving chromosome 22q: one with a standard 22q11.2 deletion (LCR22A-LCR22D); the other with a distal 22q11.21 deletion (LCR22D-LCR22F), to examine impact of the dual diagnoses on height. **Methods:** Under an IRB protocol, height in both patients was compared to the achondroplasia growth curves. **Results:** At age 16 months, Patient 1, with 22q11.2DS (LCR22A-LCR22D) and achondroplasia, measured 63.5 cm (10% on the achondroplasia chart; 2% on the 22q11.2DS growth curve). Conversely, at 11 years, Patient 2, with a distal 22q11.21 deletion (LCR22D-LCR22F) and achondroplasia, measured 96 cm (<1%; 50% for 7.5 years on the achondroplasia growth curve). This is notable given the mean adult height for female patients with a standard 22q11.2 deletion is 156 cm and overall, we have found significant short stature in our patients with distal 22q11.21 deletions, particularly those patients with a deletion involving the LCR22D-LCR22E region. This finding suggests that a gene/genes within this region may impact linear growth. **Conclusions:** Short statue is often noted in young children with the standard 22q11.2 deletion but tends to normalize over time. However, a distal 22q11.2 LCR22D-LCR22E/LCR22D-LCR22F deletion appears to significantly impact height, including in a child with a predisposition for short stature due to the skeletal dysplasia, achondroplasia. These findings may support identification of genotype-phenotype correlations.

154: Enhanced serological protection after pneumococcal polysaccharide vaccine in a child with 22q11.2 deletion syndrome and recurrent sinopulmonary infection *

Annika Malmgren[1], Jenny Lingman Framme[2,3], Solveig Oskarsdottir[1,3]

[1]Department of Pediatrics, Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden; [2]Department of Pediatrics, Halland hospital, Halmstad, Sweden; [3]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Background: In children with 22q11.2 deletion syndrome (22q11.2DS), recurrent sinopulmonary infections are a major contributor to morbidity. Pneumococcal vaccination may reduce this burden, although the optimal strategy is unclear due to altered immune function. T-cell–dependent responses to conjugated pneumococcal vaccines (PCV) are often impaired, while responses to polysaccharide vaccines (PPV) remain incompletely studied. **Methods:** We administered PPV-23 to an 8-year-old boy with A–D deletion and recurrent sinopulmonary infections despite three doses of PCV-13 in infancy and PCV-15 at age 6 years. Lymphocyte counts, T-cell proliferation after mitogen stimulation (FASCIA), and immunoglobulin levels were measured. Specific pneumococcal antibodies were assessed using a 21-plex assay; values >0.35 µg/mL after PCV and >1.3 µg/mL after PPV were considered protective against invasive disease, and significant vaccine response was defined as a fourfold titer increase. **Results:** The patient had low T-cell counts (CD3 0.68, CD4 0.34, naïve CD4 0.18, CD8 0.28×10^9/L) and reduced proliferation to phytohaemagglutinin, but normal response to pokeweed mitogen. Total IgG was slightly decreased, with normal IgG2. He was immune to tetanus. Thirteen months after PCV-15, protective antibody levels were present for 6/13 evaluated PCV-15 serotypes. Five weeks after PPV-23, protection was observed for 10/13 PCV-15 serotypes and two additional PPV-23 serotypes. Titers increased more than fourfold for 16/21 serotypes. No infectious episodes have occurred following PPV-23 administration. **Conclusions:** PPV-23 boosted and induced serological protection in this child with 22q11.2DS. Vaccine boosters in immunodeficient individuals may be beneficial, and PPV may offer an advantage in T-cell–deficient patients by eliciting T-cell–independent responses. Further studies should evaluate the long-term serological and clinical impact of PPV.

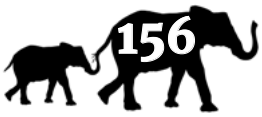


155: Cardiopulmonary findings in teenagers with right circumflex aortic arch in 22q11 deletion syndrome

Julie Martin[1], Manbir Sanghera[2], Matthew M. Feldt[1], Nikita Raje[1], Maria Kiaffas[1], Sanket Shah[1]

[1]Children's Mercy Hospital-University of Missouri, Kansas City, MI, USA; [2]Kansas City University, Kansas City, MI, USA.

Background: Circumflex aortic arch is a rare aortic anomaly caused by retroesophageal crossing of the aorta to the contralateral side due to different situs of the ascending and descending aorta. In 22q11DS patients, this often forms a vascular ring when a right ascending aorta with left-sided ligamentum arteriosus and aberrant left subclavian artery are present. Since surgical intervention varies, residual cardiopulmonary sequelae may persist in teenagers. **Methods:** Between 2010-2025, 628 patients with 22q11.2DS and 22q11.2DupS were evaluated. We identified 2 patients with circumflex aortic arch anomalies; at least 5 years follow up were completed. **Results:** Case 1: A 5-year-old child with 22q11 Deletion was diagnosed with a right circumflex aortic arch. On subsequent CT angiogram an aberrant left subclavian artery and vascular ring anatomy was further delineated. Family declined surgical intervention. Although initially asymptomatic, currently the 13-year-old has low energy levels, a less active lifestyle, and airway obstruction as assessed by pulmonary function tests during exercise stress tests. Case 2: A neonate thought to have coarctation of aorta and was found to have a vascular ring with right circumflex aortic arch with a left ductal ligament during surgery. Surgical ligamentum division relieved the vascular ring in infancy, but due to lack of circumflex arch repair, coarctation of transverse aortic arch remains. Now at 18 years, she has developed minimal symptoms of hypertension, subtle left ventricular hypertrophy, and left ventricular diastolic dysfunction. **Conclusions:** Chromosome 22q11 deletion can be associated with circumflex right aortic arch and vascular ring. Diagnosis is often suspected on fetal or post-natal echo. Cross-sectional imaging with CT/MRI is vital for precise anatomical diagnosis and physiological assessment. An aortic uncrossing operation can be considered in infancy to potentially prevent respiratory and cardiac vascular functional sequelae later in life. A multidisciplinary team approach results in optimal outcomes.



156: Very early onset inflammatory bowel disease in children with 22q11.2 deletion syndrome

Maire Conrad[1,2], Judith Kelsen[1,2], Kathleen Sullivan[2,3,4], Soma Jyonouchi[2,3,4], Audrey Olson[3,5], Donna M. McDonald-McGinn[2,3,5], and Maria Mascarenhas[1,2,3]

[1]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [3]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [5]Division of Genetic and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: Very early onset inflammatory bowel disease (VEO-IBD) typically diagnosed before age 6 years, can be driven by monogenic defects involving immune regulation, and presents with severe, treatment-refractory inflammation. Children with 22q11.2DS exhibit immune dysfunction ranging from mild T-cell abnormalities to significant immunodeficiency, predisposing them to polyautoimmunity with gastrointestinal manifestations. Here we present 3 cases with varying presentation. **Methods**: We performed a retrospective chart review under IRB approval of children with 22q11.2DS and VEO-IBD. **Results: Patient-1**, 12-year-old male with duodenal and colonic Crohn disease diagnosed at 7 years old initially presenting with diarrhea. Additional findings included: congenital heart disease, systemic capillary leak with tortuous thoracic duct, hypoparathyroidism, short stature, osteoporosis, fracture, specific antibody deficit, GERD, constipation, gastroparesis, TPN dependence, feeding intolerance, G-tube with Nissen, recurrent CLABSIs, scoliosis, chronic urticaria, obstructive sleep apnea, pulmonary insufficiency, pneumonias, polymicrogyria, epilepsy, and cognitive deficits. Marked improvement of capillary leak on monthly IVIG. Remission achieved on ustekinumab, bactrim prophylaxis, and antihistamines. **Patient-2,** 19-month-old male diagnosed with colonic predominant VEO-IBD at 13 months with diarrhea, electrolyte abnormalities including hypocalcemia and moderate malnutrition. Additional findings included: hypoparathyroidism, significant lymphopenia, low T regulatory cells, and acute CMV hepatitis. Clinical remission achieved on ruxolitinib. **Patient-3**, 11-year-old male diagnosed at 9 years old with duodenal and colonic Crohn disease with chronic diarrhea and sudden weight loss. Additional finding included: feeding difficulties, G-tube dependence, dilated ascending aorta and cervical aortic arch with aberrant right subclavian artery, short stature, hypoparathyroidism, hypocalcemia, hypovitaminosis D, thrombocytopenia, medullary nephrocalcinosis, obstructive sleep apnea, submucosal cleft palate/VPI, insomnia, ADHD, autism, generalized anxiety disorder, migraines, normal immunoglobulin levels, mild humoral deficits, and low T cells requiring SMP/TMX prophylaxis. Achieved remission with budesonide and vedolizumab. **Conclusions:** Emerging case reports suggest that VEO-IBD can occur in patients with 22q11.2DS and immunodeficiency, warranting careful immune evaluation and tailored therapy.

157: Studying the interplay between vitamin A and hippo signaling pathways in human models of 22q11.2 deletion syndrome *

Emily Megill[1], Eleonora Stronati[1,2], Elizabeth Abraham[1], Aidan Douglas[1], Mikel Zubillaga[1], Conchi Estaras[1]

[1]Cardiovascular Sciences Department, Aging + Cardiovascular Discovery Center, Temple University, Philadelphia, PA, USA; [2]Department of Child and Adolescence Psychiatry, The Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Background: 22q11.2 microdeletion leads to a wide spectrum of developmental defects that vary considerably between patients. The mechanisms underlying this variability remain poorly understood and likely reflect the interplay between genetic background and non-genetic modifiers. In addition, studies using human developmental models of the disease remain limited, restricting our understanding of the underlying mechanisms. We hypothesize that the 22q11.2 deletion disrupts key downstream developmental pathways, and that dysregulation of these pathways contributes to the diverse phenotypes observed in affected individuals. **Methods**: We employed human developmental models including human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and patterned organoids carrying the 22q11.2 deletion alongside control lines. These models were analyzed using phenotypic assays, single-cell transcriptomics, and targeted metabolomics. **Results**: Our analyses reveal that 22q11.2DS cells display altered developmental signaling pathways, including Hippo–YAP signaling and Vitamin A/Retinoic acid metabolism. In addition, pathways regulating cell survival and apoptosis appear differentially regulated in 22q11.2DS models. Previous work from our group has shown that Hippo–YAP and RA signaling cooperate during cardiac specification, suggesting that disruption of this interaction may contribute to disease phenotypes. **Conclusions**: Our ongoing work identifies Hippo–YAP and RA signaling as altered pathways in human models of 22q11.2DS and suggests that the interplay between these pathways may contribute to the developmental variability observed in this syndrome, particularly in organs such as the heart.

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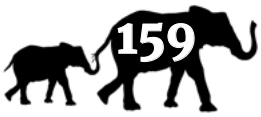
158: Development of a screening protocol for *TANGO2* deficiency in pediatric patients with 22q11.2 deletion syndrome: initial findings and insights

Maria Mills[1], Lex Powers[1], Matthew Blessing[1,2], Kimberly Liekweg[1,2], Lindsey Benedict[1], Suzanne Siegel[1], Emily Gallagher[1,2]

[1]Seattle Children's Hospital, Seattle, WA, USA; [2]University of Washington, Seattle, WA, USA.

Background: Individuals with 22q11.2 deletion syndrome (22q11.2DS) are at increased risk of autosomal recessive conditions related to genes within the deleted region. Biallelic loss of function of the *TANGO2* gene, located at 22q11.21, causes a metabolic condition termed TANGO2 deficiency. TANGO2 deficiency is associated with baseline symptoms—including developmental delay, speech difficulties, seizures, and hypothyroidism—that overlap significantly with symptoms of 22q11.2DS. Additionally, individuals with TANGO2 deficiency are at risk of acute, life-threatening symptoms—such as metabolic and cardiac crises—not associated with 22q11.2DS. Timely diagnosis of TANGO2 deficiency improves health outcomes, as B-vitamin supplementation reduces risk of acute crises. However, preemptive diagnosis is challenging in individuals with 22q11.2DS, where the first distinguishing symptom may be a life-threatening crisis. Currently, there is no published literature evaluating systematic implementation of screening for TANGO2 deficiency within a 22q11.2DS cohort. It remains unknown how many patients in this high-risk group have TANGO2 deficiency. There is also a lack of data regarding family uptake of *TANGO2* testing. **Methods:** Our center implemented a screening protocol in November 2025 to offer testing of *TANGO2* to eligible patients in our multidisciplinary 22q clinic. This project attempts to 1) determine the diagnostic yield of *TANGO2* testing in individuals with 22q11.2DS, 2) quantify uptake of testing, and 3) identify testing barriers. **Results:** Our team collaborated with our in-house lab to develop *TANGO2* sequencing and copy number variant testing. We implemented screening of patients in 22q Clinic to determine eligibility for testing, based on deletion location and previous molecular testing. We have begun data collection on number of patients screened, family update of testing, and molecular results. Updated numbers will be presented. **Conclusions:** This work is ongoing: we've noted high testing uptake thus far. We aim to offer *TANGO2* testing to all eligible active patients by November 2027.

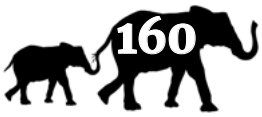


159: Diagnosing and managing complex neuropsychiatric challenges in 22q11.2 deletion syndrome

Lisa Palmer[1], Tracy Heung[1,2], Nikolai Reyes[1, 2, 4,5], Samantha D'Arcy[1], Anne S. Bassett[1,2,3]

[1]The Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada; *[2]Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada*; *[3]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada*; *[4]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [5]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada.*

Background: Adults with 22q11.2 deletion syndrome (22q11.2DS) often have complex care needs, including neuropsychiatric and psychosocial challenges that require coordinated multidisciplinary management and support. **Methods:** We conducted a comprehensive review of the lifetime clinical features, management, psychosocial and system-level challenges and supports of a 27-year-old female with a typical 22q11.2 deletion currently living in a group home residence for adults with intellectual disability with one-to-one support staff due to her high levels of support needs. **Results:** Complex neuropsychiatric clinical features include mild-to-moderate intellectual disability, epileptic and non-epileptic seizure events, myoclonus, generalized anxiety disorder and recurrent episodes of grossly disorganized behaviour, including ingestion of non-food items. This resulted in frequent hospitalizations and medical interventions, with over 180 emergency department visits in recent history and extensive community support involvement. She remains an extremely vulnerable individual who is at chronic high risk of serious harm and accidental death. Despite a psychological capacity assessment deeming her incapable of personal care decisions across health care, shelter and safety domains, she has often been assessed and treated by health care providers as "capable," contributing to inconsistent care. Over her lifespan, she has received differing psychiatric diagnoses and treatment recommendations from multiple clinicians, creating confusion for her community team regarding best-practice management. Diagnosis of treatment-resistant schizoaffective disorder led to current management involving clozapine under a Community Treatment Order, strict medication supervision, and specialized group home care with significant community supports. Frequency of hospital visits has demonstrably declined, and quality of life has notably improved from family and caregiver perspectives. **Conclusions:** This case highlights the substantial challenges involved in caring for individuals with 22q11.2DS who present with dual diagnosis and high-risk neuropsychiatric conditions. It emphasizes the critical importance of accurate psychiatric diagnosis, consistent treatment planning, and coordinated multidisciplinary management to ensure safety, stability and optimal long-term outcomes.



160: Binary predictive modeling for 22q11.2 deletion using structured clinical data: an experimental ensemble study with linear SVM and complement naive bayes

Giulia T. Barcellos[1], Vera L. Gil-da-Silva-Lopes[2], Ana E. A. Silva[1], João Pedro Moretti[1] and Guilherme P. Coelho[1]

[1]Faculty of Technology, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil; [2]Department of Medical Genetics and Genomic Medicine, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil.

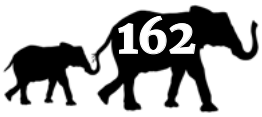
Background: Accurate screening for 22q11 deletion syndrome using routinely collected clinical data may support earlier referral for confirmatory testing. We evaluated binary prediction of 22q11 deletion using structured clinical records from CranFlow, an application linked to the Brazilian Database on Craniofacial Anomalies (UNICAMP/BDCA). Variable selection was guided by updated phenotypic domains/comorbidities ("What's New with 22q?") and by screening guidelines proposed by Monteiro et al. **Methods**: The original dataset included 298 records and 625 variables. After comprehensive preprocessing (variable harmonization/standardization, category normalization, and systematic handling of missing data) and exclusion of records not tested or lacking deletion information, the final cohort comprised 292 individuals (94 positive; 198 negative). Low-informativeness variables and free-text fields were removed, retaining standardized numerical and categorical variables. An ensemble with probabilistic soft voting combined a linear SVM (higher weight) and Complement Naive Bayes. Performance was assessed across 30 independent repetitions with stratified 70/30 train–test splits. **Results:** Mean accuracy across repetitions was 0.743. Inspection of the linear model's coefficients suggested predominance of features related to craniofacial dysmorphisms (e.g., hooded eyelids and a tubular nose), endocrine/metabolic findings, palatal/velopharyngeal and speech-related findings (e.g., hypernasal voice; signs suggestive of palatal alteration, including nasofibroscopy findings), neurodevelopmental milestones, laboratory/test abnormalities, and cardiac malformations. **Conclusions:** Using an ensemble (linear SVM + Complement Naive Bayes) applied to structured clinical data enabled robust prediction of 22q11 deletion. This strategy represents a promising pathway to automate decision support in screening workflows, contributing to faster identification of individuals who should be prioritized for confirmatory diagnostic testing.

161: Immunodeficiency presentation in a patient with a distal 22q11.23 (LCR F-H) duplication *

Kelly E. Regan-Fendt[1], Valerie J. Allegretti[1] and Elizabeth A. Lippner[2]

[1]Edwards Family Division of Genetics & Rare Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; *[2]Division of Allergy & Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA.*

Background: Distal 22q11 duplications have been reported to be associated with variable degrees of immunodeficiency, particularly, B cell defects and rarely T cell defects. Here we report a 2 year-old male who presented for immunological evaluation for a history of recurrent infections, neutropenia, mild hypogammaglobinemia and poor vaccine responses who was found to have a paternally inherited distal 22q11.23 duplication (LCR F-H). **Methods:** We summarize clinical, immunological and genetic information for a patient evaluated at Lurie Children's Hospital. **Results:** Physical exam notable for mild describable features, low weight and relatively shorter stature (11%). Developmentally, he had mild speech delay and hypotonia that improved. Infection history was notable for recurrent sinopulmonary infections. Prior immunodeficiency gene panel revealed a pathogenic *LIG1* variant without evidence of poor DNA repair, consistent with carrier status. Telomere studies revealed shortened telomere length for granulocytes and NK cells and normal telomere length in lymphocytes, naive and memory T cells and B cells, consistent with expectant variants for age. ALPS panel showed increased proportion of CD3 gamma/delta cells. TCR V-beta testing showed normal diversity of T cell receptor families. T cells showed skewed alpha/beta vs. gamma/delta T cells. Whole exome sequencing identified a distal 22q11.23 duplication (LCR F-H) and a maternally inherited *FLG* pathogenic variant. Ophthalmology evaluation revealed a posterior embryotoxon. Family history notable for psoriasis in father and paternal grandmother. **Conclusions:** In summary, we present a case of a child with a distal 22q11.23 duplication (LCR F-H) presenting with symptoms of immunodeficiency. His immunophenotype was notable for poor B cell memory and T cell skewing. He was started on IVIG in setting of high infection burden and accelerated losses of *S. pneumoniae* vaccination response, which improved after one year of treatment. Our findings contribute to the expanding immunophenotypic landscape of individuals with distal 22q11 duplications.

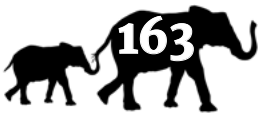


162: Parent perspectives on educational practices for students with 22q11.2 deletion syndrome in Ontario, Canada

Jane Summers[1,2,3,4], Katrina Palad[2,4], Sana Emami[2,4], Jacob Vorstman[1,2,3,4,5]

[1]Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [2]Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada; [3]Department of Psychiatry, The Hospital for Sick Children, Toronto, ON, Canada; [4]Autism Research Unit, The Hospital for Sick Children, Toronto, ON, Canada; [5]The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, ON, Canada.

Background: Despite the high prevalence of learning challenges associated with 22q11DS, there is limited data examining educational practices used in school settings. The aim of this study is to gather information about educational placements, instructional strategies and supports from the parents of children with 22q11DS residing in Ontario, Canada. **Methods**: This study will use a cross-sectional survey design. Parents of school-aged children with 22q11DS who had an integrated psychoeducational and mental health assessment at the DAGSY (Developmental Assessment of Genetically Susceptible Youth) Clinic at SickKids will be invited to complete an online questionnaire. The survey will collect information on child and family demographics, school placement and setting, use of individualized education plans, classroom accommodations, instructional strategies and access to special education and allied health services. Parent-reported changes in services and supports following the DAGSY assessment will also be examined. **Results:** Quantitative data will be analyzed using descriptive statistics and qualitative responses will be organized thematically to explore parent perceptions and priorities for improvement. **Conclusions**: By gathering parent-reported information on school-based supports and services, this study aims to describe how educational practices are implemented for children with 22q11DS within a Canadian context. Studying parent-reported changes following an integrated psychoeducational and mental health assessment may offer preliminary insight into the potential role of comprehensive evaluations in informing educational and service planning.

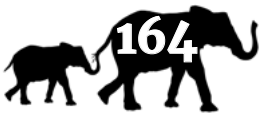


163: Trauma-related symptoms in adults with 22q11.2 deletion syndrome: exploring the efficacy of eye movement desensitization and reprocessing (EMDR) therapy

Claudia Vingerhoets[1,2], Sasja Duijff[3], Sanne Vrinzen[1], Jeltje Spapens[1], Erik Boot[1,2,4], and Therese van Amelsvoort[1]

[1]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, The Netherlands; [2]Advisium 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [3]Care4Minds, Zeist, The Netherlands; [4]The Dalglish Family 22q Clinic, University Health Network, Toronto, ON, Canada.

Introduction: Trauma-related symptoms are common in individuals with 22q11.2 deletion syndrome (22q11.2DS). A recent Dutch study found that 8% of adults with 22q11.2DS had received a diagnosis of post-traumatic stress disorder (PTSD), and 21% had experienced traumatic events. In the general population, PTSD and other serious trauma-related symptoms are generally well treated with Eye Movement Desensitization and Reprocessing therapy (EMDR), which aims to reduce the emotional intensity of distressing memories. To date, it has not been investigated to what extent EMDR is applicable and effective in individuals with 22q11.2DS, nor whether adaptations to the standard treatment protocol are necessary. **Methods:** We are currently investigating the efficacy of EMDR in adults with 22q11.2DS in a prospective naturalistic study. Participants are eligible if they have a molecular confirmed 22q11.2 deletion and a clinical indication for EMDR treatment as determined by the treating clinician. A set of standardized questionnaires consisting of the Children's Revised Impact of Events Scale (CRIES-13), Beck Depression Inventory (BDI), and the State Trait Anxiety Inventory (STAI) was used to evaluate effects on symptoms of PTSD, depression and anxiety, respectively. **Results**: To date, 7 participants (6 females, median age 27, range=17-36) completed the study. Four participants met DSM-5 criteria for PTSD. Paired t-tests showed non-significant reductions in PTSD symptoms (D= -8.0; p=0.248), depression (D= -9.8; p=0.136) and anxiety (D= -2.6; p=0.324). On average participants had 6 EMDR sessions (range 4-9). Several protocols were used (standardized adults N=1, standardized children N=2, combined adult and child protocol N=2, storytelling N=1, different N=1). **Conclusion:** Although not significant, preliminary results suggest that EMDR may have a positive effect on trauma-related symptoms in adults with 22q11.2DS. The use of different treatment protocols suggests that therapy needs to be adapted to the level of functioning. Results need to be confirmed in a larger sample.



164: Words in context: measuring the vocabulary network in children with 22q11.2 deletion syndrome *

Jantine R. Wignand[1,2], Naomi Oppeneer[1], Tessel D. Boerma[1,2], Michiel L. Houben[2] & Frank N.K. Wijnen[1]

[1]Institute for Language Sciences, Utrecht University, Utrecht, The Netherlands; [2]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.

Background: When measuring vocabulary skills/development of children, usually standardized tests measuring vocabulary size are used. Children with 22q11.2 deletion syndrome (22q11DS) generally know fewer words and have slower vocabulary growth than typically developing (TD) peers. Next to measuring *whether* children know words (i.e., recognize and/or use them), it is also relevant to measure *how* these words are connected in their vocabulary network. That way, we learn about the organization/structure of the mental lexicon, a critical factor for effective language use. By comparing children without language problems to children with language problems, we aim to contribute to this unexplored topic. **Methods**: The participants were 65 TD children and 35 children with 22q11DS, all between the ages of 9 and 12 years. To chart the organization of the vocabulary, we designed a task to gauge an individual's knowledge of (conceptual) connections between words. Children were asked to produce multiple associated words and concepts in response to a cue word, in a game context. Next to comparing TD children to children with 22q11DS, their responses were also compared to measures of the mental lexicon of adults. **Results**: Preliminary results show that for children with 22q11DS there is less overlap between their answers and adults' answers, compared to TD children. Moreover, children with 22q11DS give different kinds of answers than TD children: while TD children seem to focus on words from the same word/grammatical category as the cue word, children with 22q11DS give answers that have a different relation (e.g., syntactic) to the cue word. **Conclusions**: Investigating the organization of the vocabulary network, next to vocabulary size, is of great value, as it is contributes to acquiring effective language and communication skills. In the context of children with language problems, such as in 22q11DS, these findings hold promise for application in diagnostics and intervention.

* **Indicates Junior Investigator**

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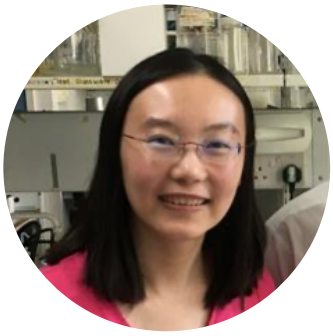
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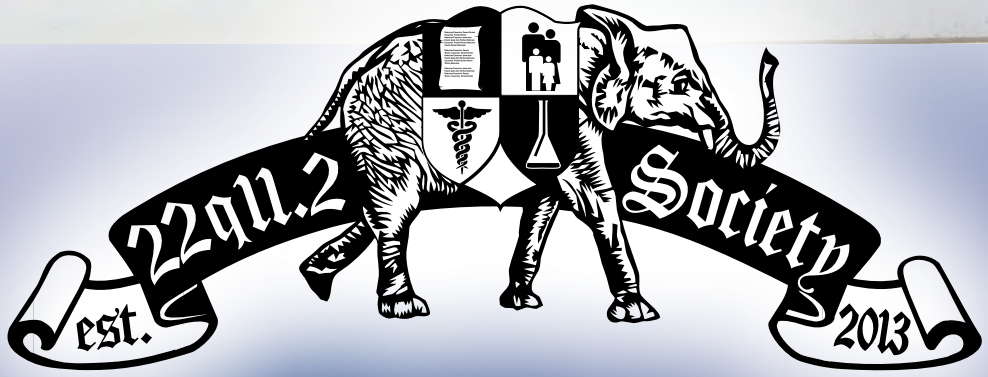

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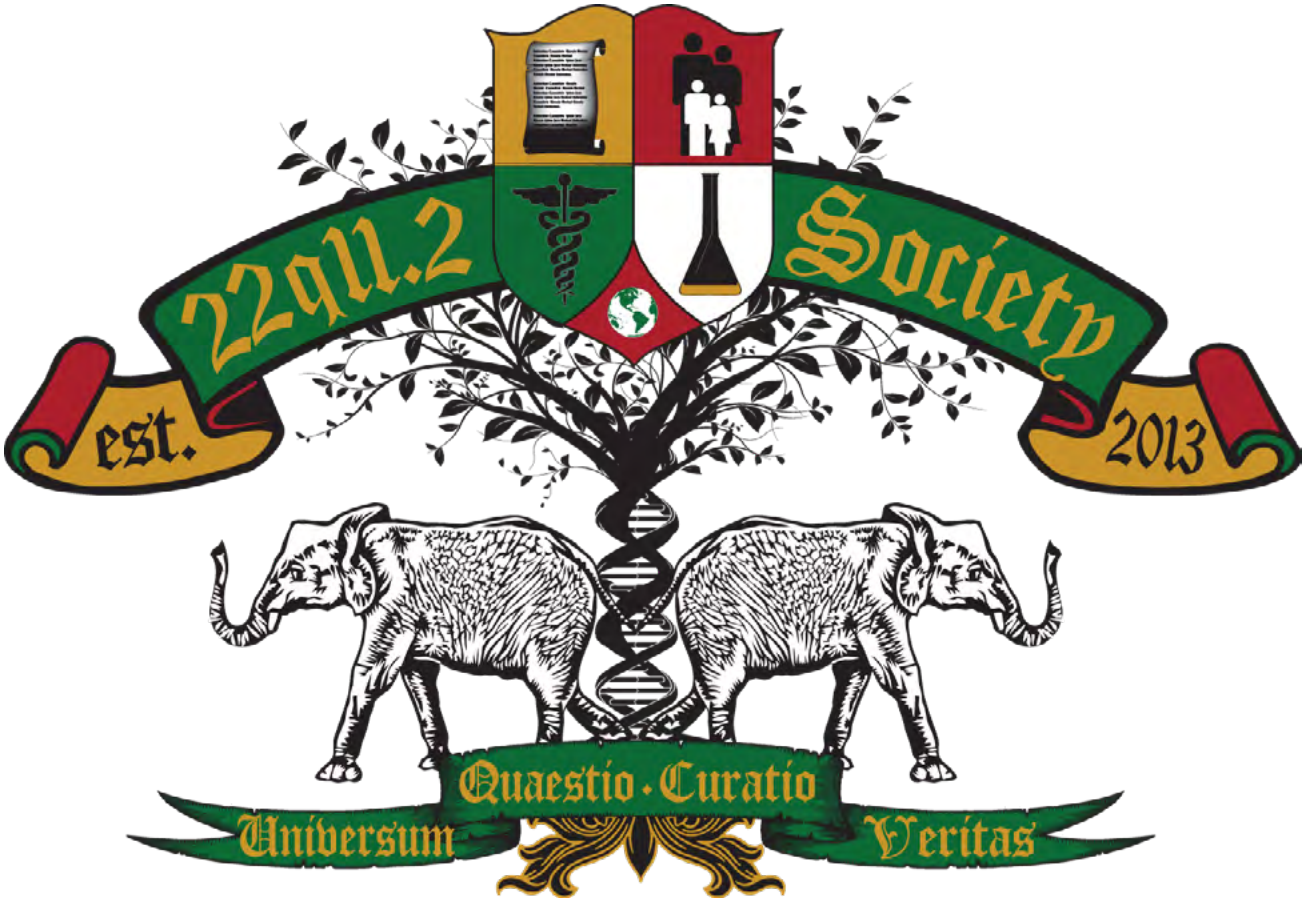

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