2024

Óbidos, Portugal on the Silver Coast

The 13th Biennial International 22q11.2 Scientific Meeting

hosted by the 22q11.2 Society

Praia D'El Rey Golf and Beach Resort
Óbidos, Portugal | July 16 - July 18, 2024

Celebrating our Silver Anniversary on the Silver Coast

The 22q11.2 Society *warmly welcomes* Attendees to the 2024 International 22q11.2 Scientific Meeting

12th Biennial International 22q11.2 Conference, Split, Croatia, June 29-July 1, 2022

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

Celebrating our Silver Anniversary

13th Biennial
International 22q11.2 Society
Conference

Dear Conference Attendees,

It is with tremendous enthusiasm that the 22q11.2 Society Trustees and Advisors welcome you to the 13th Biennial International 22q11.2 Scientific Conference where we will be celebrating our Silver Anniversary on the beautiful Silver Coast of Óbidos, Portugal. As has been the case since the inaugural meeting in Strasbourg, France in 1998, this assembly is imagined as a scientific retreat where attendees, hailing from more than twenty countries across five continents, will immerse themselves in everything 22q over the course of three full days. While enjoying ample opportunities for discussion and discovery, no doubt participants will also savor the outstanding social program and comradery that comes from sharing this time together.

As is always the ambition, this 13th conference, now over 25 years on from Strasbourg, merges basic science with interdisciplinary clinical research, with an overarching goal 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 whole genome sequencing to organoids, 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 discoveries to the forefront and sharing them here in Portugal. We are certain it will be worth the effort.

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

Obrigada,

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

Beata Nowakowska
22q11.2 Society Trustee and 2024 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, Associate Director of the Clinical Genetics 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 Laboratory of Cytogenetics at the Department of Medical Genetics at the 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

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

Gabriela Repetto

Clinical Geneticist and Director of the Center for Genetics and Genomics at Facultad de Medicina Clinica Alemana Universidad del Desarrollo, Santiago, Chile

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

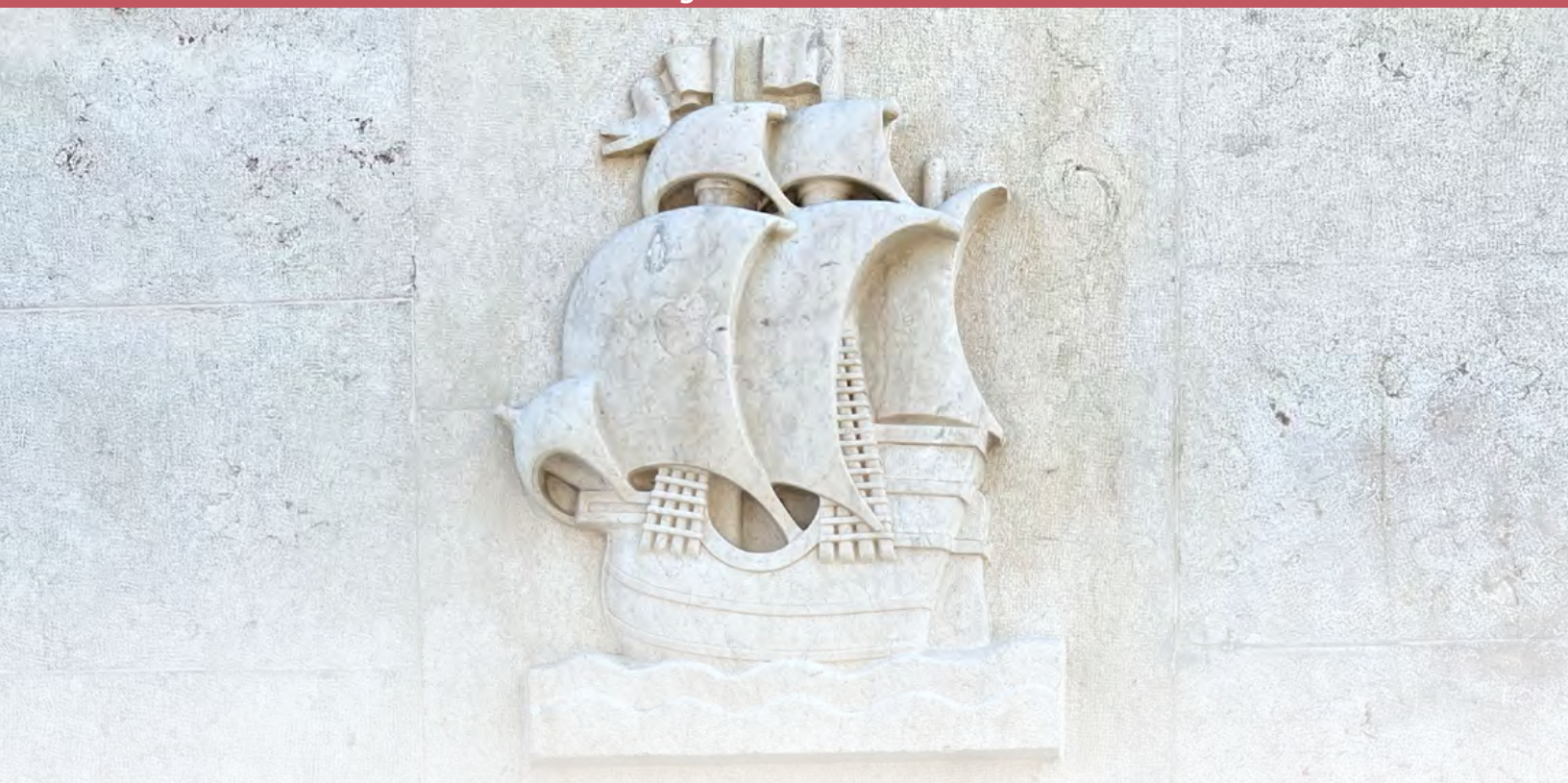
Jacob Vorstman

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

a parade of nations

Australia
Belgium
Canada
China
England
France
Germany
Hungary
Ireland
Israel
Italy
Jamaica
Japan
Morocco
Netherlands
Norway
Portugal
Serbia
Spain
Sweden
United States of America
Wales

Assembling in beautiful Óbidos, Portugal summer of 2024 for the 13th Biennial International 22q11.2 Deletion Syndrome Conference



The 13th Biennial International 22q11.2 Conference Program Committee

Beata Nowakowska
Program Chair

Anne Bassett
Associate Conference Director

Jill Arganbright

Natalie Blagowidow

Erik Boot

Ania Fiksinski

Emily Gallagher

Doron Gothelf

Bernice Morrow

Donna McDonald-McGinn
Conference Director

Sólveig Óskarsdóttir

Sulagna Saitta

Peter Scambler

Maude Schneider

Kathleen Sullivan

Ann Swillen

Elfi Vergaelen

Joris Vermeesch

Jacob Vorstman

Social Program

- **Tuesday, July 16th – 20:00 – Poolside**

  Welcome Reception including our signature cocktail and heavy hors d'oeuvres

- **Wednesday, July 17th – 19:00 – Hotel Lawn Adjacent to Pool**

  22q Olympics and **Sunset Social** followed by a Portuguese Pizza Party

  - All participants and attendees interested in participating in the **PARADE OF NATIONS** should wear "**colors representing their respective countries**." Those participating in games should also wear **athletic clothing and footwear**. All registered attendees and accompanying persons will receive an "Olympic Vest" at registration – **please bring the vest to the event**
  - Please assemble at **18:45** poolside for the **PARADE OF NATIONS**
  - Includes various games appropriate for adults of all ages. All attendees and accompanying adults are invited and encouraged to participate.

- **Thursday, July 18th – Buses depart at 19:30 – West Cliffs Club House Restaurant**

  Silver Anniversary Gala including a Traditional Portuguese Ranch Show, Dinner and Dancing, and a Special Awards Presentation

  - **In honor of the anniversary – suggested attire includes any combination of BLACK, WHITE, or SILVER**
  - **Buses depart sharply at 19:30** and will be looping back to the hotel throughout the evening. Please come with your instrument, cameras, limericks, and singing voice for this truly epic gathering
  - The Silver Anniversary Gala will celebrate more than a quarter of a century of our coming together for scientific discovery, improved care, collaboration, and friendship

Audiovisual

- All Power Point presentations must be uploaded to the designated drop box link 24 hours prior to your scheduled lecture time. This is mandatory.
- The speaker ready room is located in Foyer. Speaker ready room hours are posted at the registration desk.
- Please make sure all slides/videos are compatible prior to the presentation.
- The Program is quite full so please keep to the allotted presentation time—this is imperative in keeping the Program running as planned.
- Any presentation that exceeds the allotted time will be interrupted by the AV microphone silenced and projector darkened.

Registration – BALLROOM I: PENICHE AND SINTRA FOYER

- Badges are included for all registered attendees and must be worn at all times during the meeting.
- Accompanying person materials will also be distributed at registration.

Registration: Foyer

Registration Desk Hours:

Monday, July 15: 6:00-17:00

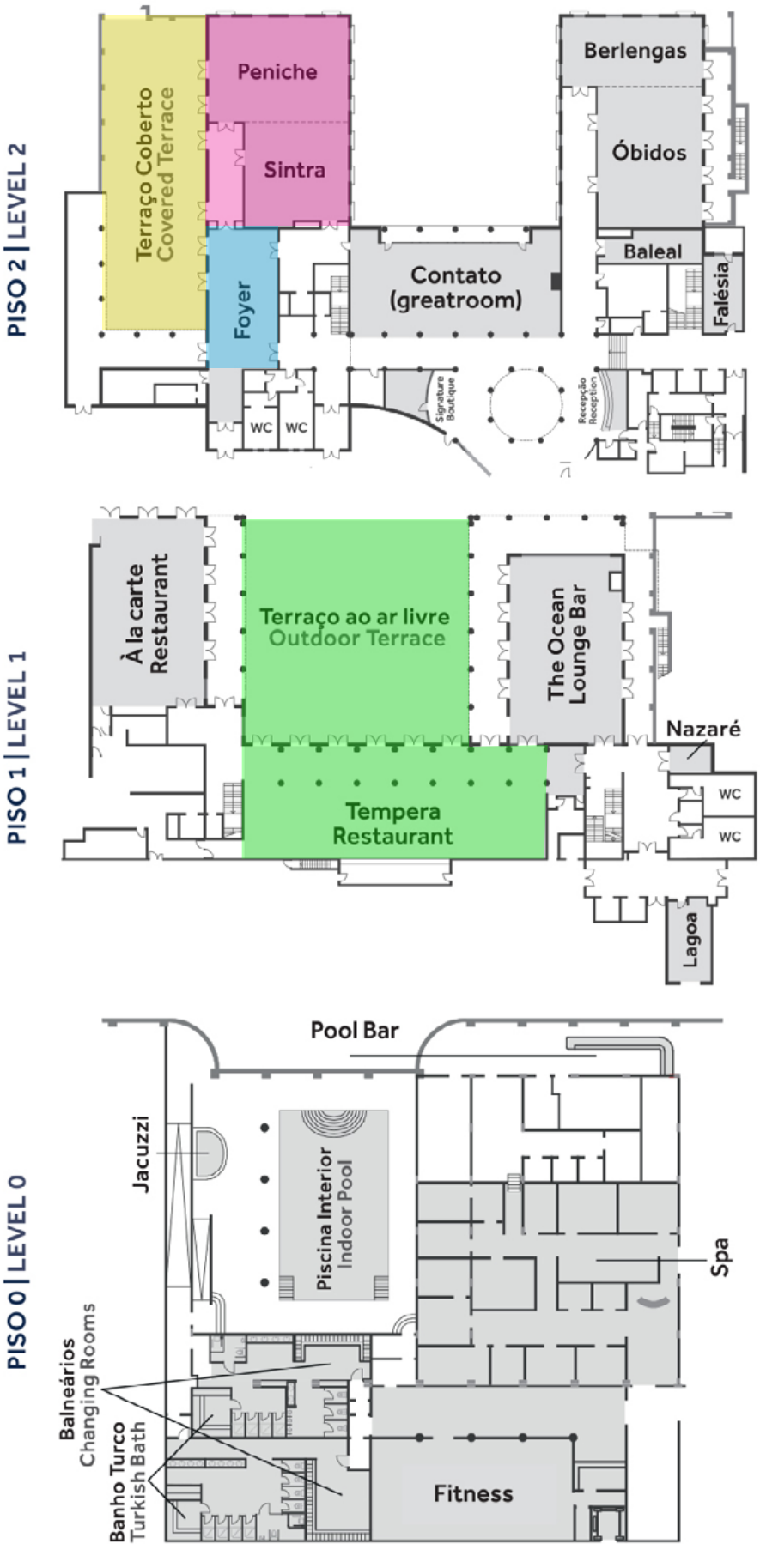
Tuesday, July 16: 6:00-17:00

Wednesday, July 17: 6:00-17:00

Floor Plans - Piso Hotel

Key

- Posters / Exhibits
- Ballroom I
- Registration
- Breakfast / Lunch



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 patientsand families affected, Exceptionally, organizations who fund or facilitate the above activities.

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 **To be Announced**

2020-2022 Recipients, Nicole Sarles-Philip and Bruno Marino

THE JUNIOR INVESTIGATOR AWARD

PRESENTED FOR OUTSTANDING 2024 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**

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.

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	To be Announced

Professor Peter Scambler, M.D.

PREVIOUS PETER SCAMBLER INVITED LECTURERS:

2022 **Robert G. Kelly**

2024 **Stephen W. Scherer**

2022 Lecturer, Robert G. Kelly

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.

Members of the 22q and You Center, Children's Hospital of Philadelphia

The 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**

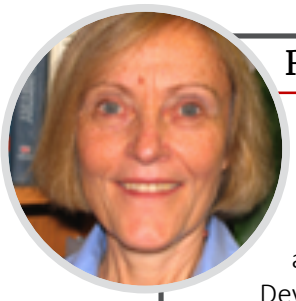
2024 **To be announced at the Silver Anniversary Gala**

2018 Recipient – 22q and You Center, Children's Hospital of Philadelphia

Shown here: Elaine Zackai - Medical Director, Donna McDonald-McGinn - Director, and Beverly Emanuel – Scientific Director

Thérèse A.M.J. Van Amelsvoort

Professor of Transitional Psychiatry and Consultant Psychiatrist at Maastricht University Medical Center, Maastricht, Netherlands



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

Beverly Emanuel

Professor of Pediatrics and Genetics and Charles E.H. Upham Endowed Chair in Pediatric Medicine at the Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Samuel Mackenzie

Assistant Professor of Child Neurology, Neuromuscular Disease, and Neuroscience at University of Rochester Medical Center, Rochester, New York, USA

Casey Gifford

Assistant Professor of Pediatrics and Genetics at Stanford University, Stanford, California, USA

Christina Miyake

Director of the Cardiovascular Genetics Arrhythmia Program at Texas Children's Hospital and Associate Professor in the Department of Molecular Physiology and Biophysics at Baylor College of Medicine, Houston, Texas, USA

Michael Granato

Professor of Cell and Developmental Biology at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Ralda Nehme

Institute scientist and principal investigator in the Stanley Center for Psychiatric Research and Director of the Stem Cell Program at the Broad Institute of MIT and Harvard, Boston, Massachusetts, USA

Randall Platt

Associate Professor of Biological Engineering at the ETH Zurich, Associate Professor at the University of Basel, and an Investigator at the Botnar Research Center for Child Health and NCCR Molecular Systems Engineering, Zurich, Switzerland

Ann Swillen

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

Peter Scambler

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

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

Stephen Scherer

Northbridge Chair in Paediatric Research and Director of The Centre for Applied Genomics at The Hospital for Sick Children in Toronto, Toronto, Canada

Irene Zohn

Associate Professor of Pharmacology and Physiology at the George Washington University School of Medicine and Health Sciences and principal investigator in the Center for Genetic Medicine Research at Children's National, Washington, DC, USA

Tuesday

JULY 16, 2024

6:00 ***REGISTRATION OPEN – BALLROOM I: PENICHE AND SINTRA FOYER***

7:00 ***BREAKFAST – TEMPERA RESTAURANT AND OUTDOOR TERRACE***

OPENING CEREMONY – BALLROOM I: PENICHE AND SINTRA

Donna M. McDonald-McGinn and Beata Nowakowska

8:00 **The 22q11.2 Society Welcomes a Parade of Nations on Our Silver Anniversary**
Donna M. McDonald-McGinn, 22q11.2 Society Chair

Bem Vindo a Portugal
Marta Sousa Santos

Program Synopsis and Acknowledgements
Beata A. Nowakowska, 22q11.2 Society Trustee and 2024 Program Chair

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

Presentation of the Clodagh Murphy Memorial Unsung Hero Award
Erik Boot, 22q11.2 Society Trustee

Opening Breath
Maria Mascarenhas

SESSION 1: GENOTYPES, PHENOTYPES, AND MECHANISMS

Chairs: Peter Scambler and Joris Vermeesch

8:30 **001** ***Invited Presentation and Lifetime Achievement Award***
Back to the Future – A Brief History of the 22q11.2 Deletion Syndrome
Beverly S. Emanuel, Philadelphia, PA, USA
Award presented by Bernice Morrow, 22q11.2 Society Trustee

8:50 **002** ***Peter Scambler Invited Lecture and Award***
Genetics of CNVs Informing Human Disorders and the Prospects for Treatment
Stephen W. Scherer, Toronto, CA
Award presented by Anne Bassett, 22q11.2 Society Treasurer

***Indicates Junior Investigator**

9:15 **Q&A**

9:20 **003** **Size Matters: Nested Chromosome 22q11.2 Deletions**
Donna M. McDonald-McGinn, Victoria Giunta, Bekah Wang, Daniel E. McGinn, Audrey Green, Lydia Rockart, Oanh Tran, Ryan LaPointe, Conner Weinberg, Sam Alperin, Vaneeta Bamba, Katherine Baum, Madeline Chadehumbe, Christopher Cielo, Malcolm Ecker, Lisa Elden, John Flynn, Brian Forbes, R. Sean Gallagher, Elizabeth Goldmuntz, Raquel E. Gur, Steven Handler, Sarah Hopkins, Oksana Jackson, Lorraine Katz, Thomas Kolon, Michele Lambert, Asim Maqbool, Maria Mascarenhas, Edward Moss, Hyun-Duck Nah, Michael Nance, Michelle Scott, Cynthia Solot, Kathleen E. Sullivan, Ian Campbell, Elaine H. Zackai, Beverly S. Emanuel, and T. Blaine Crowley

9:27 **004** **22q11.2 Deletion and Duplication Syndromes – Analysis and Refinement of Breakpoints by Array-CGH**
Joana B. Melo, Luís M. Pires, Mariana Val, Susana I. Ferreira, and Isabel M. Carreira

9:31 **005** **The Tiniest Piece Leading to a Big Picture: Nested Chromosome 22q11.2 LCR22C-LCR22D Deletions** *
Daniel E. McGinn, Victoria Giunta, Bekah Wang, T. Blaine Crowley, Audrey Green, Oanh Tran, Renee DiCicco Wright, Julie Moldenhauer, Elaine H. Zackai, Beverly S. Emanuel, and Donna M. McDonald-McGinn

9:38 **006** **22q11.2 Deletion Syndrome Parent of Origin by Sex and Race** *
Ryan Lapointe, Oanh Tran, Steven Pastor, Victoria Giunta, T. Blaine Crowley, Audrey Green, Lydia Rockart, Bekah Wang, Daniel E. McGinn, Elaine H. Zackai, Donna M. McDonald-McGinn, and Beverly S. Emanuel

9:42 **007** **Optical Mapping Reveals Significant Differences in 22q11.2 Genomic Structures Between African American and White Populations**
Steven Pastor, Oanh Tran, Ryan Lapointe, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Audrey Green, T. Blaine Crowley, Elaine H. Zackai, Donna M. McDonald-McGinn, and Beverly S. Emanuel

9:52 **008** **Proximal Nested 22q11.2 Deletions and Ancestry**
Anne S. Bassett, Tracy Heung, Erik Boot, María Ángeles Mori, María de los Ángeles Gómez Cano, Cristina Digilio, Damien Heine-Suñer, Bruno Marino, Julián Nevado Blanco, Beata Nowakowska, Federica Pulvirenti, Carolina Puttoto, Emi Rikeros, T. Blaine Crowley, Lydia Rockart, Victoria Giunta, Bekah Wang, Beverly Emanuel, the International 22q11.2 Brain and Behavior Consortium, Bernice Morrow, and Donna M. McDonald-McGinn

9:56 **009** **22q11.2DS Embryonic Stem Cell Lines with and without the Flanking Low Copy Repeats***
Marta Sousa Santos and Joris Vermeesch

***Indicates Junior Investigator**

10:00 **010** **Dissecting the Clinical Complexity of 22q11 Deletion Syndrome by Deep Phenotyping and Functional Genomics**
Maciej Geremek, Victoria Giunta, T. Blaine Crowley, Daniel E. McGinn, Audrey Green, Bekah Wang, Oanh Tran, Ryan Lapointe, Beverly S. Emanuel, Elaine H. Zackai, Donna M. McDonald-McGinn, and Beata A. Nowakowska

10:10 **011** **Two Circuits, Thirty-Two Genes, One Copy: 22q11.2 Deletion Syndrome is a Polygenic Disorder of Neural Circuit Development**
Anthony S. LaMantia

10:20 **Q&A**

10:30 ***COFFEE BREAK AND POSTER VIEWING ON THE COVERED TERRACE***
Odd Authors Present

SESSION 2: INCIDENCE, PREVALENCE, DETECTION, AND MODIFIERS

Chairs: Natalie Blagowidow and Sulagna Saitta

11:00 **012** **Cell free DNA and the Promise of Novel Biomarkers**
Joris Robert Vermeesch, Leuven, Belgium

11:15 **013** **Performance of SNP-based Cell-Free DNA Prenatal Screening for 22q11.2 Deletion Syndrome in a Commercial Population**
Wendy DiNonno, Melissa K. Maisenbacher, Georgina Goldring, Melda Balcioglu, Kayla Turner, M. Caleb Meads, Kayla Ruiz, Priyanka Arya, Jeffrey Meltzer, Katherine Howard, Sheetal Parmar

11:25 **014** **Single cell Sequencing of Circulating Extravillous Trophoblasts for Non-Invasive Fetal Copy Number Variant Screening**
Francesca Romana Grati, Tamara Stampalija, Emma Bertucci, Claudia Izzi, Paolo Volpe, Isabella Fabietti, Antonio Novelli, Lucia Pasquini, Sara Ornaghi, Elisa Bevilacqua, Dario Paladini, Tullio Ghi, Debora Lattuada, Paolo Gasparin, Fabio Facchinetti, Chiara Dordoni, Valentina De Robertis, Elena Nicastri, Valentina Parisi, Marco Bonito, Grazia Di Gregorio, Maria Verderio, Francesco Danilo Tiziano, Daniela Orteschi, Antonio Brocco, Genny Buson, Arianna Casadei, Chiara Mangano, Chiara Maranta, Martina Dori, Lorenzo Monasta, Chiara Bolognesi, Claudio Forcato, Anna Doffini, Thomas J Musci, Enrico Ferrazzi

11:35 **015** **Identification of 22q11.2 Quadruplication in Mother and Son Through Prenatal Cell-Free DNA Screening**
Natalie Blagowidow, Amy Kimball, Antonie D. Kline

11:42 **016** **Investigating the Incidence of the 22q11.2 Deletion Syndrome in Miscarriages**
Melissa K. Maisenbacher, Katrina Merrion, Jeffrey Meltzer, Katherine L. Howard, Samantha Leonard

***Indicates Junior Investigator**

11:49 **017** **Prevalence of 22q11.2 Deletion Syndrome in Offspring Conceived Via Assisted Reproductive Technology Versus Spontaneously**
Jennifer Borowka, T. Blaine Crowley, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Lorraine Dugoff, Kathleen Valverde, Donna M. McDonald-McGinn

11:55 **Q&A**

12:10 **018** **22q and Two Squared** *
Victoria Giunta, T. Blaine Crowley, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Victoria Vetter, Sarah Hopkins, Donna M. McDonald-McGinn

12:17 **019** **Unusual Cases of 22q11.2 Disorders: Phenotypes and Lessons**
Marina S. Clarke, Caroline Y. Kuo, Apisadaporn Thambundit, Gregory Perens, Chloe Rome, Sulagna C. Saitta

12:24 **020** **Hereditary Paraganglioma-Phaeochromocytoma Syndrome in a Patient With 22q11.2 Deletion Syndrome** *
Kate Rigney, TS Paran, J Pears, SM O'Connell, A James, L Bradley, W Mulcahy, S Kelleher

12:28 **021** **Influence of Polygenic Risk on Height In Individuals with a 22q11.2 Deletion** *
Shengjie Ying, Tracy Heung, Bernice Morrow, Bhooma Thiruvahindrapuram, Ryan K. C. Yuen, Anne S. Bassett

12:34 **022** **Influence of Polygenic Risk on BMI in Individuals with a 22q11.2 Deletion** *
Shengjie Ying, Tracy Heung, Bernice Morrow, Bhooma Thiruvahindrapuram, Ryan K. C. Yuen, Anne S. Bassett

12:41 **023** **Mortality and Age at Molecular Diagnosis in Adults with 22q11.2 Deletion Syndrome** *
Christina Blagojevic, Tracy Heung, Sarah L. Malecki, Sabrina Cancelliere, Maria Corral, Anne S. Bassett

12:51 **024** **Clinical Suspicion and Diagnostic Delay in a Cohort of Adults With 22q11.2 Deletion Syndrome: Are We Doing Enough?** *
Federica Pulvirenti, Eleonora Sculco, Patricia Quijada-Morales, Daniele Guadagnolo, Maddalena Sciannamea, Maria Elena Santaniello, Giulia Di Napoli, Bruno Marino, Carolina Putotto, Isabella Quinti

13:01 **025** **Rare Copy-Number Variants as Modulators of Clinical Phenotypes of Adults with 22q11.2 Deletion Syndrome** *
Federica Pulvirenti, Daniele Guadagnolo, Maddalena Sciannamea, Eleonora Sculco, Bruno Marino, Flaminia Pugnaloni, Isabella Quinti, Laura Bernardini, Carolina Putotto

***Indicates Junior Investigator**

13:10 **Q&A**

13:30 ***LUNCH – TEMPERA RESTAURANT AND OUTDOOR TERRACE***

SESSION 3: HEART, IMMUNE, AND BLOOD

Chairs: Bernice Morrow and Kathleen Sullivan

14:30 **026** ***Invited Presentation*** **- Cardiac Organoids Provide a Platform for Complex Genetic Studies of 22q11 Deletion Syndrome**
Casey Gifford, Palo Alto, CA, USA

14:45 **027** ***Tbx1*** **Promotes Maturation and Restricts Atypical Fates in Multilineage Progenitor Cells Needed to Form the Cardiac Outflow Tract**
Bernice E. Morrow, Kevyn Jackson, Alexander Ferrena, Deyou Zheng

14:55 **028** **Cell Compensation Associated with Heart Defects in a Mouse Model of 22q11.2 Deletion Syndrome**
Bingruo Wu, Punit Bhattachan, Deyou Zheng, Bernice Morrow, Bin Zhou

15:05 **029** **Spectrum of Congenital Heart Disease in a National Cohort of Patients with 22q11.2 Deletion Syndrome**
Ciara Ryan, Wesley Mulcahy, Suzanne Kelleher, Colin J. McMahon

15:09 **030** **The "Hidden" Cardiac Anomalies in Patients Presenting Without Major Congenital Heart Disease in 22q11.2 Deletion Syndrome**
Elizabeth Goldmuntz, Michelle Litvak, Brande Latney, Kristen Reed, T. Blaine Crowley, Ian Campbell, Beverly S. Emanuel, Victoria Giunta, Audrey Green, Daniel E. McGinn, Bekah Wang, Elaine H. Zackai, Donna M. McDonald-McGinn

15:16 **031** **Cardiac Disease in Patients with Distal 22q11.21-3 Deletions (LCR22D-E, D-F, D-G, E-F)**
Tanner J. Nelson, Daniel E. McGinn, Bekah Wang, Victoria Giunta, Lydia Rockart, Audrey Green, Oanh Tran, Daniella Miller, Elaine H. Zackai, T. Blaine Crowley, Beverly S. Emanuel, Elizabeth Goldmuntz, Bernice Morrow, and Donna M. McDonald-McGinn

15:20 **032** **Chromatin Modifiers to Elucidate the Phenotypic Variability of Congenital Heart Disease in 22q11.2DS** *
Daniella Miller and Bernice E. Morrow

15:25 **Q&A**

***Indicates Junior Investigator**

15:40 **033** **Ipsc-Derived Thymic Epithelial Cells Promote Tcrab and Regulatory T Cell Reconstitution in Athymic NSG-Nude Mice**
Hanh Dan Nguyen, Abdulvasey Mohammed, Wenqing Wang, Kelsea M. Hubka, Martin Arreola, Zihao Zheng, Priscila Slepicka, Benjamin D. Solomon, Vittorio Sebastiano, Andrew Gentles, and Katja G. Weinacht

15:50 **034** **Single Cell RNA-Seq Identifies Significant Differences in CD4 T Cell Populations Between 22q11.2 Deletion Syndrome and Controls**
Nouf Alsaati, Montana Knight, Kelly Maurer, and Kathleen Sullivan

16:00 **035** **Elucidating Humoral Immunity and Vaccine Response in Pediatric Patients with 22q11.2 Deletion Syndrome: A Retrospective Case Series** *
Laura Gutierrez, Raul Escobar, Hanadys Ale

16:07 **036** **Four Patients with Severe Immune Related Complications Including Lymphoma and Interstitial Lung Disease**
Jenny Lingman Framme, Annika Malmgren, Vanda Friman, Sólveig Óskarsdóttir

16:14 **037** **A Cohort Study Demonstrating Atypical Characteristics of Iron Deficiency in Patients With 22q11.2DS**
T Blaine Crowley, Donna M McDonald-McGinn, and Michele P Lambert

16:20 **Q&A**

16:30 ***AFTERNOON TEA AND POSTER VIEWING ON THE COVERED TERRACE***
Even Poster Authors Present

SESSION 4: THYROID, PARATHYROID, AND GROWTH

Chairs: Emily Gallagher and Sólveig Óskarsdóttir

17:00 **038** **Occurrence of Hypothyroidism and Hyperthyroidism in 22q11.2 Deletion Syndrome**
Vaneeta Bamba, Bekah Wang, T. Blaine Crowley, Victoria Giunta, Audrey Green, Elaine H. Zackai, Beverly S. Emanuel, Donna M. McDonald-McGinn, Edna E. Mancilla, Lorraine Katz

17:07 **039** **Association of thyroid and parathyroid disease in 22q11.2 deletion syndrome patients followed at Nationwide Children's Hospital** *
Bianca Zapanta, Cole Simons, Kathryn Stephens Obrynba, Scott E. Hickey

17:14 **040** **Outcomes of Provocative Growth Hormone Testing in Patients with 22q11.2 Deletion Syndrome and Short Stature** *
Rachel Brown, Ian Campbell, T. Blaine Crowley, Victoria Giunta, Daniel McGinn, Beverly S. Emanuel, Elaine H. Zackai, Donna M. McDonald-McGinn, Vaneeta Bamba, Lorraine E.L. Katz

***Indicates Junior Investigator**

17:21 **041** **Growth Hormone Treatment in Patients with 22q11.2 Deletion Syndrome and Short Stature**

Lorraine E. Levitt Katz, Rachel Brown, Ian Campbell, T. Blaine Crowley, Victoria Giunta, Audrey Green, Daniel E. McGinn, Bekah Wang, Edna Mancilla, Beverly S. Emanuel, Elaine H. Zackai, Donna M. McDonald-McGinn, Vaneeta Bamba

17:28 **042** **Association Between Congenital Heart Defects and Growth in the 22q11.2 Deletion Syndrome**

Lisa Briel, Cas L.J. Kruitwagen, Martijn G. Slieker, Hanneke M. van Santen, Michiel L. Houben

18:05 **043** **Children and Young Adults with 22q11.2 Deletion Syndrome and Fractures: A Case Series**

Lama Alzoebie, Bekah Wang, T. Blaine Crowley, Victoria Giunta, Audrey Green, Elaine H. Zackai, Beverly S. Emanuel, Donna M. McDonald-McGinn, Vaneeta Bamba, Lorraine Katz, Victor Ho-Fung, and Edna E. Mancilla

18:12 **044** **Obesity and Metabolic Syndrome in Adults with 22q11.2 Deletion Syndrome**

Hester Jaspers Faijer-Westerink, Emma N.M.M. von Scheibler, Elisabeth F.C. van Rossum, Thérèse A.M.J. van Amelsvoort, Agnies M. van Eeghen, Erik Boot

18:19 **045** **Non-Fasting Triglyceride-Glucose Index as a Marker of Metabolic Syndrome In 22q11.2 Deletion Syndrome**

Sabrina Cancelliere, Tracy Heung, Anne S. Bassett

18:26 **046** **Trajectory of Cardiometabolic Conditions in Adults with 22q11.2 Deletion Syndrome**

Sarah L. Malecki, Tracy Heung, Samantha Morais, Refik Saskin, Drew Wilton, Anne S. Bassett

18:35 **Q&A**

18:45 ***FAMILY VOICES – MARC AND BARBI WEINBERG***

19:00 **Adjourn**

20:00 POOLSIDE WELCOME RECEPTION

Signature Cocktail
and Heavy Hors d'oeuvres

***Indicates Junior Investigator**

Wednesday

JULY 17, 2024

6:00 *REGISTRATION OPEN – BALLROOM I: PENICHE AND SINTRA FOYER*

7:00 *BREAKFAST – TEMPERA RESTAURANT AND OUTDOOR TERRACE*

SESSION 5: HEENT, EARLY DEVELOPMENT, AND SLEEP

Chairs: Jill Arganbright and Ann Swillen

8:00 **047** **Ophthalmologic Manifestations Associated with 22q11.2 Copy Number Variants: An Update**

Brian J. Forbes, Lydia Rockart, Victoria Giunta, Daniel E. McGinn, Audrey Green, Bekah Wang, Oanh Tran, Elaine H. Zackai, Beverly S. Emanuel, Jane C. Edmond, Monte Mills, William Anninger, Gil Binenbaum, T. Blaine Crowley, and Donna M. McDonald-McGinn

8:07 **048** **Prevalence of Preterm Birth and Polyhydramnios in Association with 22q11.2 Deletion Syndrome**

Hayley Ron, T. Blaine Crowley, Jennifer Borowka, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Oanh Tran, Beverly S. Emanuel, Oksana Jackson, Ian Jacobs, Karen Zur, Lisa Elden, Maria Mascarenhas, Julie Moldenhauer, Elaine H. Zackai, Ian Campbell, Kathleen Valverde, and Donna M. McDonald-McGinn

8:14 **049** **Tracheoesophageal Anomalies in Association with the Chromosome 22q11.2 Deletion Syndrome** *

Bekah Wang, Daniel E. McGinn, Victoria Giunta, T. Blaine Crowley, Audrey Green, Erica Schindewolf, Julie Moldenhauer, Lisa Elden, Ian Jacobs, Karen Zur, Beverly S. Emanuel, Elaine H. Zackai, Maria Cristina Digilio, and Donna M. McDonald-McGinn

8:21 **050** **Gastroesophageal Reflux Disease and Associated Comorbidities in Patients with 22q11.2 Deletion Syndrome**

Asim Maqbool, T. Blaine Crowley, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Lauren Lairson, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Ian Campbell, Donna M. McDonald-McGinn, Prasanna Kapavarapu, Maria Mascarenhas

8:27 **051** **Prevalence of Enteral Feeding and Subsequent Intervention in Patients with 22q11.2 Deletion Syndrome**

Maria Mascarenhas, Victoria Giunta, T. Blaine Crowley, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Asim Maqbool, Prasanna Kapavarapu, Donna M. McDonald-McGinn

***Indicates Junior Investigator**

8:34 **052** **Dysphagia in Children with 22q11.2 Deletion Syndrome and 22q Duplication Syndrome**
Jill Arganbright, Jana Ghulmiyyah, Srivats Narayanan, Lauren Bartik, Meghan Tracy, Hung-Wen Yeh, Janelle Noel-MacDonnell, Jake Schneider

8:41 **053** **Exploring the Presentation and Mechanism of Dysphagia in Adults with 22q11.2 Deletion Syndrome**
Samantha D'Arcy, Tracy Heung, Nikolai Reyes, Anne S. Bassett

8:45 **054** **Dental Caries and Malocclusion in Patients with 22q11.2 Deletion and Duplication Syndromes** *
Shalin N. Shah, Cynthia Solot, Oksana Jackson, Audrey Green, Bekah Wang, Victoria Giunta, T. Blaine Crowley, Beverly S. Emanuel, Elaine H. Zackai, Lorraine L. Katz, L. Yap, Donna M. McDonald-McGinn, Hyun Duck Nah

8:49 **055** **Guidelines on the Dental Management of Individuals With 22q11.2DS** *
Charlotte Lenes, Rohan Dasari, Michelle Scott

8:53 **056** **Surgical Decision Making for Patients with 22q11.2 Deletion Syndrome and Velopharyngeal Dysfunction: A Clinical Update**
Jill M Arganbright

9:00 **057** **Long-term Changes in Post-Operative Hypernasality Over Time in Patients with 22q11.2 Deletion Syndrome and Velopharyngeal Insufficiency**
Sylvie Render, Alexander Szymczak, Laura H. Swibel Rosenthal

9:07 **058** **Prevalence of Permanent Hearing Loss and Ear Malformations in Children with Distal LCR22D-LCR22E 22q11.2 Deletions**
Lisa Elden, Daniel E. McGinn, Victoria Giunta, Bekah Wang, Audrey Green, Lydia Rockart, Oanh Tran, Beverly S. Emanuel, Conor Devine, Scott P. Bartlett, Elaine H. Zackai, T. Blaine Crowley, and Donna M. McDonald-McGinn

9:13 **Q&A**

9:25 **059** **Factors Supporting Better Language Outcomes in Children With 22q11.2 Deletion Syndrome**
Cynthia Solot, Victoria Giunta, Daniel E. McGinn, Lydia Rockart, Bekah Wang, Audrey Green, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Oksana Jackson, Katherine Baum, Edward Moss, T. Blaine Crowley, and Donna M. McDonald-McGinn

***Indicates Junior Investigator**

9:32 **060** **Language Abilities of School-Aged Children With 22q11.2 Copy Number Variants: A Two-Site Study** *

Jente Verbesselt, Cynthia B. Solot, Ellen Van Den Heuvel, Jeroen Breckpot, Donna M. McDonald-McGinn, Inge Zink and Ann Swillen

9:36 **061** **Linguistic Profile in Children and Adolescents with 22q11 Syndrome** *

Noelia Santos-Muriel, Noelia Pulido García, Javiera Espinosa Villarroel, Patricia López Resa, Esther Moraleda Sepúlveda

9:42 **062** **Serial Order Short-Term Memory and Vocabulary In 22q11.2 Deletion Syndrome** *

Jantine Wignand, Tessel Boerma, Iris Selten, Emma Everaert, Michiel Houben & Frank Wijnen

9:46 **063** **Early Development and Longitudinal Data in Children With 22q11.2 Duplication** *

Jente Verbesselt, Jeroen Breckpot, Inge Zink and Ann Swillen

9:53 **064** **A Comprehensive Overview of Neurodevelopmental Symptoms in Adolescents with 22q11.2 Deletion Syndrome – A Dimensional Perspective** *

Iris Selten, Jill Blok, Tessel Boerma, A. A. A. Manik J. Djelantik, Michiel Houben, Frank Wijnen, Janneke Zinkstok, & Jacob A. S. Vorstman & Ania M. Fiksinski

9:57 **065** **Irritability in Young People With Copy Number Variants Associated With Neurodevelopmental Disorders (ND-Cnvs), Including 22q11.2 Deletion Syndrome** *

Jessica H. Hall, Samuel. J.R.A Chawner, IMAGINE-ID consortium, Jeanne Wolstencroft, David Skuse, Peter Holmans, Michael J. Owen, Marianne B.M. van den Bree

10:01 **066** **Polysomnography Findings in Patients With 22q11.2 Deletion Syndrome Related To Tonsillectomy**

Jill Arganbright, Bryan Hankey, Hannah Brown, Meghan Tracy, Janelle Noel-Macdonnell, Yaslam Balfaqih, Dave Ingram, Lisa Elden, Oksana Jackson, Blaine Crowley, Christopher Cielo, Donna McDonald-McGinn

10:05 **067** **Tonsillectomy in Children With 22q-Related Disorders**

Jill Arganbright, Hannah Brown, Bryan Hankey, Meghan Tracy, Janelle Noel-MacDonnell

10:09 **068** **Sleep Difficulties Related to Psychopathology and Neurocognition in People With 22q11.2 Deletion Syndrome**

Raquel E. Gur, Margaret C. Souders, Kosha Ruparel, Tyler M. Moore, T. Blaine Crowley, Elaine H. Zackai, Beverly S. Emanuel, Donna M. McDonald-McGinn, Ruben C. Gur

10:13 **069** **Sleep and Cognition in Individuals with 22q11.2 Deletion Syndrome** *

Kathleen P. O'Hora, Charles Schleifer, Jennifer Xu, Elizabeth Bondy, Hoki Fung, Leila Kushan-Wells, Jared M. Saletin, Carrie E. Bearden

***Indicates Junior Investigator**

10:20 **Q&A**

10:30 ***COFFEE BREAK AND POSTER VIEWING ON THE COVERED TERRACE***
Even Authors Present

SESSION 6: SPINE AND BRAIN

Chairs: Madeline Chadehumbe and Elfi Vergaelen

11:00 **070** **Prospective Natural History Study of Idiopathic-like Scoliosis in Patients with 22q11.2 Deletion Syndrome, Starting Before its Pathological Onset** *
Lafranca Peter, de Reuver S, Abdi A, Kruijt MC, Houben ML, Ito K, Castelein RM, Schlösser TPC

11:04 **071** **Tethered Spinal Cord in Association with 22q11.2 Deletion Syndrome**
Madeline Chadehumbe, Sarah E. Hopkins, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Sam Alperin, T. Blaine Crowley, and Donna M. McDonald-McGinn

11:11 **072** **Possible Causes of Lower Extremity Pain in Children with 22q11.2 Deletion Syndrome - A Retrospective Cohort Study**
Michiel L. Houben, Femke G.M. van den Helder

11:15 **073** **Occipital Frontal Circumference in 22q11.2 Deletion Versus 22q11.2 Duplication Syndromes**
Sarah Hopkins, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Lauren Lairson, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, T. Blaine Crowley, Ian Campbell, Sam Alperin, Madeline Chadehumbe, Donna M. McDonald-McGinn

11:22 **074** **Neuroradiological Findings in a Large, Unselected Clinical Sample of Individuals with 22q11.2 Deletion Syndrome (22q11.2DS)**
J. Eric Schmitt, Jenna Schabdach, 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

11:29 **075** **Neuroradiologic Findings in 22q11.2 Duplication Syndrome and Comparison to 22q11.2 Deletion Syndrome***
Samuel Alperin, Sarah E. Hopkins, T. Blaine Crowley, Daniel E. McGinn, Lauren Lairson, Victoria Giunta, Beverly S. Emanuel, Elaine H. Zackai, and Donna M. McDonald-McGinn

***Indicates Junior Investigator**

11:36 **076** **Local Cerebellar Dysplasia and Motor Learning Deficit in 22q11.2 Deletion Syndrome are Attributed to a Skeletal Deformity**

Tae-Yeon Eom, J Eric Schmitt, Yiran Li, Audrey Bonnan, Christopher M. Davenport, Khaled Khairy, David R. Roalf, Raquel E. Gur, Beverly S. Emanuel, Donna M. McDonald-McGinn, Jason M. Christie, Paul A. Northcott, Stanislav S. Zakharenko

11:45 **Q&A**

11:55 **077** **Presence, Severity, and Functional Associations of Incomplete Hippocampal Inversion in 22q11.2 Deletion Syndrome**

David Roalf, Donna M. McDonald-McGinn, J. Eric Schmitt, Sarah Hopkins, Adam Czernuszenko, Ally Atkins, Margaret Pecsok, Aaron Alexander-Bloch, T. Blaine Crowley, R. Sean Gallagher, Emily McClellan, Daniel E. McGinn, Paul J. Moberg, Kosha Ruparel, Bruce I. Turetsky, Lauren White, Elaine H. Zackai, Ruben C. Gur & Raquel. E. Gur

12:02 **078** **Synaptic-related Developmental Dysconnectivity in 22q11.2 Deletion Syndrome**

Filomena Grazia Alvino, Silvia Gini, Antea Minetti, David Sastre-Yagüe, Charles Schleifer, Alexia Stuefer, Marco Pagani, Caterina Montani, Alberto Galbusera, Francesco Papaleo, Michael Vincent Lombardo, Massimo Pasqualetti, Carrie E. Bearden, Alessandro Gozzi

12:09 **079** **22q11.2 Gene Dosage Effects on Cerebello-cortical Functional Connectivity**

Hoki Fung, Charles Schleifer, Kathleen O'Hora, Leila Kushan, Elizabeth Bondy, Carrie E. Bearden

12:16 **080** **Neurite Orientation Dispersion and Density Imaging in 22q11.2 Deletion and Duplication carriers** *

Rune Boen, Julio Villalon-Reina, Leila Kushan, Nadine Parker, Ibrahim A. Akkouh, Dag Alnæs, Sergiu Pasca, Ruth O'Hara, Matthew John Marzelli, Lara Foland-Ross5, Christina French Chick, Isabelle Cotto, Allan Reiss, Joachim Hallmayer, Ole A. Andreassen, Ida E. Sønderby, Carrie E. Bearden

12:20 **081** **Focal Volumetric Reductions in Subthalamic Nuclei in the 22.11.2 Deletion Syndrome (22q11DS)**

J. Eric Schmitt, David Roalf, Donna M. McDonald-McGinn, Simon Smerconish, Sarah Hopkins, Aaron Alexander-Bloch, T. Blaine Crowley, R. Sean Gallagher, Daniel E. McGinn, Kosha Ruparel, Lauren K. White, Elaine H. Zackai, Anne Bassett, Stanislav Zakharenko, Ruben C. Gur, and Raquel. E. Gur

12:27 **082** **Altered GABA-ergic Short-term Synaptic Plasticity in Prefrontal Cortex of a Mouse Model of 22q11DS**

Gregg W. Crabtree

12:31 **083** **7-Tesla in-vivo 1H-magnetic Resonance Spectroscopy of Glutamate and GABA in 22q11.2 Copy Number Variants.**

Claudia Vingerhoets, Amy Sylvester, Chaira Serrarens, Esther Steijvers-Peeters, Kim Brouwers, David E. J. Linden, Desmond HY Tse and Therese van Amelsvoort

***Indicates Junior Investigator**

12:35 **084** **Unique Functional Neuroimaging Signatures of Genetic Versus Clinical High Risk for Psychosis**

Charles H. Schleifer, Sarah E. Chang, Carolyn M. Amir, Kathleen P. O'Hora, Hoki Fung, Leila Kushan-Wells, Jee Won Kang, Eileen Daly, Fabio Di Fabio, Marianna Frascarelli, Maria Gudbrandsen, Wendy R. Kates, Declan Murphy, Jean Addington, Alan Anticevic, Kristin S. Cadenhead, Tyrone D. Cannon, Barbara A. Cornblatt, Matcheri Keshavan, Daniel H. Mathalon, Diana O. Perkins, William Stone, Ming Tsuang, Elaine Walker, Scott W. Woods, Lucina Q. Uddin, Kuldeep Kumar, Gil Hoftman, Carrie E. Bearden

12:42 **085** **Neuromelanin-sensitive Magnetic Resonance Imaging as a Proxy for Dopamine and Norepinephrine Dysfunction in 22q11.2 Deletion/Duplication Syndrome: Interim Results***

Amy Sylvester, Jeltje Spapens, Chaira Serrarens, Amée Wolters, Nikos Priovoulos, Desmond Tse, Dimo Ivanov, Benedikt Poser, David Linden, Thérèse van Amelsvoort & Claudia Vingerhoets

12:45 **Q&A**

13:00 ***LUNCH – TEMPERA RESTAURANT AND OUTDOOR TERRACE***

SESSION 7: TRANSITION, TRANSCRIPTION, AND iPSCS

Chairs: Ania Fiksinki and Beata Nowakowska

14:00 **086** ***Invited Presentation*** **- Transition from Youth to Adult Care, Most Recent Insights and Future Challenges**

Therese van Amelsvoort, Maastricht, the Netherlands

14:10 **087** ***Invited Presentation*** **- Cognitive, Adaptive and Daily Life Functioning in Adults with 22q11.2 Deletion Syndrome**

Ann Swillen, Leuven, Belgium

14:20 **088** **Global Burden of Clinical Conditions in 405 Canadian Adults with 22q11.2 Deletion Syndrome ***

Christina Blagojevic, Tracy Heung, Sarah L. Malecki, Sabrina Cancelliere, Vikita Mehta, Brigid Conroy, Anne S. Bassett

14:27 **089** **Secular and other Trends in 22q11.2 Deletion Syndrome at Transition to Adult Care and Beyond**

Tracy Heung, Christina Blagojevic, Lisa Palmer, Samantha D'Arcy, Maria Corral, Anne S. Bassett

***Indicates Junior Investigator**

14:34 **090** **An Examination of Select Functional Outcomes in Adults with 22q11.2 Deletion Syndrome**
Lisa Palmer, Tracy Heung, Sierra McNulty, Maria Corral, Anne S. Bassett

14:40 **Q&A**

14:50 **091** ***Invited Presentation*** **- Systematic Genetic Dissection of 22q11.2-Linked Genes In Vivo With AAV-Perturb-Seq**
Randall J. Platt, Zurich, Switzerland

15:05 **092** **Premature Neurogenesis Prefigures Loss of Upper Layer Cortical Neurons in 22q Model Mice**
Thomas Maynard, Shah Rukh, Zachary Erwin, Anthony LaMantia, Daniel Meechan

15:15 **093** **Subtype-specific Alterations in Interneuron Activity During Learning in the 22q11.2 Deletion CA1**
Stephanie Herrlinger, Bovey Y Rao, Anna L Tuttman, Haroon Arain, Bert Vancura, Tristan Geiller, Erdem Varol, Joseph A Gogos, Attila Losonczy

15:25 **094** **Transcriptional Regulation of Basal Progenitor Cells in the Developing Cortex of 22q11DS Model** *
S. Rukh, D. W. Meechan, T. M. Maynard, Z. Erwin, C. Siggins, A.S. LaMantia

15:32 **095** **Investigating Convergent Cellular Phenotypes of 22q11 and 3q29 Deletions**
Ryan H. Purcell, Maxine I. Robinette, Erica J. Duncan, Joseph F. Cubells, Zhexing Wen, Jennifer G. Mulle, Victor Faundez, Gary J. Bassell

15:35 **Q&A**

15:50 **096** **Generation of Induced Pluripotent Stem Cells Carrying 22q11.2 CNVs as a Model System for Studying Neurodevelopmental Disorders**
Danijela Drakulic, Natasa Kovacevic-Grujicic, Olena Petter, Mina Peric, Goran Cuturilo, Ivana Simeunovic, Jovana Kostic, Danijela Stanisavljevic Ninkovic, Adrian J. Harwood, Milena Stevanovic

15:54 **097** **Protein and RNA levels in 22q11.2DS iPSC Derived Neurons Compared to Controls over a 100-day Time Course** *
Sabrina Burton, Gemma Wilkinson, Adrian Harwood, Lawrence Wilkinson

16:00 **098** **Multi-modality Functional Genomics Analysis of the Effects of the 22q11.2 Deletion in Multiple Cell Types, Obtained with Multiple Cell-reprogramming Methods**
Alexander E Urban

***Indicates Junior Investigator**

16:04 **099** **Generation and Characterization of Human Induced Pluripotent Stem Cell Derived Neuronal Models from Patients with Microdeletion Syndrome and Microduplication Syndrome 22q11.2**

Franziska Radtke, Deniz Gücsavas, Rhiannon V. McNeill, Matthias Nieberler, Georg C. Ziegler, Zora Schickardt, Carolin Kurth, Marcel Romanos, Sarah Kittel-Schneider

16:10 **Q&A**

16:20 ***FAMILY VOICES – CAROL CAVANA***

16:30 ***AFTERNOON TEA AND POSTER VIEWING ON THE COVERED TERRACE***

Odd Authors Present

17:00 ***SPECIAL PRESENTATION: STREAMLINE - MODELING NEURODEVELOPMENTAL DISORDERS***

STREAMLINE Horizon Europe iPSC Project Description and Report of Current Results

Danijela Drakulic, Belgrade, Serbia
Adrian Harwood, Cardiff, Wales, and Maastricht, the Netherlands
Janet Harwood, Cardiff, Wales
Goran Cuturilo, Belgrade, Serbia

18:00 **Adjourn**

19:00 **22q OLYMPICS AND SUNSET SOCIAL**

Indicates Junior Investigator

Thursday

JULY 18, 2024

6:00 ***REGISTRATION OPEN – BALLROOM I: PENICHE AND SINTRA FOYER***

7:00 ***BREAKFAST – TEMPERA RESTAURANT AND OUTDOOR TERRACE***

SESSION 8: COORDINATION, INTERVENTIONS, AND OUTCOMES

Chairs: Anne Bassett and Raquel Gur

8:00 **100** **The 22q and You Center – A Model for Comprehensive Multidisciplinary Coordinated Care**

T. Blaine Crowley, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Audrey Green, Lydia Rockart, Oanh Tran, Ryan LaPointe, Conner Weinberg, Sam Alperin, Sarah Hopkins, Madeline Chadehumbe, Vaneeta Bamba, Lorraine Katz, Katherine Baum, Ed Moss, Malcolm Ecker, John Flynn, Lisa Elden, Steven Handler, Brian Forbes, Elizabeth Goldmuntz, Oksana Jackson, Cynthia Solot, Thomas Kolon, Asim Maqbool, Maria Mascarenhas, Michael Nance, Kathleen Sullivan, Beverly S. Emanuel, Ian Campbell, Elaine H. Zackai, and Donna M. McDonald-McGinn

8:07 **101** **Characterizing the Spectrum of Clinical Manifestations in 22q11.2 Duplication Syndrome: Insights from an Institutional Experience** *

Gail Budhu, Kristen Facey, Raghuram Reddy, Karla Santoyo, Raul Escobar, Brian Cauff, Hanadys Ale

8:11 **102** **Clinical Review of a Large 22q11.2 Cohort at a Tertiary Centre** *

Megan Dunlop, Alice Roueché, Julia Kenny

8:15 **103** **An Overview of 22q11.2 Diagnostic and Research Facilities in the Countries of The Western Balkan Region**

Goran Cuturilo, Danijela Drakulic, Natasa Kovacevic-Grujicic, Mina Peric, Milena Stevanovic

8:19 **104** **Overview of 22q11.2 Deletion Syndrome: A First Moroccan Pediatric Series**

Asmaa Gaadi, Said Trhanint, Laila Boughenouch, Karim Ouldim, Ahmed Aziz Bousfiha, Mouna Lehlimi

***Indicates Junior Investigator**

8:23 **105** **Establishing a Support Framework for Children with 22q11.2DS in School Settings in Japan**
Simon Elderton, Chiaki Kitamura, Ai Muro, Yuma Chino, Hiroki Ishiguro, Yasue Horiuchi, Nobuhiko Hayashi, Satoko Nakagomi

8:27 **106** **No-show Clinic Appointments and the Social Determinants of Health in Pediatric Patients with 22q11.2 Deletion Syndrome and 22q Duplication Syndrome**
Jill Arganbright, Meghan Tracy, Adrian Williamson

8:31 **107** **Parent Acceptability of a 22q Multidisciplinary Infant Assessment Clinic to Assess Motor and Cognition in Infants with 22q** *
Cindy Trevino, Tracy Brundage, Emily Gallagher

8:35 **108** **Animation Genetic Counselling Aid for Adults with 22q11.2DS and their Caregivers**
Lisa Palmer, Emily Tjan, Nicholas Woolridge, Samantha D'Arcy, Joanne Loo, Anne S. Bassett

8:40 **Q&A**

8:50 **109** ***Invited Presentation*** **- Neurobiological Insights from Human Cellular Models of the 22q11 Deletion Syndrome**
Ralda Nehme, Boston, MA, USA

9:05 **110** ***Invited Presentation*** **- A Report from the International 22q11.2 Brain and Behavior Consortium and Genes 2 Mental Health Network**
Raquel E. Gur, Philadelphia, PA, USA

9:15 **111** **CNVs Elucidate Rare-variant Associations and Genotype-phenotype Relationships across 6 Major Psychiatric Disorders**
Jonathan Sebat, Omar Shanta, Worrowat Engchuan, Marieke Klein, Adam Maihofer, Jeff MacDonald, Bhooma Thiruvahindrapuram, James Guevara, Oanh Hong, Guillaume Huguet, Maria Kalyuzhny, Caroline Nievergelt, Sandra Sanchez-Roige, Patrick Sullivan, Sebastien Jacquemont, Steve Scherer, and the Autism, ADHD, Bipolar Disorder, Major Depressive Disorder, PTSD, Schizophrenia, and CNV Working Groups of the Psychiatric Genomics Consortium.

9:22 **112** **The Clinical Course of Individuals with 22q11.2 Deletion Syndrome Converting to Psychotic Disorders: a Long-term Multi-center Retrospective Follow-up**
Katerina Kulikova, Maude Schneider, Donna M. McDonald McGinn, Shira Dar, Michal Taler, Stepan Eliez, Raquel E. Gur, Doron Gothelf

9:29 **113** **The Core PsychoPathology Summary (C2PS): A Novel Tool to Harmonize Large Scale Neuropsychiatric Phenotype Collection for Genomic Studies**
Danielle Baribeau, Ania Fiksinksi, Genes to Mental Health Network (G2MH), Carrie E. Bearden, Jacob A.S. Vorstman

***Indicates Junior Investigator**

9:36 **114** **Neuropsychiatric Presentation in de novo and Inherited 22q11.2 Deletion Syndrome**
Ruben C. Gur, R. Sean Gallagher, Emily J. McClellan, T. Blaine Crowley, Daniel E. McGinn, Elaine H. Zackai, Kosha Ruparel, Tyler M. Moore, Beverly S. Emanuel, Donna M. McDonald-McGinn, Raquel E. Gur

9:45 **Q&A**

9:57 **115** **Integrative Health and 22q11.2 Copy Number Variants: Results of a Patient-family Survey** *
Lydia Rockart, Robin Miccio, Lisa Squires, T. Blaine Crowley, Audrey Green, Victoria Giunta, Donna M. McDonald-McGinn, Maria Mascarenhas

10:04 **116** **Use of Auricular Acupressure for Symptom Control in a Child with 22q11.2 Deletion Syndrome**
Maria R. Mascarenhas, Lisa Squires, Christina L. Szperka, Melissa Crawford, and Donna M. McDonald-McGinn

10:08 **117** **Evaluating the Impact of an Online Coaching Intervention for Parents of Children Diagnosed with the 22q11.2 Deletion Syndrome** *
Holly Carbyn, Patricia Lingley-Pottie, Lisa D. Palmer, Andrea Shugar, Donna M. McDonald-McGinn, Patrick J. McGrath, Anne S. Bassett, Cheryl Cytrynbaum, Ann Swillen & Sandra Meier

10:15 **118** **Assessing the Dietary Impact of an Online Nutrition Program for Adults with 22q11.2 Deletion Syndrome**
Samantha D'Arcy, Lisa Palmer, Maria Corral, Anne S. Bassett

10:20 **Q&A**

10:30 ***COFFEE BREAK AND POSTER VIEWING ON THE COVERED TERRACE***

SESSION 9: DIET, VITAMINS, AND TRADITIONAL THERAPEUTICS

11:00 **119** ***Invited Presentation*** **- Maternal Diet as a Modifier of Congenital Heart Disease in 22q11.2 Deletion Syndrome**
Irene Zohn, Washington, DC, USA

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11:15 **120** **Tbx1 Haploinsufficiency Causes Brain Metabolic and Behavioral Anomalies in Adult Mice which are Corrected by Vitamin B12 Treatment**
Marianna Caterino, Debora Paris, Giulia Torromino, Michele Costanzo, Gemma Flore, Annabella Tramice, Elisabetta Golini, Silvia Mandillo, Diletta Cavezza, Claudia Angelini, Margherita Ruoppolo, Andrea Motta, Elvira De Leonibus, Antonio Baldini, Elizabeth Illingworth and Gabriella Lania

11:22 **121** **Exploring the Epigenetic Impact of Vitamin B12 Supplementation on Cardiac Phenotypes in a 22q11.2DS Mouse Model** *
Llull-Albertí, M.V, Ventayol-Guirado, M, Amengual-Cladera, E, Hernández-Rodríguez, J, Merkel, A, Asensio, VJ, Muncunill, J, Rocha, J, Torres-Juan, L, Santos-Simarro, F, Martínez, I, Baldini, A, Illingworth, E, Lania, G, Esteller, M, Heine-Suñer, D

11:29 **122** **Changes in Dietary Vitamin A Dosage Disrupt Compensatory Mechanisms in the Cardiac Phenotype of a 22q11.2 Deletion Syndrome Mouse Model** *
Llull-Albertí, M.V, Amengual-Cladera, E, Ventayol-Guirado, M, Hernández-Rodríguez, J, Asensio, VJ, Muncunill, J, Rocha, J, Torres-Juan, L, Santos-Simarro, F, Martínez, I, Baldini, A, Illingworth, E, Lania, G, Heine-Suñer, D

11:36 **123** **Real-world Treatment of Schizophrenia in Adults with a 22q11.2 Microdeletion**
Anne S. Bassett, Tracy Heung, Lily Van, Nikolai Gil D. Reyes, Erik Boot, Eva W. C. Chow, Maria Corral

11:46 **124** **Historical Perspective of the Role of Fasoracetam in Neurodevelopmental Disorders**
Hakon Hakonarson, Donna M. McDonald-McGinn

11:50 **125** **A Randomized, Double-blind, Placebo-controlled Phase 2 Clinical Trial of NB-001 (fasoracetam) for Neuropsychiatric Symptoms in Children and Adolescents with 22q11 Deletion Syndrome (22q11DS)**
Madeline Chadehumbe, Sarah Hopkins, Raquel E. Gur, Donna M. McDonald-McGinn, Emily R. Gallagher, Kerry D. Conant, Naomi J.L. Meeks, Hakon Hakonarson, Nancy J. Butcher, Danielle Baribeau, Jacob Vorstman

11:57 **126** **Riluzole as Cognitive Enhancer in 22q11.2 Deletion Syndrome?**
Claudia Vingerhoets, Amy Sylvester, Desmond Tse, Chaira Serrarens, Paddy Janssen, Ann Swillen, Elfi Vergaelen, Annick Vogels, Janneke Zinkstok & Therese van Amelsvoort

12:00 **Q&A**

***Indicates Junior Investigator**

12:15 **127** **TANGO2: What's it to You?**
Donna M. McDonald-McGinn, Victoria Giunta, Daniel E. McGinn, Bekah Wang, Lydia Rockart, Audrey Green, Oanh Tran, Ryan Lapointe, Elaine H. Zackai, Beverly S. Emanuel, T. Blaine Crowley, Madeline Chadehumbe, Sarah Hopkins, Jeroen Breckpot, Ann Swillen, Joris Vermeesch, Maciej Geremek, and Beata A. Nowakowska

12:20 **128** ***Invited Presentation*** **- Prevention, Recognition, and Life Saving Treatment: TANGO2 Deficiency Disorder and Life-Threatening Cardiac Risks among 22q11.2 Patients**
Christina Y. Miyake, Houston, TX, USA

12:30 **129** ***Invited Presentation*** **- Episodic Dystonia, Ataxia, and Weakness in Children with 22q11.21 Deletion Syndrome Should Prompt Consideration of Co-morbid TANGO2 Deficiency Disorder**
Samuel J. Mackenzie, Rochester, NY, USA

12:40 ***FAMILY VOICES- DEBBIE DELOACH***

12:50 **Q&A**

13:00 ***LUNCH – TEMPERA RESTAURANT AND OUTDOOR TERRACE***

SESSION 10: MOVEMENT AND MITOCHONDRIA

Chairs: Erik Boot and Therese van Amelsvoort

14:00 **130** ***Invited Presentation*** **- Using Zebrafish to Functionally Define Unique and Overlapping Developmental and Behavioral Roles of Genes Deleted in 22q11.2**
Michael Granato, Philadelphia, PA, USA

14:15 **131** **Neurovascular Mitochondrial Susceptibility in the 22q11.2 Deletion Syndrome Impacts Blood-Brain Barrier Function and Behavior**
Crockett, A. M, Vélez Colón, M. C, Kebir, H, Iascone, D. M, Cielieski, B, Rossano, A, Sehgal, A, Anderson, S. A, Alvarez, J. I

14:25 **132** **Synaptic Energetics in Schizophrenia Risk and Treatment in the Context of 22q11.2 Deletion Syndrome**
Eleonora Stronati, Adam Rossano, Minna Kim, Raquel Gur, Donna McDonald-McGinn, Stewart Anderson

14:32 **133** **Transcriptional Response to Mitochondrial Dysfunction, and Treatment, in Developing Cortical Projection Neurons**
Daniel Meechan, Shah Rukh, Abra Roberts, Zachary Erwin, Thomas Maynard, Anthony LaMantia

***Indicates Junior Investigator**

14:38 **Q&A**

14:53 **134** **Prevalence of Parkinson's Disease in 22q11.2 Deletion Syndrome: A Multicenter Study**
Emma N.M.M. von Scheibler, Ann Swillen, Gabriela M. Repetto, Nikolai Gil D. Reyes, Anthony E. Lang, Connie Marras, Mark L. Kuijf, Rob P.W. Rouhl, Agnies M. van Eeghen, Carlos Juri, Annick Vogels, Thérèse A.M.J. van Amelsvoort, Anne S. Bassett, Erik Boot

15:03 **135** **Increased Striatal Dopamine Transporter Binding in 22q11Del versus 22q11Dup Individuals**
Therese van Amelsvoort, Carmen van Hooijdonk, Rik Schalbroeck, Erik Boot, Claudia Vingerhoets, en Jan Booij

15:10 **136** **Expanding the Phenotypic Spectrum of Movement Disorders in 22q11.2 Deletion Syndrome: a Retrospective Study** *
Nikolai Gil D. Reyes, Talyta Cortez-Grippe, Marcus Callister, Emilio Q. Villanueva, Tracy Heung, Anne S. Bassett, Anthony E. Lang

15:20 **Q&A**

15:30 ***AFTERNOON TEA AND POSTER VIEWING ON THE COVERED TERRACE***

SESSION 11: METABOLOMICS AND PROTEOMICS

Chairs: Donna McDonald-McGinn and Beata Nowakowska

16:00 **137** **Proteomic Analysis of Plasma in 22q11.2DS**
Kathleen Sullivan, Valentina Frusone, Kelly Maurer, Raquel Gur, T. Blaine Crowley, Beverly S. Emanuel, Donna McDonald-McGinn

16:10 **138** **A Follow-up Study Indicates Inflammatory Factors as Predictors to Cognitive Decline and Psychosis in Individuals With 22q11.2 Deletion Syndrome**
Katerina Kulikova, Shira Dar, Noam Matalon, Ehud Mekori, Ronnie Weinberger, Doron Gothelf, Michal Taler

16:17 **139** **Altered Metabolomic and Proteomic Profiles in Individuals with 22q11.2 Deletion Syndrome**
Marwa Zafarullah, Kathleen Angkustsiri, Hannah Culpepper, Austin Quach, Seungjun Yeo, Blythe P Durbin-Johnson, Heather Bowling, Flora Tassone

16:24 **140** **The Contribution of Genome-wide Tandem Repeat Expansions to Schizophrenia in 22q11.2 Deletion Syndrome**
Ryan K. C. Yuen, Muyang Cheng, Tracy Heung, Yue Yin, Anne S. Bassett

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16:35 **Q&A**

16:45 **141** ***Invited Presentation*** **– The Future is Now**
Peter Scambler, London, UK

17:05 **Q&A**

17:10 ***FAMILY VOICES: AN INTERNATIONAL PERSPECTIVE - CAROL CAVANA, DEBBIE DELOACH, ANNE LAWLOR, KIM VAN BEKKUM, MARC AND BARBI WEINBERG, AND JULIE WOOTTON***

Junior Investigator Awards
Beata A. Nowakowska, Daniel McGinn, and Daniella Miller

Closing Remarks and 2026 Meeting Location Reveal
Donna M. McDonald-McGinn

17:30 **Wellness Close**
Maria Mascarenhas

19:30 Buses Depart Hotel Entrance

20:00 SILVER ANNIVERSARY GALA

Portuguese Traditional Ranch Show, Dinner, and Dancing
Special Awards Presentation
West Cliffs Club House Restaurant, Óbidos, Portugal

Poster
PRESENTATIONS

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Christina Parrish

143 **Implementation of RN Clinic Prep for Pediatrician Visits using a 22q Focused Assessment Checklist**
Christina Parrish

144 **Bridging the Care Gap: A Multidisciplinary Approach for Adults with 22q11.2 Deletion Syndrome in Florida** *
Hanadys Ale, Evana Valenzuela-Scheker, Roman Yusupov, Joshua Saef, Marea Kefalas, Courtney Laczko, Nancy Carranza, Todd Roth

145 **Co-producing a Healthcare Passport to Improve Quality of Care and Communication Engagement for Young People Living with 22q11DS**
Wesley Mulcahy, Suzanne Kelleher

146 **Transition to Adult Care from a Pediatric 22q Center: Midway Through a Pilot Project**
Hannah Berntson, Matthew Blessing, Emily Gallagher, Patricia Harriman, Anna Meehan, Maria Mills, Christina Parrish, Lex Powers

147 **Genetic Breakthroughs in Neonatal Medicine: Advancements Transforming Newborn Care**
Asmaa Gaadi, Hind Dehbi, Ahmed Aziz Bousfiha, Mouna Lehlimi

148 **Integrated Care for Young People with 22q.11.21 Deletion Syndrome – a Patient, Provider Initiative**
Wesley Mulcahy, Suzanne Kelleher, Marie Louise Healy, Anne Lawlor

149 **Surgical Needs of Patients with 22q11.2 Deletion or Velocardiofacial Syndrome**
Emma Martin, Alyssa Smith, Laura Rosenthal

150 **Prevalences of Comorbid Cardiovascular, Psychiatric, Orthopedic, Endocrinologic and Development-related Diseases in Patients with 22q11.2 Duplication Syndrome – a Systematic Review** *
Carina Sauter, Paula Franz, Laura Kettenstock, Klara Henrich, Matthias Linhardt, Marcel Romanos, Franziska Radtke

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151 **Examining Parent of Origin in Patients with de novo 22q11.2 Duplication Syndrome** *
Oanh Tran, Ryan Lapointe, Victoria Guinta, T. Blaine Crowley, Audrey Green, Lydia Rockart, Bekah Wang, Daniel E. McGinn, Steven Pastor, Elaine H. Zackai, Donna M. McDonald-McGinn, and Beverly S. Emanuel

152 **Supernumerary Nipple in Association with 22q11.2 Deletion Syndrome** *
Audrey Green, Victoria Giunta, T. Blaine Crowley, Daniel E. McGinn, Bekah Wang, Lydia Rockart, Lauren Lairson, Oanh Tran, Beverly S. Emanuel, Elaine H. Zackai, Donna M. McDonald-McGinn

153 **Telangiectasia in the Distribution of the Superior Vena Cava – a Novel Phenotype in 22q11.2 Deletion Syndrome: A Case Report**
A. Hollywood, Kate Rigney, A. Irvine, S. Kelleher

154 **Development, Evaluation and Implementation of a Psychoeducation Program for Families Affected by 22q11DS** *
Ania M. Fiksinski, N. van Wijngaarden, K. van Bekkum, J.A.S. Vorstman, H. de Veye, M.L. Houben

155 **The Sleep Detectives: Co-Designing a Protocol for Longitudinal Tracking of Sleep Health and Cognition in Children and Young People Living with Copy Number Variants**
Matt W. Jones, Meg Attwood, Abiola Saka, Christopher Jarrold, Nicholas Donnelly, Julie Clayton, Jeremy Hall, Alexander D. Shaw and Marianne van den Bree

156 **Anxiety and Adaptive Function in Teens with Chromosome 22q11.2 Deletion Syndrome**
Aishworiya Kolli, Jonathan Bystrynski, Byrn Ritter, Flora Tassone, Kathleen Angkustsiri

157 **Talking to the Teacher: the Value of Behavioral Observations of Children with 22q11DS in the Classroom**
Jane Summers, Matisse Blundell, Sarah McGaughey, Katrina Palad, Jacob Vorstman

158 **Leveraging Early Genetic Diagnoses: The Exemplary Case of 22q11.2 Deletion Syndrome in Addressing Caregiver Needs in Neurodevelopmental Disorders**
Polina Perlman Danieli, Jacob Vorstman, Ny Hoang, Jane Summers, Danielle Baribeau, Jessie Cunningham, Benoit H. Mulsant

159 **Development and Delivery of Psychoeducational and Parenting Programmes for 22q11.2DS Families in Ireland**
Veselina Gadancheva, Ahmed Khan, Wesley Mulcahy, Suzanne Kelleher, Fiona McNicholas

160 **Semi-structured Interviews with Parents/Caregivers of Children with 22q11.2 Deletion Syndrome Highlight Areas Where Support is Needed**
Emily R. Gallagher, Brent Collett, Cindy Ola Trevino

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161 **Evaluating the Relationship Between Parent Mental Health, Parenting Skills, and Child Behavioural Issues in Families Affected by 22q11.2 Deletion Syndrome** *
Holly Carbyn, Patricia Lingley-Pottie, Lisa D. Palmer, Andrea Shugar, Donna M. McDonald-McGinn, Patrick J. McGrath, Anne S. Bassett, Cheryl Cytrynbaum, Ann Swillen & Sandra Meier

162 **Co-Production: a Transition Clinic for Young People with 22q11.2 Deletion Syndrome**
Wesley Mulcahy, Suzanne Kelleher, Marie Louise Healy, Anne Lawlor

163 **BE-WEHL Wellness Education for Families of Children with Behavioral Health Challenges**
Robin Miccio, Lisa Squires, T. Blaine Crowley, Audrey Green, Lydia Rockart, Donna M. McDonald-McGinn, Maria Mascarenhas

164 **Characteristics of Motor Patterns in Infants with 22q11.2DS: Bayley Trends and Early Signs of Neuromotor Impairment**
Tracy Brundage, Cindy Ola Trevino, Emily Gallagher

165 **Investigating Convergence of Neurodevelopmental Mechanisms between 16p11.2 CNV and Cullin3 (Cul3) using Brain Cortical Organoids**
Luca Trovò, Aline Martins, Gimena Gomez, John Yates III, Alysson R. Muotri, and Lilia M. Iakoucheva

166 **Changes in Brain Structure and Associated Functions in Children with 22q11.2 Deletion Syndrome versus Controls: A six-year Longitudinal Study** #
Stephen R. Hooper, Vandana Shashi, Kelly Schoch, & Matcheri S. Keshavan

167 **Neurodevelopmental Disorders and Executive Function in a Clinical Sample of Children and Adolescents with 22q11.2**
Rygvold TW, Midtlyng E, Michael B. Lensing

168 **Threat Sensitivity and Neuropsychiatric Disorders in Individuals with 22q11.2 Deletion Syndrome** #
Lauren K. White, Tyler M. Moore, R. Sean Gallagher, Emily J. McClellan, David R. Roalf, T. Blaine Crowley, Victoria Giunta, Audrey Green, Daniel E. McGinn, Bekah Wang, Beverly S. Emanuel, Donna M. McDonald-McGinn, Ruben C. Gur, and Raquel E. Gur

169 **22q Microdeletion Predisposes iPSC derived Microglial like Cells to Increased Activity** *
Kieona Cook, Sonial Lomboroso, Daniel Iascone, Amita Seghal, F. Chris Bennett, Stewart Anderson

170 **Convergent Biology among Copy Number Variants Associated with Schizophrenia**
Mulle Jennifer G, Pollak RM, Pato M, Pato C, Pang Z, Hart R

171 **Analyzing Mitochondrial Deficits in 22q11.2 Deletion in Developing Neural Models** *#
Maxine I. Robinette, Victor Faundez, Ryan H. Purcell, Gary J. Bassell

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172 **The Role of Screening Tools in the Psychiatric Evaluation of Children with 22q11.2 DS**
Ahmed Khan, Veselina Gadancheva, Rae Lyz Yee, Suzanne Kelleher, Fiona McNicholas

173 **Psychophysiological Deficits in 22q11DS ***
David Parker, Sid Imes, Gabrielle Ruban, Brett Henshey, Nicholas Massa, Grace Lee, Bruce Cuthbert, Opal Ousley, Elaine Walker, Erica Duncan, Joseph Cubells

174 **Environmental Influence on the Patients with 22q11.2 and 16p11.2 Deletions and Duplications ***
Yelyzaveta Snihirova, Therese van Amelsvoort, Claudia Vingerhoets, Mieke van Haelst, David E.J. Linden & Dennis van der Meer

175 **Working Group of European 22q11 Expertise Centers: Organizational Differences, Similarities and Opportunities**
Michiel L. Houben, Ania M. Fiksinski, Aebele B. Mink van der Molen

176 **Phenotypical Characteristics of Children with 22q11 Duplication Syndrome: A Clinical Chart Review Analysis**
Jette A. Boxem, M.L.Houben, A.M. Fiksinski A.B. Mink van der Molen

177 **Maternal 22q11.2 Triplication (LCR22A-LCR22D) Resulting in a 22q11.2 Duplication (LCR22A-LCR22D) in Two Siblings***
Kelly Regan-Fendt, Bekah Wang, Daniel E. McGinn, Audrey Green, Victoria Giunta, Lydia Rockart, Emma Schiavone, Conner Weinberg, Oanh Tran, T. Blaine Crowley, Beverly S. Emanuel, Elaine H. Zackai, and Donna M. McDonald-McGinn

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001: Back to the Future – A Brief Walk Through the History of 22q11.2 Deletion Syndrome

Beverly S. Emanuel, Ph.D.
The Division of Human Genetics and "22q and You Center", The Children's Hospital of Philadelphia, and the Department of Pediatrics of the Perelman School of Medicine of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

The original description of what would ultimately come to be known as the chromosome 22q11.2 deletion syndrome occurred in the mid 1960s in Philadelphia with the publication by Angelo DiGeorge of congenital athymia associated with hypoparathyroidism. Later, congenital heart disease was added, leading to the "triad" of DiGeorge syndrome (DGS). In time, the causal deletion of human chromosome 22 was established with DGS, as well as numerous conditions previously described clinically (VCFS, CTAF, a subset of Opitz G/BBB, and Cayler Cardiofacial syndrome), due to rearrangements facilitated by the presence of region-specific low copy repeats (LCRs) resulting in nonallelic homologous recombination (NAHR) between paralogous genomic segments. 22q11.2 has been classified as one of the more unstable regions of the human genome, harboring eight low-copy repeats LCR22A-LCR22H mediating NAHR. LCR22A and LCR22D, the largest of the LCR22s, mediate the most common 22q11.2 deletions and duplications. 22q11.2DS has been identified in 1/2000 live births and is the most frequent microdeletion syndrome - causing multiple congenital anomalies, serious medical problems, cognitive deficits, and psychiatric illness, all far extending the original description by DiGeorge. Most individuals with 22q11DS have a de novo hemizygous 3 mega base deletion due to NAHR between flanking LCR22s during meiosis. Most deletions are flanked by LCR22A and LCR22D, which vary considerably in size and organization. The LCR22s are comprised of modules containing intermingled genes and pseudogenes. Attempts to determine the role of these modular segments in causing the deletion as well as modifying the phenotype will be discussed as will attempts to understand the basis of phenotypic variability. However, detailed analysis of the LCR22s is difficult because of their variably large size, complex organiz ɪtion, and duplicated individual segments. This complexity has hampered attempts to determine whether there are major variations between individuals and racial groups.

002: Genetics of CNVs Informing Human Disorders and the Prospects for Treatment

Stephen W. Scherer, PhD, DSc, FRSC
Genetics & Genome Biology Program, The Hospital for Sick Children, Toronto, Canada

Our team has pursued genome-wide technologies, and for the past decade most notably whole genome sequencing, to resolve the role of sporadic and rare-inherited copy number and structural variation (CNV/SV) and the genes impacted, in the human condition. We have sequenced tens of thousands of genomes from individuals with human disorders, their family members, and population controls to generate highly-valuable, and highly-utilized resources, for both discovery and comparative analyses (as part of the Earth Biogenome Project we also complete telomere-to-telomere *de novo* genome assemblies of mammalian species native to Canada). Our early-adopted approach of characterizing all classes of genetic variation in combination has allowed us to develop several new strategies to help to diagnose neurodevelopmental disorders. For example, in our research following ~5,000 families from North America having a diagnosis of Autism Spectrum Disorder, our whole genome sequencing work has enabled the identification of >100 'penetrant' genes and CNVs including some that identify entirely genetic new pathways offering novel therapeutic targets for modulation, which will be discussed in this seminar. Building upon these genomic-driven advances, our hospital has also adopted a universal 'Precision Child Health' movement that will enrol every relevant paediatric subject and their family to gather all health record data ("genetic code to postal code") and to use this resource to increase prospects for impactful treatment.

003: Size Matters – Phenotypes Associated with Nested Chromosome 22q11.2 Deletions

Donna M. McDonald-McGinn[1,2,3,4], Victoria Giunta[1,2], Bekah Wang[1,2], Daniel E. McGinn[1,2,5], Audrey Green[1,2], Lydia Rockart[1,2], Oanh Tran[1,2], Ryan LaPointe[1,2], Conner Weinberg[1,2], Sam Alperin[1,3,6], Vaneeta Bamba[1,3,7], Katherine Baum[1,8], Madeline Chadehumbe[1,9], Christopher Cielo[1,3,10], Malcolm Ecker[1,11,12], Lisa Elden[1,12,13], John Flynn[1,11,12], Brian Forbes[1,11,14], R. Sean Gallagher[1,15], Elizabeth Goldmuntz[1,3,16], Raquel E. Gur,[1,17,18], Steven Handler[1,12,13], Sarah Hopkins[1,3,6], Oksana Jackson[1,12,19], Lorraine Katz[1,3,7], Thomas Kolon[1,11,20], Michele Lambert[1,3,21], Asim Maqbool[1,3,22], Maria Mascarenhas[1,2,22], Edward Moss[1,6], Hyun-Duck Nah[1,12,19], Michael Nance[1,12,23], Michelle Scott[1,12,19], Cynthia Solot[1,24], Kathleen E. Sullivan[1,3,25], Ian Campbell[1,2,3], Elaine H. Zackai[1,2,3], Beverly S. Emanuel[1,2,3], and T. Blaine Crowley[1,2]

[1]22q and You Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Division of Human Genetics, 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 Human Biology and Medical Genetics, Sapienza, University, Rome, Italy; [5]Mitochondrial Medicine Program, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [7]Division of Endocrinology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [8]Malamut and Moss, Bryn Mawr, PA, USA; [9]NeurAbilities, Voorhees, NJ, USA; [10]Division of Pulmonary and Sleep Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [11]Division of Orthopaedic Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [12]Department of Surgery, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [13]Division of Otolaryngology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [14]Division of Ophthalmology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [15]Neurodevelopment and Psychosis Section of the University of Pennsylvania's Department of Psychiatry; Philadelphia, PA, USA; [16]Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [17]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [18]Department of Child and Adolescent Psychiatry, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [19]Division of Plastic, Reconstructive, and Oral Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [20]Division of Urology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [21]Division of Hematology and Oncology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [22]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [23]Division of General Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [24]Center for Childhood Communication, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [25]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Background: 22q11.2DS results from non-allelic homologous recombination due to low copy repeats A, B, C, and D. Most deletions extend from LCR22A-LCR22D (A-D) and include FISH probes within A-B and important developmental genes *TBX1* (A-B) and *CRKL* (C-D). Here we report deletion size and associated features in a large 22q11.2DS cohort towards establishing genotype-phenotype correlations. **Methods:** We examined findings in 1667 patients with 22q11.2DS evaluated between 1992 and 2024; 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), categorized according to Billet (2008), was statistically significant across breakpoints ($p < .01$): **A-D** deletions (n=1095; 66% - 18% complex, 25% moderate, 23% simple,); **A-B** (n=69; 73% - 31% complex, 15% moderate, 27% simple); **A-C** (n=24; 76% - 41% complex, 12% moderate, 24% simple); **B-D** (n=57; 26% - 6% complex, 4% moderate, 16% simple); **C-D** (n=31; 38% - 15% complex, 0% moderate, 23% simple). Hypocalcemia was reported in: A-D (52%), A-B (27%), A-C (42%), B-D (2%), C-D (0%). Chronic infection, thyroid disease, and growth hormone deficiency were relatively equally distributed across deletion types. In patients with C-D deletions none had palatal or structural brain anomalies, and scoliosis (8%), idiopathic seizures (3%), and ADHD (3%) were uncommon. Mean FSIQ by deletion type revealed: A-D (77.3; n=312), A-B (87.8; n=16); A-C (81.0; n=6); B-D (78.3; n=5); and C-D (87.7; n=3), although standard deviations were wide-ranging. 12.5% (66/527) of A-D deletions were familial, compared with A-B (22%), A-C (17%), B-D (71%), and C-D (67%). **Conclusions:** This data suggests deletion size significantly impacts phenotypic features and is key in providing specific healthcare guidance, identifying causative genes, and providing recurrence risk counseling.

004: 22q11.2 Deletion/duplication Syndromes - Analysis and Refinement of Breakpoints by Array-CGH

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Introduction: Deletions and duplications of 22q11.2 region are one of the most frequent genetic alterations in human genome. The phenotype is variable, including conotruncal heart defects, learning and behavioral problems, immunological deficiency and facial anomalies with widely variable expressivity. The critical region contains a cluster of four distinct low-copy-number repeated sequences (LCRs), responsible for deletions or duplications of this region by Non-allelic homologous recombination (NAHR). The LCR22A-D deletion is the most common recurrent microdeletion syndrome, known as DiGeorge syndrome and the reciprocal microduplication with a frequency of 1/700 in the intellectual disability population. Other less frequent deletions and duplications at 22q11.2 region, distal to the 3 Mb common deleted regions have been reported. Chromosomal breakpoints are believed to be located in the LCRs, but there are few publications addressing more precise breakpoints. The proximal LCR22A is located at 22q11.2 from 19,037 to 19,083 Mb, while the distal LCRD is located from 21,535 to 21,670 Mb. **Methods:** A cohort of 97 patients with 22q11.2 deletion/duplication was studied using high-resolution Agilent oligonucleotide-based 180K microarray, in order to refine the imbalances breakpoints. **Results:** Deletions and duplications occurred more commonly on the LCR22A-D region, with 2.5Mb alterations with breakpoints spanning the region from 18,9 to 21,5 Mb. 1.5 Mb alterations involving LCR22A-B region, spanning from 18,9 to 20,3 Mb were also observed. Both regions include over 30 genes, namely the *DGCR6*, *PRODH*, *TBX1* genes. Some patients presented a smaller deletion/duplication extending from LCR22B–D or C–D. The distal breakpoints spanned the regions from 21,5 to 25,0 Mb. **Conclusions:** The presence or absence of genes in the breakpoints, depending on the size of the imbalance, plus variation in the rest of the genome due to copy number variations, likely contribute to the variable phenotype associated with 22q11.2 deletions and duplications.

005: The Tiniest Piece Leading to a Big Picture: Nested 22q11.2 LCR22C-LCR22D Deletions *

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Introduction: Nested chromosome 22q11.2 LCR22C-LCR22D deletions (22q11.2C-Ddels) are infrequently observed (~1%) and small (0.7Mb) compared with standard LCCR22A-LCR22D deletions (22q11.2A-Ddels) (84%; 3.0Mb). Although tiny, this region involves eleven genes, including *CRKL*, a renal and cardiac developmental driver (Racedo 2015; Lopez-Rivera 2017). Additional genes associated with disease include *LZTR1* (Noonan; Schwannomatosis Type II), *PI4KA* (hypomyelinating leukodystrophy, cerebellar hypoplasia, polymicrogyria, nystagmus, IBD, combined immunodeficiency), *SNAP29* (CEDNIK), and *SERPIND1* (Heparin co-factor deficiency 2). Here we report findings in these rare patients to catalog associated features, highlight variable expressivity, and ultimately establish genotype-phenotype correlations. **Methods:** Records on 27 CHOP patients with 22q11.2C-Ddels were retrospectively reviewed under an IRB approved protocol. 24 had sufficient data to report. **Results:** Patients were identified prenatally through 45 years. 41.7% were inherited compared with 6% in 22q11.2A-Ddels. Five had additional CNVs (17q12 deletion, 16p13.11 duplication (3), 22q11.2D-E duplication). Notable findings included: CHD (33.3%), e.g., tetralogy of Fallot with pulmonary atresia (3); Endocrine (20.8%) includir ʒ GHD (2) and hypothyroidism (2); ENT (50.0%) e.g., TEF; GI (54.2%) e.g., anterior anus with perineal fistula (2); Hematology (8.3%) thrombocytopenia; Immunology (37.5%) T cell lymphopenia, low B cells, low NK cells; Neurology (58.3%) including tethered cord; Ophthalmology (25%) nystagmus, anisometropia; Orthopedics (20.8%) scoliosis; Renal (33.3%) single kidney (2), dysplastic kidney; Development/speech delay/ID (33.3%), and autism (3). Cognitive abilities varied widely as three parents had graduate degrees. Of note, none had palatal anomalies. **Conclusion:** Patients with 22q11.2C-Ddels have recurrent features overlapping with 22q11.2A-Ddels including structural anomalies, recurrent medical problems, neurocognitive/behavioral differences, but at lower frequencies and with wider variability. Notable differences include the high rate of familial transmission, and lack of palatal anomalies and psychiatric illness, notwithstanding the limited denominator influenced by the rarity of the condition. Examination of the intact allele, particularly in patients with features reported in association with PI4KA will be essential.

006: 22q11.2 Deletion Syndrome Parent of Origin by Sex and Race *

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Background: We previously reported that Black patients with 22q11.2 deletion syndrome (22q11.2DS) are under-represented compared with white patients. This is thought to be the result of differences in Low Copy Repeats (LCR) within the 22q11.2 region that may alter the frequency of Non-Allelic Homologous Recombination (NAHR) events in different populations. Of note, prior parent-of-origin studies revealed more maternal v. paternal occurrence of *de novo* deletions but did not consider race as a potential confounder. Here we examine this question. **Methods:** Under IRB approval, parent-of-origin studies were performed using microsatellite markers between deletion breakpoints on probands with 22q11.2DS. GeneMarker software (Version 3.0) was employed to analyze Polymerase Chain Reaction fragments from probands and unaffected parents. Informative markers included a parent with no matching fragments to the proband's remaining 22q11.2 allele. At least three informative markers were required to determine parent-of-origin. Offspring of mixed backgrounds were grouped by the parent-of-origin reported race: Black (N=44); white (N=99). In cases where only a proband and parent duo were available, parent-of-origin was assigned to the parent without available DNA, if eight or more markers were uninformative. **Results:** Parent-of-origin was found to be maternal in 26 of 44 (59%) Black patients and 59 of 99 (60%) white patients. Therefore, no differences in parent-of-origin based on race were identified. However, as was previously reported by Delio, et.al., where 456 of 801 (57%) *de novo* deletions were maternal in origin, we too found a preponderance of 22q11.2 deletions of maternal origin. **Conclusions:** Enhanced maternal parent-of-origin for *de novo* 22q11.2 deletions is observed in our cohort, regardless of race. This is notable, given the overall under-representation of Black patients compared with white patients and the hypothesis that differences in LCRs accounts for this discrepancy. Thus, additional investigation is still required to truly understand this complex region and racial discrepancy.

007: Optical Mapping Reveals Significant Differences in 22q11.2 Genomic Structures Between an African American Population and Whites

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Background: Racial disparities in 22q11.2DS patient cohorts appear to be rather striking. More whites of European descent are diagnosed with 22q11.2DS than African Americans and the reason is unclear. In a previous study performed at the Children's Hospital of Philadelphia, the proportion of 22q11.2DS African American patients was not reflective of the overall hospital population of African Americans, indicating an under-representation of African Americans diagnosed with 22q11.2DS. To date, no studies have sought to explain this discrepancy. We hypothesize the decreased incidence of 22q11.2DS in African Americans may be due in part to differences in genomic structures near the 22q11.2 deletion breakpoints and these structures may reduce non-allelic homologous recombination (NAHR) leading to the 22q11.2 deletion in African Americans. **Methods:** Optical mapping was performed on 50 genomes from the African American in the Southwest population, 50 genomes from a white population, 30 white 22q11.2DS families, and 5 African American 22q11.2DS families. Individual haplotypes of the 22q11.2 region were obtained. Using these haplotypes, we compared the genomic features in 22q11.2 between the 4 groups to determine if they might explain the under-representation of African American 22q11.2DS patients with implications in NAHR. **Results:** Variability in copy number and orientation of segmental duplications in LCR22A and LCR22D was observed across all genomes, regardless of population group. This translated into group differences in the haplotype-specific structures of LCR22s. There were more unique LCR22A haplotypes in African Americans as compared to white-associated LCR22A haplotypes, indicating population stratification. Overall, in both LCR22s, haplotype configurations, inversions, and increased inter-LCR22 distances may explain the reduced frequency for 22q11.2DS in African Americans by reducing the number of potentially favorable recombination loci. **Conclusions:** Overall, our results indicate significant variation in genomic structures between African Americans and whites, which ultimately may help explain the decreased incidence of 22q11.2DS in African Americans.

008: Proximal Nested 22q11.2 Deletions and Ancestry

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Background: Most individuals with 22q11.2 deletion syndrome (22q11.2DS) have a 2.5 Mb LCR22A-LCR22D 22q11.2 deletion, with proximal nested LCR22A-LCR22B/LCR22A-LCR22C deletions usually reported in <10% of individuals. There is emerging evidence that ancestry, specifically African, may affect the flanking low copy repeat sequences and propensity to deletion occurrence. We found no studies that examined ancestry in the context of nested deletions. We hypothesized that individuals of non-European ancestry may be more likely to have proximal nested deletions than those of European ancestry. **Methods:** We used data on deletion extent and ancestry of unrelated individuals with "typical" deletions (i.e., involving LCR22A-LCR22B), from our Toronto sample of adults with 22q11.2DS (n=429), after excluding those of African ancestry. We compared those of non-European (non-EUA) and of European (EUA) ancestry on the prevalence of proximal nested vs the common LCR22A-LCR22D 22q11.2 deletion. We also examined data by ancestry and deletion size from Philadelphia (n=1210), Maastricht (n=98), Rome (n=312), and Madrid/Palma (n=155). **Results:** Within the Toronto cohort, consistent with our hypothesis, the non-EUA subgroup was enriched for proximal nested 22q11.2 deletions (15/98, 15.31% vs 28/331, 8.46%; χ^2 3.93, df 1, p=0.047). There were no significant effects of sex, major congenital cardiac disease or psychotic illness, or parent of origin of *de novo* deletions (data available for n=198), on prevalence of proximal deletions. Data from the additional cohorts will be discussed. **Conclusion:** The results suggest that there may be (background) ancestry effects on the relative likelihood of the occurrence of proximal nested vs the most common (LCR22A-LCR22D) 22q11.2 deletions, perhaps involving the flanking low copy repeat sequences. It is also possible that ancestry may affect ascertainment and/or clinical genetic testing. The findings reinforce the need for efforts to achieve greater diversity of ancestry in ascertainment, to consider ancestry in all analyses, and to determine 22q11.2 deletion extent for all individuals with 22q11.2DS. Larger sample sizes and detailed examination of LCRs are needed.

009: 22q11.2DS Embryonic Stem Cell Lines With and Without the Flanking Low Copy Repeats *

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The 22q11.2 deletion syndrome (22q11.2DS) results from '*de novo'* rearrangements occurring between Low Copy Repeats (LCRs) within the 22q11.2 locus. In 90% of the cases, the LCR22-A and LCR22-D recombine leading to the syndrome's characteristic 3Mb deletion. We demonstrated that the recombination sites within the LCRs are variable. Different 22q11.2DS deletions retain variable sizes of the LCRs. Whether this variability (indirectly) affects gene expression and could influence phenotypic variability, remains unknown. Using CRISPR/Cas9-mediated genome editing we have engineered a human embryonic stem cell (hESC) line to generate 22q11.2 deletions inclusive and exclusive of LCR22-A and LCR22D. We have successfully created and characterized different heterozygous and homozygous lines. These cell lines have the potential to be differentiated in any cell type from the three embryonic tissue layers and will provide a new model to dissect the consequences of the deletion.

010: Dissecting the Clinical Complexity of 22q11 Deletion Syndrome by Deep Phenotyping and Functional Genomics

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Background: The 22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal deletion in humans. Associated phenotypic features are broad and variable making clinical recognition challenging. This is especially true when atypical features are present. Some already reported in association with CNVs/SNVs on the intact chromosome 22q11.2 allele include, for example, variants in *GP1BB* and Bernard-Soulier, *CDC45* associated with craniosynostosis/CGS syndrome, *SNAP29* causing CEDNIK syndrome, *LZTR1* and Noonan syndrome, *SCARF2* and van den Edna Gupta syndrome, *PRODH* and proline dehydrogenase deficiency, and *TANGO2* leading to metabolic encephalopathy and sudden death. However, identification of individual genes within the 22q11.2 region still does not fully explain the wide variability amongst patients with 22q11.2DS. Here we examine common and atypical features associated with 22q11.2DS using whole genome sequencing and RNAseq in a large well phenotyped cohort to identify possible etiologies for reported findings, as well as to explain variability. **Methods:** We performed expression analysis and genome sequencing on samples acquired from 170 deeply phenotyped patients with 22q11.2DS followed in Philadelphia or Warsaw. **Results:** Differential gene expression analysis was performed for all patients, with a focus on investigating phenotypic traits present in more than ~15% of patients, where a minimum of 30 patients had the specific phenotypic feature in question. **Conclusions:** We compared whole transcriptome profiles in patients with selected phenotypic features to those wit hout those same features. This led to identification of gene expression changes associated with specific clinical characteristics. Detailed findings will be discussed.

011: Two Circuits, Thirty Genes, one Copy: 22q11DS is a Polygenic Disorder of Neural Circuit Development

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Background: 22q11.2 Deletion Syndrome (22q11DS) is associated with enhanced risk for clinically defined psychiatric disorders including Schizophrenia (Scz), Autistic Spectrum (ASD), Attention Deficit/Hyperactivity (ADHD) and Anxiety Disorder (AnxD). Recently, a consensus has emerged that these disorders—all of which are thought to originate during brain development—have polygenic, rather than monogenic origins. Accordingly, the genes deleted heterozygously in 22q11DS may contribute, as a group, to Scz, ASD, ADHD, and AnxD polygenic risk by cumulative, concerted network action on shared mechanisms of neural circuit development. **Methods**: We used multiple approaches in mouse models of 22q11.2 deletion and related single gene mutations to characterize the developmental trajectory of two neural circuits: a brainstem/cranial nerve circuit for suckling, feeding and swallowing, an essential innate behavior, and an association cortico-cortical circuit for processing for cognitive behaviors. **Results**: These two circuits, which serve distinct functions, are found in separate brain regions and develop at different times are nevertheless disrupted at each neurodevelopmental fundamental step—patterning, progenitor specification/neurogenesis, migration/process growth, and synaptogenesis—via parallel, 22q11 gene-dependent mechanisms. These disruptions prefigure physiological circuit dysfunction as well as related behavioral deficits that parallel those that are seen in individuals with 22q11DS. Thus far, none of these disruptions have been directly matched by constitutive heterozygous deletion of individual 22q11 genes. **Conclusion**: Consistent mechanistic disruption at key steps of development of two neural circuits by heterozygous deletion of most of 30 genes that comprise the 22q11DS minimal critical region collectively define a broader polygenic network that regulates fundamental mechanisms of neural circuit development. Their deletion, independent of circuit location, function or time of differentiation, compromises foundational, shared mechanisms of neural circuit development that are shared across broader, clinically defined “disorders of neural circuit development” including Scz, ASD, ADHD and AnxD, all of which are associated with 22q11DS.

012: Cell free DNA and the Promise of Novel Biomarkers

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Circulating cell-free DNA (cfDNA) fragments have characteristics that are specific to the cell types that release them. As a consequence, cfDNA analysis is used as a biomarker for non-invasive prenatal screening and cancer screening, diagnosis, and monitoring. Current methods for cfDNA deconvolution typically use disease tailored marker selection such as mutations, copy number alterations and epigenetic differences between a limited number of bulk tissues or cell lines. We hypothesized that mining the patterns of cfDNA shallow whole-genome sequencing datasets from patients versus controls would enable disease informed fragmentation patterns to be uncovered. In addition, we explored the use of single cell transcriptome data as a comprehensive cellular reference set for disease-agnostic cfDNA cell-of-origin analysis. We correlate cfDNA-inferred nucleosome spacing with gene expression to rank the relative contribution of over 490 cell types to plasma cfDNA. In 744 healthy individuals and patients, we uncover cell type signatures in support of emerging disease paradigms in oncology and prenatal care. Most recently, we have been exploring the utility of this approach to study rare diseases with a focus on 22q11.2DS. I will present the use of fragmentomics as a means to learn about disease and provide preliminary data on the potential in the study of rare diseases.

013: Performance of SNP-based Cell-free DNA Prenatal Screening for 22q11.2 Deletion Syndrome in a Commercial Population

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Background: Early diagnosis of 22q11.2 deletion syndrome (DS) allows for better pregnancy management and improves neonatal outcomes. We evaluated positive predictive value (PPV) of 22q11.2 DS with SNP-based prenatal cell free DNA (cfDNA) screening in a commercial population. **Methods**: This study included all domestic high risk 22q11.2 DS cfDNA results over a 21-month period. Suspected maternal 22q11.2 DS results were excluded. Diagnostic testing and ultrasound (u/s) results were collected. PPVs were calculated for samples with confirmatory testing performed prenatally, postnatally or on products of conception. **Results**: Out of 1,057,710 cases, 753 (0.071% or 1/1400) were high-risk for fetal 22q11.2 DS. Average (avg) maternal age was 30.2 yrs (range 18-46); avg maternal weight 165.6 lbs (91-321 lbs; n=723/753); avg gestational age 14.0 wks (7.0-35.4); avg fetal fraction 7.9% (2.8-28.6%). Outcomes were obtained in 155 cases (20.6%). Overall PPV was 47.0%. When suggestive u/s findings were included, the PPV was 56.7%. 46.3% of confirmed positive cases did not have u/s finding(s). For cases with u/s anomalies (n=73), PPV was 78.4%. When u/s findings were limited to a cardiac (CHD) or renal anomaly (n=51), PPV was 92.6%. **Conclusions**: This study shows a PPV ~50% for 22q11.2 DS in an average risk prenatal population and >90% in fetuses with cardiac and/or renal abnormalities. Importantly, ~ 50% of true positive cases had no u/s findings typically associated with 22q11.2 DS. Without prenatal cfDNA screening, cases lacking u/s findings may be missed leading to a diagnostic odyssey and delayed diagnosis. A previous prospective study (SNP-based Microdeletion and Aneuploidy RegisTry: SMART) showed a similar PPV of 52.6% in a cohort of 18,020 pregnant individuals containing 12 affected pregnancies. Results of the current study confirm a PPV of ~50% in a larger, real-world study and illustrate the limitations of u/s findings as an indication for 22q11.2 DS.

014: Single Cell Sequencing of Circulating Extravillous Trophoblasts for Non-invasive Fetal Copy Number Variant Screening

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Background: Pathogenic microdeletions/duplications (pCNVs) account for a significant perinatal morbidity/mortality and have a 1/100-200 prevalence in the general prenatal population. Cell-free DNA noninvasive testing (cfNIPT) shows significant limitations for comprehensive profiling of pCNVs <7Mb in size. A proof-of-concept study demonstrated the feasibility of a novel cell-based NIPT (cbNIPT) for circulating extravillous trophoblasts (cEVTs) isolation and single cell sequencing for fetal CNV detection down to ~800kb. We aimed to demonstrate cbNIPT scientific validity in a large blinded prospective performance study comparing the fetal genomic result with that of cEVTs screening. **Methods:** 1388 high-risk pregnancies were enrolled to obtain a statistically significant pCNV/aneuploidies number. Blood was collected from pregnant women at 11-22+6 gestational weeks (gw) before invasive diagnostic procedure and processed with proprietary laboratory workflow not optimized for recovery rate. **Results:**1070 patients had CMA±karyotype with the remainder karyotype only. Screen positive rate for aneuploidies and (likely)pathogenic CNV (pCNV) was 18.9% and 11.2%, respectively. A total of 203 pCNVs ≥1Mb were detected; 84.2% of them (171/203) were of 1-7Mb. Of note, pCNVs<1Mb were also detected. Five 22q11.2DS (three 3Mb A-D and two 600kb B-D) and two 22q11 duplications (one 3Mb A-D and one 1.5Mb A-B) were detected. At the time of submission, the clinical database was locked and confirmatory clinical data analysis was ongoing. **Conclusions**: Analysis of circulating trophoblasts from maternal blood offers the detection of genomewide pCNV below the resolution of cell-free DNA screening. In the general pregnancy population, this could provide for a significant reduction of residual risk for pCNV at early gestational weeks, including nested atypical 600kb 22q11.2 deletions not detectable by cfDNA test. CbNIPT clinical performance data will be provided together with an estimated rate of detection compared to cfNIPT.

015: Identification of 22q11.2 Quadruplication in Mother and Son Through Prenatal Cell-free DNA Screening

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Background: Cell-free DNA screening (cfDNA) for aneuploidy has been incorporated into routine prenatal care, with the option of screening for specific microdeletions. This screening has led to the identification of unexpected maternal findings, with consequences for patient and family. **Case report:** A 34-year-old gravida 2 para 1 patient was seen for genetic counseling after her SNP-based cell-free DNA results indicated high risk for 22q11.2 deletion syndrome, maternal deletion suspected. The patient elected to have a chromosomal microarray which found a 22q11.21 triplication, with a 1.8 Mb interstitial gain. The patient was counseled that there was a potential 50% risk of transmission of this triplication, and 100% transmission risk if due to a double duplication in trans. She was informed of the findings seen in the 4 published 22q11.2 triplication syndrome cases: all had cognitive deficiencies, 3 had cardiac anomalies, and 2 had hearing impairment. The duplication 22q11.2 phenotype was reviewed as well, including risk of autism. The patient had a history of learning disabilities related to reading comprehension; she had completed some college courses. She was hypothyroid, had kidney stones, but denied cardiac or auditory issues. She reported speech delay in her 3-year-old son. The patient declined definitive prenatal diagnosis. After delivery her newborn daughter had a normal microarray. The patient's son was seen for genetic consultation; speech delay and behavioral issues were noted. He had chronic otitis media, s/p tubes, normal growth and normal exam. Microarray found the same triplication seen in the mother. The patient and son were referred for echocardiogram and audiology testing, and son for renal ultrasound. **Conclusions:** The identification of the maternal quadruplication led to diagnosis of the patient's son with the same finding. Counseling challenges include intra- and extrafamilial variability seen with microdeletions and duplications/triplications, and limited data on patients with 22q11.2 triplication.

016: Investigating the Incidence of the 22q11.2 Deletion Syndrome in Miscarriage

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Background: Data regarding the incidence of 22q11.2 deletion syndrome (DS) in miscarriages is limited. Here we defined the incidence of segmental abnormalities associated with the 22q11.2 DS in pregnancy loss. **Methods:** Product of conception (POC) singleton cases over an 11-year period were reviewed. DNA extracted from POC and maternal blood samples were analyzed at a single reference laboratory by chromosomal microarray analysis (SNP-CMA) using Illumina CytoSNP-12b with bioinformatics to detect aneuploidy, full and mosaic copy number changes, deletions and duplications, uniparental isodisomy and heterodisomy, and regions of homozygosity, while evaluating for maternal cell contamination and parental origin of abnormalities. Clinical information was collected on the test requisition form. **Results:** Of the 84,509 fresh cases with fetal results, 82 had a deletion of the 22q11.2 region: 60 had an isolated deletion; 22 had additional findings. Parental origin of the deletion was 45 maternal, 33 paternal and 4 unknown. Average gestational age: 82.9 days (range 37-241 days): 51 first trimester losses, 11 second trimester losses, and 3 third trimester losses (17 unknown). Average maternal age: 32.6 years (range 19.0-47.0 years). Deletion size range: 0.7-4.8 Mb. **Conclusions:** SNP-CMA testing of POC samples provides detection, sizing, and parental origin of segmental abnormalities associated with the 22q11.2 DS. The 22q11.2 DS is not associated with advanced maternal age and was identified throughout all trimesters of pregnancy. In this cohort, the incidence of the 22q11.2 DS was 1/1150, higher than the published pediatric incidence (1/2000-1/4000), but similar to the published prenatal incidence (1/1000 - 1/1500). Comparatively, the 22q11.2 DS is more common than trisomy 13 and trisomy 18 in women <39 years and <35 years respectively. Offering genetic testing that can detect the 22q11.2 DS in miscarriages allows healthcare providers to counsel patients about recurrence risk, possible cause of the loss, and parental medical management.

017: Prevalence of 22q11.2 Deletion Syndrome in Offspring Conceived via Assisted Reproductive Technology Versus Spontaneously

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Background: Most chromosome 22q11.2 deletions are *de novo* (>90%) and result from meiotic non-allelic homologous recombination (NAHR). While 22q11.2 deletion syndrome (22q11.2DS) associated phenotypes are well characterized, risk factors leading to NAHR are not fully understood, including the potential relationship to assisted reproductive technology (ART). This study compared the rate of ART conceptions in a cohort of patients with 22q11.2DS to the general population. We also assessed differences in medical comorbidities in ART vs spontaneously conceived (SC) patients with 22q11.2DS. **Methods:** Secondary analysis of 1,182 patients enrolled in a prospective IRB approved study was performed. All patients had a molecularly confirmed *de novo* chromosome 22q11.2 deletion. ART conceptions included IVF and ICSI methods. 22q11.2 deletion size, obstetric, family, and medical histories were abstracted from the medical records. **Results:** 30 pregnancies were conceived using ART (2.54%), comparable with the U.S. general population rate of 2.3% (p-value=0.6602). ART and SC sub-cohorts demonstrated no significant difference in deletion size nor perinatal outcome, including the prevalence of preterm birth, singleton vs. multiples, presence of polyhydramnios, or congenital heart disease. Controlling for these same factors, neonates conceived via ART were more likely to be admitted to the ICU (aOR=6.13) but birth weight was not found to be a factor, requiring further investigation. **Conclusions:** Pregnancies conceived via ART, and later found to be affected by 22q11.2DS, demonstrated no significant differences in prevalence compared with the U.S. general population frequency of ART. Moreover, perinatal outcome measures did not differ between groups. Thus, importantly, NAHR seems to not be impacted by ART and associated phenotypic features are likewise not related, with perhaps the exception of frequency of ICU admissions. This finding will be reassuring to those families where ART was employed to conceive children with 22q11.2DS and where they were seeking a potential causal relationship.

018: 22q and Two Squared *

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Background: 22q11.2 deletion and duplication syndromes (22q11.2DS and 22q11.2DupS) are multisystemic conditions with variable clinical presentations. Despite the variety of associated features certain findings are commonly observed. These primarily include cardiovascular, endocrinological, gastrointestinal, immunological, palatal, and neurodevelopmental/psychiatric differences. However, some patients present with atypical features not explained by their primary diagnosis of a 22q11.2 copy number variant (CNV). We previously reported 13 patients with 22q11.2DS and coexisting conditions (Cohen 2018) – "22q and Two". Here, we report additional cases where testing for atypical features led to a dual diagnosis. **Methods:** We performed a retrospective chart review under an IRB approved protocol on the records of 1787 patients evaluated between 1992-2024 to identify additional variants on clinical genetic testing. Patients with nested and distal 22q11.2CNVs were also included in this review. **Results:** 11 patients with atypical features had supplementary genetic testing that confirmed a coexisting condition. 8/11 patients had 22q11.2DupS while 3/11 patients had 22q11.2DS. These included a patient with maternally inherited standard 22q11.2DupS (LCR22A-LCR22D) and ataxia found to be heterozygous for two pathogenic variants in the ATM gene, consistent with autosomal recessive ATM-related ataxia-telangiectasia. Also included was a patient with paternally inherited standard 22q11.2DupS (LCR22A-LCR22D) and prolonged QTc found to have a mutation in the KCNJ2 gene, associated with Long QT 7/Andersen-Tawil syndrome. One patient with 22q11.2DS (LCR22A-LCR22B), failure to thrive, encephalopathy and significant developmental delay was found to have a maternally inherited variant in the KIAA2022 gene on chromosome Xq13.3, associated with X-linked intellectual disability. Moreover 9 patients had incidental pathogenic variants identified on genetic testing and 23 patients that lacked atypical features were incidentally found to have variants of uncertain significance. Additional cases and details will be discussed. **Conclusion:** This data continues to support genome-wide testing in these complex patients to identify the diagnosis in its entirety to provide personalized management and genetic counseling.

019: Unusual Cases of 22q11.2 Disorders: Phenotypes and Lessons

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Complex 22q11 disorders prompt individualized management. We highlight four unusual cases followed at our multidisciplinary clinic that required tailored approaches to patient care. **Case 1**: 4-year-old female with maternally inherited chr22q11.2 A-D deletion and 16p11.2 proximal duplication presumably inherited from her father who has intellectual disability (ID), psychosis and is unhoused. Our patient has polymicrogyria, tonic-clonic seizures, poor expressive speech, submucous cleft palate (SMCP) and immune dysfunction and was adopted by family members. Her affected biological mother has intellectual disability (ID), scoliosis, hypocalcemia and hypothyroidism, anxiety and emotional lability. **Case 2**: 8-year-old female with unbalanced translocation 45,X der(X;22)(p22.31;q11.21) resulting in features of 22q11 deletion syndrome and Turner syndrome: hypernasal speech, global delays, short stature, autism, and sleep apnea. Microarray showed ~8.7 Mb Xp22 deletion and 4 Mb 22q11.2 deletion extending from the CES region to the B segmental duplication. Parental FISH analysis did not reveal any structural abnormalities involving chromosomes X and 22. **Case 3**: 8-year-old male with typical A-D chr22q11 deletion and associated features including SMCP, truncus arteriosus type 2, global delays, and immunodeficiency. We noted his 2-year-old brother had global delays but no anatomic findings. The 2-year-old brother's array revealed a paternally inherited chr22q11.2 B-D deletion, with distinct phenotypes and cognitive profiles in each affected family member. **Case 4**: 43-year-old non-dysmorphic female with clinically diagnosed DiGeorge Syndrome, infantile hypocalcemia, congenital sensorineural hearing loss due to cochlear defect, immunodeficiency s/p thymic transplant, and normal intellect. Family history: mother with bilateral cochlear defect, cleft palate, and full sibling died at age 3 months from tetralogy of Fallot. Sequencing showed heterozygous pathogenic frameshift variant in *TBX1*. Each complex case requires thoughtful diagnostic, management and genetic counseling approaches, underscoring intrafamilial variable expressivity, distinct genotypes, and assortative partnering due to phenotypic characteristics seen among patients with this disorder.

020: Hereditary Paraganglioma-Phaeochromocytoma Syndrome in a Patient with 22q11 Deletion Syndrome *

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Background: We aim to present the first known case of 22q11 deletion syndrome and hereditary paraganglioma-phaeochromocytoma syndrome. **Methods:** A 13-year-old girl presented with pallor, diaphoresis, palpitations, and weight loss (6kg) over several months. She has a background of maternally inherited 22q11 deletion syndrome, repaired truncus arteriosus and autism. Known family history of maternal aunt with Lynch syndrome (PMS2 gene mutation). She was admitted and initially treated as suspected infective endocarditis. She was tachycardic and hypertensive, (SBP up to 170mmHg) and was commenced on bisoprolol. **Results:** Bloods, including TFTs, were unremarkable. Echocardiogram showed no change from baseline. Ophthalmological exam, CXR, CT-brain and ultrasound abdomen were unremarkable. However, her urine catecholamines and metanephrines were raised. CT-TAP revealed a 4.4 x 3.5 x 4.6cm rounded intensely enhancing lesion with a hypodense centre arising from the left adrenal gland. Phenoxybenzamine was commenced. She subsequently underwent a left nephrectomy and adrenalectomy and was discharged 6 days post-operatively. Histology confirmed a phaeochromocytoma, metastatic to a regional lymph node. Immunohistochemical staining confirmed loss of SDHB expression, and further germline genetic testing was advised. The patient and her mother were found to have a pathogenic variant in the SDHB gene, consistent with a diagnosis of hereditary paraganglioma-phaeochromocytoma syndrome. Her mother was also found to have a pathogenic variant of the PMS2 gene, consistent with Lynch Syndrome, which our patient also has a 50/50 risk of inheriting. **Conclusion:** This case supports the law of Hickam's dictum which states 'a patient can have as many diseases as they please'[1]. This case highlights the importance of holistic care for children with medical complexity, which is best provided by a general paediatrician. Furthermore, this case outlines the importance of cascade genetic testing. Our patient will require genetic consultation in adulthood for predictive PMS2 testing, and to discuss recurrence risks and prenatal options for all three conditions. **References:** Mani N, Slevin N, Hudson A. What Three wise men have to say about diagnosis. BMJ. 2011;343(dec19 2):d7769–d7769. doi:10.1136/bmj.d7769

021: Influence of Polygenic Risk on Height in Individuals with a 22q11.2 Deletion *

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Background: Height is a complex heritable trait where common genetic variation (SNPs) play a well-established role. Previously, we showed that the 22q11.2 deletion, especially the LCR22A-LCR22D deletion, is associated with increased risk for short stature compared to population norms. In this study, we aimed to investigate whether common genetic variation, captured in a polygenic risk score (PRS), can influence height in individuals who have a baseline predisposition for shorter height conferred by the 22q11.2 deletion. **Methods**: Overall, we had 313 adults with a typical 22q11.2 deletion with available genome sequencing and phenotypic data, including 260 of European ancestry. We used an ~1 million SNP height-PRS derived from a recent GWAS (GIANT Consortium, 2022). Multivariable linear regression was used to assess for the effect of the PRS on height, adjusting for clinical variables and 22q11.2 deletion extent. **Results**: Among the 260 individuals with a 22q11.2 microdeletion of European ancestry, each standard deviation increase in PRS was associated with a 3.56 ± 0.40 cm increase in height ($p<2.22e-16$), in a multivariable linear regression model (adjusted $R^2= 0.569$, $p_{model}<2.22e-16$). Significant predictors associated with shorter height in this model include female sex ($p<2.22e-16$), LCR22A-LCR22D 22q11.2 deletion extent (relative to LCR22A-LCR22B/LCR22A-LCR22C deletions) ($p=0.00212$), and congenital heart disease ($p=1.94e-04$). When stratified by quintiles of PRS, 36.5% (n=19/52) of those in the lowest quintile had short stature (<3rd percentile of population norms) compared to 3.8% (n=2/52) of those in the highest quintile (odds ratio=14.07, Fisher's exact $p=4.23e-05$). Results were similar when individuals of non-European ancestry were included in analyses (total n=313) although with modestly reduced effect sizes. **Conclusions**: These results suggest that a general population-derived height-PRS is associated with adult height in individuals with a 22q11.2 deletion, and may contribute to modifying the deletion's effect on increasing risk for short stature.

022: Influence of Polygenic Risk on BMI in Individuals with a 22q11.2 Deletion *

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Background: Body mass index (BMI) is a complex quantitative trait influenced by both lifestyle/environmental and genetic factors. Previously, we reported that the 22q11.2 deletion is associated with an approximately 2-fold increased risk for obesity beginning in young adulthood, compared to population norms. In this study, we aimed to assess whether common variants associated with BMI in the general population, captured in a polygenic risk score (PRS), could modify BMI in individuals with a 22q11.2 deletion. **Methods**: In our cohort, there were 313 adults with a typical 22q11.2 deletion (mean age 32 years) with genome sequencing and phenotypic data available, including 260 of European ancestry. We used an ~2 million SNP PRS derived from a previously published PRS constructed from UK BioBank data (Khera et al. 2019) and multivariable linear regression to assess for the effect of the BMI-PRS on BMI in 22q11.2 deletion syndrome, adjusting for clinical variables and 22q11.2 deletion extent. **Results**: Among the 260 individuals with a 22q11.2 microdeletion of European ancestry, each standard deviation increase in BMI was associated with a 2.13 ± 0.49 kg/m^2 increase in BMI ($p=1.93e-05$) in a multivariable linear regression model (adjusted $R^2= 0.111$, $p_{model}=4.74e-06$). Other significant predictors associated with higher BMI in this model include female sex ($p=0.0255$), older age ($p<0.00981$), and LCR22A- LCR22B/ LCR22A- LCR22C 22q11.2 deletion extent (relative to LCR22A-LCR22D deletions) ($p=0.0215$). Including individuals with non-European ancestry in analyses (n=313) produced similar results but with modestly reduced effect sizes. **Conclusions:** The results demonstrate that genome-wide common variation associated with BMI in the general population may modify BMI and influence risk for obesity in individuals who are at an elevated baseline risk for obesity conferred by the 22q11.2 microdeletion. Possible differential effects of proximal nested deletions require further study.

023: Mortality and Age at Molecular Diagnosis in Adults With 22q11.2 Deletion Syndrome *

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Background: We continue to learn about premature mortality in adults with 22q11.2 deletion syndrome (22q11.2DS). Previous research has shown an effect of major congenital heart disease (CHD). In this study, we investigated whether the burden of other lifetime clinical features per individual or age at molecular diagnosis of the 22q11.2 microdeletion were associated with premature death in adults with 22q11.2DS. **Methods:** We studied mortality in 404 well-characterized Canadian adults aged ≥ 18 years with 22q11.2DS (median age 32.7, range 18.1-76.3, years; 52.0% female). In addition to major CHD, we assessed the number of 76 other lifetime clinical conditions (that were present in ≥5% of the overall sample), and used the number per individual to represent burden of other illnesses. We used linear regression modeling to identify predictors of mortality, accounting for sex, ethnicity, major CHD, burden of other illnesses, and age at molecular diagnosis. **Results:** There were 50 deaths in the sample (12.4%) that occurred at median age 45.5 (range 18.1-76.3) years. Older age at molecular diagnosis of 22q11.2 microdeletion (p<0.0001) and major CHD (p<0.0001), but not sex, ethnicity, or burden of other illnesses, were significant independent predictors of mortality (model R^2 0.17, p<0.0001). Within the subgroup with no major CHD, results were similar, but with the burden of other illnesses also a significant predictor of premature mortality (p=0.0388). **Conclusions:** The results suggest some effect of later age at molecular diagnosis of 22q11.2DS, in addition to major CHD and global illness burden, on the likelihood of premature mortality in adults with 22q11.2DS. The findings support initiatives to increase prenatal and neonatal diagnosis, as part of improving opportunities for health screening, anticipatory care, and lifelong follow-up for 22q11.2DS.

024: Clinical Suspicion and Diagnostic Delay in a Cohort of Adults with 22q11.2 Deletion Syndrome: Are We Doing Enough? *

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Background. 22q11.2 deletion syndrome (DS) is the most common genomic disorder characterized by a wide variability of clinical manifestations. Significant progress has been made in the early treatment of babies with severe congenital disorders. However, due to the high clinical heterogeneity, the diagnosis of 22q11.2DS can be challenging, leading to diagnostic delay, late access to care, and inadequate prenatal counseling. **Methods**. Retrospective monocentric study to assess the diagnostic delay in 22q11.2DS patients aged >16 years. **Results**: Of the 80 patients, 13% were diagnosed at birth, 28% during childhood, 30% during adolescence, and 34% during adulthood. The main individual indications for genetic testing in the neonatal period, infancy, and adolescence were congenital heart disease (CHD) (86%), psychomotor development delay (32%), and psychiatric illness (46%), whereas in early (<35 years) and late (> 35 years) adulthood they were psychiatric illness (55%) and positive family history for 22q11.2DS (86%). Major CHD and congenital gastrointestinal disease were most prevalent in patients with neonatal diagnosis. However, the frequency of congenital hypocalcemia, ENT anomalies, skeletal disorders, speech difficulties, and growth delay were similar between groups. Psychomotor development delay was similarly observed in those diagnosed in the neonatal, adolescent, and early adult periods. Notably, 70% and 43% of those diagnosed in early and late adulthood presented at least three 22q11.2DS manifestations in infancy, including CHD. The first clinical manifestation attributable to 22q11.2DS was observed in the neonatal period in 81% of those diagnosed in childhood, in 71% of those diagnosed in adolescence, and in 45% and 57% of those diagnosed in early and late adulthood, with a median diagnostic delay of 1.5, 14, 25, and 34 years, respectively. **Conclusion:** Patients with 22q11.2 still experience a high diagnostic delay, especially those without CHD. Improving diagnosis by disseminating warning signs should be the first step towards improving access to treatment and ameliorating the quality of life for patients and their families.

025: Rare Copy-number Variants as Modulators of Clinical Phenotypes of Adults with 22q11.2 Deletion Syndrome *

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Background. The 22q11.2 deletion syndrome (DS) is the most common genomic disorder characterized by a marked variability of clinical manifestations. The wide spectrum of clinical manifestations includes immune deficiency, congenital heart diseases, palatal abnormalities, learning difficulties, and neuropsychiatric disorders. Significant progress has been made in understanding the complex molecular genetic etiology of 22q11.2 DS contributing to the heterogeneity of phenotypic features. Here we aimed to investigate the rate of concurrent rare CNVs, and how those might influence the clinical spectrum among patients with the 22q11.2 deletion. **Methods:** To examine the presence of additional CNV possibly affecting the phenotype, we performed CGH array in 88 adults living with 22q11.2. Overall, we identified 23 patients (26%) carrying at least one additional CNVs outside of the 22q11.2 region, 2 being pathogenic, the others being of uncertain significance. In particular, a patient was found to simultaneously carry a typical pathogenic de novo 22q11.2 microdeletion and a maternally inherited pathogenic 7p22.1 microduplication, while a further patient carried both a de novo 22q11.2 microdeletion and distal 16p11.2 microdeletion Both patients presented a more severe neurodevelopmental and psychiatric phenotype compared to other individuals from the cohort, suggesting an additive effect. This indicates that in 2.3% of cases, additional CNVs are likely to contribute to the clinical presentation. Our data revealed that the extension of diagnostics with genome-wide methods in 22q11.2 DS patients can reveal additional clinically relevant changes with clinical, familial, and reproductive implications.

026: Cardiac Organoids Provide a Platform for Complex Genetic Studies of 22q11 Deletion Syndrome

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While structural heart defects present at birth, or congenital heart disease (CHD), are found in approximately 1% of the overall population, a particular class of CHD termed conotruncal defects are found in 50-80% of patients that carry a 22q11 deletion. CHDs frequently associated with this cohort include various right sided lesions such as tetralogy of fallot, pulmonary atresia and interrupted aortic arch. However, our collective understanding of disease pathogenesis for both syndromic and nonsyndromic CHDs is incomplete due to the disease's multifactorial nature and model systems that are difficult to scale and perturb. To expand our understanding of the gene regulatory networks (GRNs) that contribute to CHD in the context of 22q11, we have adapted an in vitro cardiac-organoid system derived from hiPSCs termed 'cardioid'. Our single-cell RNA sequencing studies reveal that after modulation of multiple signal transduction pathways essential for embryonic development, cardioids ultimately include many cell types found in the heart (e.g. cardiomyocytes, vascular smooth muscle, endocardium and septal-like cells). We find that 22q11DS-derived cardioids continue to proliferate during differentiation unlike WT cells, and do not contract. Similar to in vivo studies, reducing WNT activation rescued both the proliferative and contraction phenotypes. To define perturbed GRNs associated with CHD in 22q11DS patients, we next generated single cell(sc) RNA sequencing(seq) of cardioids derived from human induced pluripotent stem cells (hiPSCs) from patients diagnosed with 22q11DS. This analysis revealed delayed differentiation in the cardiac neural crest-like cells in the cardioids from those with both 22q11DS +CHD compared to controls. This work has illustrated the power of hiPSC-derived organoids to identify latent dysregulated mechanisms involved in dysregulated organogenesis associated and provides a platform to prioritize additional genetic variants that contribute to complex genetic mechanisms.

027: *Tbx1* Promotes Maturation and Restricts Atypical Fates in Multilineage Progenitor Cells Needed to form the Cardiac Outflow Tract

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Background: *TBX1,* encoding a T-box transcription factor, is a key gene for congenital heart disease and craniofacial muscle hypotonia in patients with 22q11.2DS. The cardiopharyngeal mesoderm (CPM) in early embryos are needed to form these structures affected in 22q11.2DS. Inactivation of *Tbx1* in the CPM in mice results in perinatal lethality with a persistent truncus arteriosus and failed formation of branchiomeric (craniofacial) muscles. We recently identified a multilineage progenitor (MLP) population within the CPM that is affected by loss of *Tbx1*. **Methods:** We performed single cell RNA-sequencing (scRNA-seq) of the CPM to determine how transcriptional profiles changed upon inactivation of *Tbx1*. We then performed bioinformatic analysis and validated changes of expression of genes in MLPs by RNAscope *in situ* analysis. Gene ontology analysis was performed to understand the function of genes that were changed in expression in the MLPs in control versus *Tbx1* mutant embryos. We also analyzed ATAC-seq data to identify differentially accessible chromatin sites in genes affected by loss of *Tbx1*. **Results:** We found that genes reduced in expression that also showed differential accessible regions by loss of *Tbx1*, function in cell proliferation as well as cardiac and muscle cell fate commitment, thereby promoting MLP cell maturation. Those that increased in expression by loss of *Tbx1* were not typically expressed in mesoderm cells and included neuronal and other genes. Upon examination of cell types and proportions within MLPs, we found that there is a switch of cell state by loss of *Tbx1*, in which cells that promote maturation were replaced by those that express atypical non-mesodermal genes in early embryos. **Conclusions:** We found that loss of *Tbx1*, a critical gene for 22q11.2DS, promotes expression of genes for maturation and restricts expression of non-mesodermal genes in MLPs in early mammalian embryos, thereby contributing to cardiac and muscle developmental defects.

028: Cell Compensation Associated with Heart Defects in Mouse Model of 22q11.2 Deletion Syndrome

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Background: Patients with 22q11.2 deletion syndrome (22q11.2DS) have cardiac outflow tract (OFT) defects including Tetralogy of Fallot (TOF) and persistent truncus arteriosus (PTA). The OFT defects involving abnormal OFT septation are highly variable. Mesenchymal cells derived from distinct embryonic origins including neural crest, cardiomyocytes, and endocardial cells participate in OFT septation. It is not known whether altered interactions between mesenchymal cells of different origins, in time and space, contributes to varied OFT phenotypes. **Methods:** In this study, we attempted to answer this question by applying genetic-based cell lineage tracing and single cell RNA sequencing (scRNA-seq) analyses to the *LgDel*$^{+/-}$ mice, a mouse model of 22q11.2DS. We examined the embryonic hearts when the OFT is being divided by invasion of mesenchymal cells derived from neural crest and endocardial cells. **Results:** We found decreased neural crest- as well as endocardial-derived mesenchyme in the dividing OFT of embryonic *LgDel*$^{+/-}$hearts by cell lineage tracing. We also observed a striking reduction in the endocardial-derived mesenchyme in the atrioventricular canal (AVC) in *LgDel*$^{+/-}$ embryonic hearts. Surprisingly, the total number of mesenchymal cells in the AVC was not decreased, suggesting compensation by the non-endocardial derived cells. Similar compensation, but to less extent, was present in the OFT, to supplement the loss of neural crest- and endocardial-derived mesenchyme. The cell lineage findings were supported by scRNA-seq, which showed increased mesenchymal contribution in the OFT and AVC by cardiomyocytes. Mechanistically, scRNA-seq analysis and functional validation revealed molecular and cellular defects in endocardial to mesenchymal transformation (EndMT) in the OFT and AVC. **Conclusions:** Our findings show that defective EndMT is part of cellular mechanism of abnormal OFT septation in the *LgDel*$^{+/-}$ 22q11.2DS mouse model. Our findings also suggest cell compensation as a surviving mechanism affecting the expression of disease severity in 22q11.2DS, which requires further investigation.

029: Spectrum of Congenital Heart Disease in a National Cohort of Patients with 22q11.2 Deletion Syndrome

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Background: Congenital Heart Disease (CHD) is present in up to two thirds of children with 22q11.2 deletion syndrome. The spectrum of pathology varies from critical, duct dependent lesions such as interrupted aortic arch, to anatomical variations such as right sided aortic arch. Children with severe CHD are more likely to be detected than those with asymptomatic lesions which are likely under diagnosed. **Methods:** A retrospective clinical review was carried out of patients up to the age of 18 who attend a specialist 22q11.2 deletion syndrome clinic were included. Clinical records, echocardiogram database, theatre and cardiac catheterisation lab logs were reviewed. Data was collected on the types of congenital heart disease identified, as well as the details of transcatheter and surgical interventions required in childhood. Children over the age of 18, who have transitioned to adult services, were not included. **Results:** 158 patients were identified for inclusion, 47% (n=75) of whom were male. Of these, 71% (n=112) had abnormal findings on echocardiogram with 53% (n=84) requiring intervention in childhood. Conotruncal defects including truncus arteriosus, tetralogy of Fallot and interrupted aortic arch accounted for 32% (n=51) of congenital heart defects. Of those who required intervention 19% (n=16) were treated by cardiac catheterisation alone, with 45% (n=38) undergoing cardiac surgery alone and 36% (n=30) requiring both cardiac catheterisation and open surgical procedures. In patients requiring intervention, the median number of cardiac catheterisations was 1.5 (IQR 2) and median number of cardiac surgeries was 1 (IQR 1). 14% (n=23) had a right sided aortic arch. **Conclusions:** The prevalence of congenital heart disease in patients with 22q11.2 deletion syndrome is significant and over half of children require invasive treatment in childhood for management of these conditions. Routine cardiac screening is required in order to identify these lesions early and manage them as part of a multidisciplinary team.

030: The "Hidden" Cardiac Anomalies in Patients Presenting Without Major Congenital Heart Disease in 22q11.2 Deletion Syndrome

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Background: Approximately 65-75% of patients with 22q11.2 deletion syndrome (22q11.2DS) have congenital heart disease (CHD) most commonly including conotruncal and septal defects. Many infants are diagnosed with 22q11.2DS when they present with characteristic CHD but many are diagnosed at later ages with noncardiac phenotypes. Our goal was to better define the cardiac phenotype of patients with 22q11.2DS that often present beyond infancy without significant intracardiac anomalies. **Methods**: We reviewed medical records of patients seen in our center who were not reported to have significant CHD (i.e. did not have conotruncal, septal or other major intracardiac defects). We recorded aortic valve anatomy, aortic root size (Z-score), and aortic arch sidedness and branching pattern. **Results**: Of N=524 cases without major CHD, 21 (4%) had a bicuspid aortic valve (BAV), of which 17 included aortic root dimensions at the level of the sinuses of Valsalva. The median Z-score for the aortic root was 2.3 and the Z-score was >2 in 8/17 BAV cases. Of N=524 cases, 160 (30%) patients had normal intracardiac anatomy, a normal aortic valve and documented aortic arch anatomy: 57% had a normal left-sided aortic arch with normal branching pattern, 26% had a left sided aortic arch but abnormal branching pattern, 16% had a right sided aortic arch, and 1% had double aortic arch. By way of comparison, the median aortic root Z-score available for 157/160 patients was 0.87 and the Z-score was >2 in 19 cases. **Conclusions**: BAV is not an uncommon diagnosis and aortic arch anomalies, some of which form vascular rings, are common in 22q11.2DS. The median aortic root dimensions in both populations are above normal and seemingly more so in the subset with BAV. The patient diagnosed with 22q11.2DS for noncardiac reasons nonetheless warrants a complete cardiac evaluation.

031: Congenital Heart Disease in Patients with Distal 22q11.21-3 Deletions (LCR22D-E, D-F, D-G, E-F)

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Background: Most patients with 22q11.2DS have standard LCR22A-LCR22D deletions (85%) with ~two-thirds having cardiac disease (CD) due to haploinsufficiency of *TBX1*+/-*CRKL*. Patients with distal deletions beyond LCR22D also have CD but data is limited primarily to case reports. Here we describe cardiac findings in patients from a single Center with deletions spanning the LCR22D-LCR22G (D-G) region to better understand associated CD. **Methods:** We retrospectively reviewed medical records from 40 patients with distal deletions involving the D-G region, specifically: D-E (n=19), D-F (n=8), D-G (n=4), and E-F (n=9), examining the presence of CD and comparing our findings to those of 60 patients from the literature: D-E (n=27), D-F (n=15), D-G (n=10), and E-F (n=8). **Results:** 16/40 (40%) of our patients had CD including: **D-E** (8/19; 42%) [VSD (4), truncus arteriosus (TA), TOF, BAV+VSD, BAV+cardiomyopathy]; **D-F** (6/8;75%) [VSD (3), ASD+VSD (2), aortic stenosis+BAV+VSD]; **D-G** (1/4; 25%) [VSD]; and **E-F** (1/9;11%) [AV canal]. As with our cohort, CD occurred more frequently in patients from the literature with distal deletions overlapping the D-E region: **D-E** (15/27; 56%) [VSD (5), TA (3), ASD+VSD (2), BAV (2), AV canal, DORV, dextrocardia]; **D-F** (10/15; 67%) [VSD (2), cardiomyopathy (2), ASD, TA, TA+IAA-B, ASD+VSD, aortic coarctation, TGA+double inlet left ventricle]; and **D-G** (5/10; 50%) [VSD (3), TA, ASD+VSD], compared with **E-F** deletions where only 2 of 8 patients (25%) had CHD [pulmonary stenosis+VSD and ASD]. **Conclusions:** Combining our results with those from the literature, we found CD to be frequently associated with 22q11.21-3 deletions, particularly those overlapping the D-E region (23/46; 50%) compared with E-F deletions (3/17; 18%). Thus, our data suggests that all patients with distal 22q11.21-3 deletions will benefit from a cardiac evaluation. Moreover, genes within the D-E region, such as *HIC2, MAPK1,* and *YPEL1*, should be further investigated as cardiac developmental drivers.

032: Chromatin Modifiers to Elucidate the Phenotypic Variability of Congenital Heart Disease in 22q11.2DS *

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Background: Congenital heart disease (CHD) presents a worldwide health burden as the most common type of birth defect, affecting ~1% of live births. While it remains the leading contributor to birth defect mortality, the causes of most CHD remain to be uncovered. In 22q11.2 deletion syndrome (22q11.2DS), *TBX1* is an important causative gene of CHD, and yet its haploinsufficiency is not sufficient to explain the variability in clinical presentation and severity. Therefore, 22q11.2DS represents a unique population in which to uncover genetic modifiers of CHD. **Methods:** To identify potential modifiers, our lab performed whole genome sequence analysis on 1,182 subjects with 22q11.2DS and discovered chromatin regulatory genes occurring in 8.5% of the subjects with CHD. This study aims to investigate the interaction of these genes, specifically the histone methyltransferases *Kmt2c* and *Kmt2d*, with *Tbx1* in mouse models. To test this interaction, mouse crosses were generated with the conditional deletion of *Kmt2c*, *Kmt2d*, and *Kmt2c/d* in the *Tbx1* cell lineage. **Results:** Conditional deletion of *Kmt2d* in the *Tbx1* lineage leads to perinatal lethality in all mutants, with a significant subset (~40%) presenting with aortic arch anomalies, including aberrant right subclavian artery and interrupted aortic arch type B. Assessment of the pharyngeal arch arteries (PAAs) earlier in developmental time revealed either absence or hypoplasia of the 4th PAAs in 100% of mouse mutants. This suggests that *Tbx1* and *Kmt2c/d* genetically interact in critical developmental processes, including those involved in CHD. **Conclusions:** Further characterization of defects in mice will be performed using molecular and cellular approaches, as well as functional genomics studies that will delineate the shared and unique developmental roles of *Kmt2c/d* and *Tbx1*. This will further the understanding of the genetic architecture of heart development and the etiology of CHD in 22q11.2DS, knowledge of which will improve diagnosis and treatment.

033: iPSC-derived Thymic Epithelial Cells promote TCRab and regulatory T cell reconstitution in athymic NSG-nude mice

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Background: Congenital Athymia (CA) is the most severe immune manifestation of 22q11 Deletion Syndrome. HLA-unmatched allogenic thymic tissue transplantation (ATTT) remains the only curable therapy for CA. However, ATTT is associated with a high rate of autoimmunity, leading to significant morbidity and mortality in this patient cohort. Thus, HLA-matched regenerative thymic epithelial cells hold great therapeutic promise. **Methods:** Here, we elucidated pathways instructing commitment and specialization of the human thymic epithelial stroma through complementary single cell transcriptomic approaches. First, we identified gene regulatory networks that define fetal thymic epithelium in the thus far unexplored context of other anterior foregut-derived organs; then, we characterized lineage trajectories within the thymic epithelial compartment across embryonic, fetal, and early postnatal stages. **Results:** Activation of interferon response gene regulatory networks distinguished epithelial cells of the thymus from those of all other anterior foregut-derived organs. Interferon signals were processed differentially within thymic cortical and medullary lineages. We have translated the core set of gene regulatory networks identified in our transcriptomic study into a morphogen-based approach to advance the differentiation of iPSCs into thymic epithelial cells (TECs). TECs derived from this protocol demonstrated high transcriptional fidelity with primary human fetal intertypic (mc)TECs that can give rise to cortical and medullary lineages. To test the functional capacity of iPSC-derived TECs to give rise to human T cells, and specifically to execute positive and negative selection, we transplanted iPSC-derived TECs into humanized athymic NSG-nude mice (NSG-Foxn1^{Null}). Sixteen weeks after transplantation, flowcytometric analysis of dissociated TEC grafts showed robust human TCRab T cell development recapitulating the physiologic progression from double-negative to double-positive to TCRab-rearranged single CD4 and CD8 positive T cells observed in primary human thymus. In addition, we observed the development of regulatory T cells based on immune phenotype, FOXP3 expression and TSRD demethylation. **Conclusions:** These results provide proof of concept that transplantable human iPSC-derived TECs can promote TCRab and regulatory T cell reconstitution *in vivo* and have potential as a regenerative thymic replacement therapy for patients suffering from thymic developmental defects.

034: Single cell RNA-seq Identifies Significant Differences in CD4 T cell Populations Between 22q11.2 Deletion Syndrome and Controls

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Introduction: Our previous work has shown that despite having a small thymus with a limited T cell repertoire, majority of 22q11.2 deletion syndrome patients have a normal T cell function at young age. As these patients age their T cell subset number normalizes yet about 25% of them seem to be at risk of developing recurrent sinopulmonary and autoimmune disease. Given the crucial role that CD4 helper T cells play in induction of class switching of B cells, and autoimmunity development, we sought to take a closer look at CD4 T cell population. **Methods:** Using 3' RNA sequencing technique, we compared 13 patients with 22q11.2 deletion syndrome to 11 controls. Age range 8 years to 41 years. Ran a Pearson's Chi-squared test to determine significance. **Results:** The cell type proportions of CD4 naïve and memory were significantly different among patient and control groups using the Pearson's Chi-squared test, p-value < 0.0001. Patients with 22q112 deletion syndrome had an increase in memory CD4 T cells of 47% compared to 40% in controls. Additionally, patients had a lower CD4 naïve subset of 46% compared to 52% in control. The T regulatory population was similar in both groups. **Conclusion:** Our data shows that patients with 22q11.2 deletion syndrome have an inverted CD4 helper T cells population when compared to healthy controls with statistical significance at an RNA expression level. We suspect that patients with an inverted ratio will likely be the sub-group of patients most at risk of autoimmune and recurrent sinopulmonary infections.

035: Elucidating Humoral Immunity and Vaccine Response in Pediatric Patients with 22q11.2 Deletion Syndrome: A Retrospective Case Series *

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Background: 22q11.2 Deletion Syndrome (22q11.2DS) is the most common chromosomal microdeletion syndrome, affecting 1 in 3,000 to 6,000 live births. It leads to diverse developmental and health issues, including significant immunodeficiencies, ranging from mild to life-threatening. While T-cell abnormalities due to TBX1 gene deletion are well-documented, humoral immunity aspects remain less explored. This study aims to elucidate the humoral immune response and vaccine efficacy in pediatric patients with 22q11.2DS. **Methods:** A retrospective analysis was performed on 151 genetically confirmed 22q11.2DS patients at the Joe DiMaggio Hospital's 22q Clinic. Immunological evaluations, including immunoglobulin levels, vaccine titers, and T and B-cell counts, were conducted for patients referred to immunology due to recurrent infections. Patients found to have low titers to streptococcus pneumonia received a booster vaccine. Post-booster vaccine responses to pneumococcal antigens were re-assessed at 6 weeks and one year. **Results:** Among the 90 patients assessed for immune function, the average IgG level was 1043 (range: 322-3289), and average for available CD19 B-cell counts was 869 (Range: 107-4242, n=76). Eighty five percent had completed the full pneumococcal vaccination schedule. Streptococcus pneumonia titers were collected in 54 (60%) patients of whom 42 (46%) demonstrated suboptimal protection of initial streptococcus pneumonia vaccine titers and were recommended a booster vaccine. An improved but transient vaccine response was noted, suggesting adequate initial immune response with diminished sustainability over time. Demographically, the study encompassed a diverse age range and ethnicity, with nearly balanced gender representation. **Conclusions:** The study highlights the complexity of humoral immunity in 22q11.2DS, revealing an adequate but short-lived vaccine response. Despite normal IgG and lymphocyte counts, the transient nature of vaccine efficacy points to potential B-cell dysfunction alongside the known T-cell abnormalities. These findings underscore the need for ongoing immunological monitoring and further research into the mechanisms underlying immune dysfunction in 22q11.2DS patients.

036: Four patients with Severe Immune Related Complications Including Lymphoma and Interstitial Lung Disease

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Background: The 22q11.2-deletion syndrome (22q11DS) is associated with thymus hypoplasia, leading to T-lymphocytopenia in most infants with the syndrome. The immune deficiency in 22q11DS may also include low levels of protective immunoglobulins. Common variable immunodeficiency (CVID) is an inborn error of immunity, with unknown genetic cause in most cases. It is characterized by hypogammaglobulinemia and poor antibody response to vaccinations. CVID presents during or after the second decade of life, with frequent infections, often combined with autoimmunity. A proportion of patients with CVID, particularly those with autoimmune manifestations, develop non-infectious lymphoproliferation, as a potentially serious complication. There are a few previous reports on CVID-like disease in adults with 22q11DS, but only occasional reports of lymphoproliferation in this context. **Aim:** To describe patients from our 22q11DS cohort with lymphoproliferative complications. **Methods:** We performed retrospective chart reviews of patients with 22q11DS and severe lymphoproliferative disease. **Results:** We identified four female patients with 22q11DS and lymphoproliferative complications. Two were diagnosed with 22q11DS in childhood (5 and 13 years), and two as adults (29 and 46 years). All four had a history of frequent respiratory infections and autoimmune manifestations (three had autoimmune hematological disease, one had psoriasis). All had splenomegaly. Three developed chronic low-grade fever and initially discrete respiratory symptoms, leading to a diagnosis of granulomatous-lymphocytic interstitial lung disease (GLILD). Two had lymphadenopathy and fever, leading to diagnosis of malignant lymphoma. All had immunoglobulin A deficiency and progressively low levels of immunoglobulin G and M. Three had low T helper cells. **Conclusions:** These four cases illustrate that both children and adults with 22q11DS can develop a progressive immune deficiency, with serious complications. The symptoms of both GLILD and lymphoma may initially be vague and overlooked, warranting vigilance in clinicians seeing patients with 22q11DS. Early recognition and treatment is needed to improve outcome.

037: A Cohort Study Demonstrating Atypical Characteristics of Iron Deficiency In Patients with 22q11.2DS.

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Background: Prior studies have demonstrated that patients with chromosome 22q11.2 deletion syndrome (22q11.2DS) have lower platelet counts (PC) compared to non-deleted populations. They also have an increased mean platelet volume. Other blood count abnormalities have primarily been associated with autoimmune phenomenon and changes in the immune profile. Iron deficiency and iron deficiency anemia are prevalent worldwide and accounts for 50% of the world's anemia burden. In resource enriched countries, iron deficiency is common in early childhood during transition to cow's milk and in menstruating individuals, particularly in adolescence. Other causes include food insecurity, inadequate iron absorption or occult bleeding. **Methods:** We examined available iron studies including ferritin, serum iron, transferrin, transferrin saturation, and total iron binding capacity as well as hemoglobin and mean corpuscular volume in patients with 22q11.2DS evaluated at our institution in the last 10 years. Data was identified by query of electronic medical records under an IRB approved protocol. **Results:** We identified 47 patients with abnormal ferritin levels and 22q11.2DS in the past 10 years. 37 had low ferritin levels or iron deficient anemia. The median nadir hemoglobin was 10.8 g/dL (range 6.7-13.3g/dL); median nadir MCV was 80.7 fL (range 64.3-99.4fL); median ferritin was 8.7 mg/dL (range <1 to 191 mg/dL). 17 were males (45.9%) with a Median age of 8 years (3-20y); Median age for females was 12 years (3 months – 18y). Compared with age distribution of low ferritin levels in non-deleted individuals, there was a difference in the ages when iron deficiency was more common. **Conclusions:** We found iron deficiency and iron deficient anemia in individuals with 22q11.2DS without microcytosis, producing a normocytic anemia and occurring in children of school age and adolescence rather than in toddlers and young women more typical of non-deleted individuals. Determining the reason why is under investigation.

038: Occurrence of Hypothyroidism and Hyperthyroidism in 22q11.2 Deletion Syndrome

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Background: Thyroid disorders have been described in 22q11.2 deletion syndrome (22q11.2DS); thyroid dysfunction occurs in up to 20% of children and adolescents. This study characterizes thyroid disorders in patients with 22q11.2 DS from one tertiary care center. **Methods:** Under an IRB-approved protocol, we retrospectively reviewed medical charts of children with 22q11.2DS seen from 1992-2023. We included patients with confirmed diagnoses of autoimmune thyroid disease and thyroid cancer using diagnosis codes, medications, and labs. **Results:** Of 1629 patients with 22q11.2DS, we identified 117 patients with thyroid disease. Autoimmune hypothyroidism was the most common (n=104, 89%) followed by autoimmune hyperthyroidism (n=10, 8.5%). Two (1.7%) had thyroid cancer: 1 medullary, 1 follicular. Females comprised 55% (n=57) of the hypothyroid group and 80% (n=8) of the hyperthyroid group. Deletion sizes in the hypothyroid group: 94 patients with standard deletion in LCR22A-LCR22D, 7 patients diagnosed by FISH, 2 patients with atypical deletions encompassing *TBX1*, 8 patients with nested deletion in LCR22A-LCR22B, 1 patient with nested deletion in LCR22B-LCR22D, and 2 patients with nested deletion in LCR22C-LCR22D. Deletion sizes in the hyperthyroid group: 8 had standard A-D deletion and 2 were diagnosed by FISH, unknown breakpoints. **Conclusions:** We identified 117 patients (7.2%) with 22q11.2DS had thyroid disorders, mostly hypothyroidism. We also found more cases of hyperthyroidism (10/1629) than expected compared to the general population, which is 1 per 5000 children and adolescents. Clinicians should have a high rate of suspicion for thyroid disorders, including autoimmune hyperthyroidism, in patients with 22q deletion syndrome.

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039: Association of Thyroid and Parathyroid Disease in 22q11.2 Deletion Syndrome Patients Followed at Nationwide Children's Hospital *

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Background: Patients with 22q deletion syndrome present with a wide spectrum of clinical features including thyroid disease. There is limited literature regarding the prevalence of thyroid and parathyroid disease in this population. **Objective**: To evaluate the prevalence of thyroid and parathyroid disease in patients with 22q deletion syndrome. **Methods**: An electronic data set was created based on all patients at NCH with the diagnosis of 22q deletion syndrome. From this, a manual retrospective review of laboratory data and charts of all patients with 22q deletion syndrome evaluated at NCH. Analysis components included review of cohort characteristics and laboratory data. **Results**: We studied a cohort of 366 patients with 22q deletion syndrome, 165 females and 201 males with a mean age of 12.9 years. Of this cohort, 43 (12%) had a diagnosis of a thyroid or parathyroid abnormality. Of these patients, 4 had a diagnosis of hyperthyroidism, 10 had a diagnosis of hypothyroidism, and 29 had hypoparathyroidism. Of the 14 patients with known thyroid disease, 9 (64%) were found to have a cardiac defect. Of the 29 patients with hypoparathyroidism, 20 (69%) were found to have a cardiac defect. **Conclusion**: Thyroid and parathyroid disease is prevalent amongst patients with 22q deletion syndrome. This confirms the importance of routine surveillance of thyroid and parathyroid function. **References**: Levy-Shraga Y, Gothelf D, Goichberg Z, Katz U, Somech R, Pinhas-Hamiel O, Modan-Moses D. Growth characteristics and endocrine abnormalities in 22q11.2 deletion syndrome. Am J Med Genet A. 2017 May;173(5):1301-1308. doi: 10.1002/ajmg.a.38175. Epub 2017 Feb 16. PMID: 28421700. Shugar AL, Shapiro JM, Cytrynbaum C, Hedges S, Weksberg R, Fishman L. An increased prevalence of thyroid disease in children with 22q11.2 deletion syndrome. Am J Med Genet A. 2015 Jul;167(7):1560-4. doi: 10.1002/ajmg.a.37064. Epub 2015 May 5. PMID: 25944702.

040: Outcomes of Provocative Growth Hormone Testing in Patients with 22q11.2 Deletion Syndrome and Short Stature *

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Background: It is estimated that 39 to 67% of youth with chromosome 22q11.2 deletion syndrome (22q11.2DS) have short stature. The etiology of growth restriction is multifactorial, and growth curves have now been developed for patients with 22q11.2DS. We previously reported growth hormone deficiency in 22q11.2 DS at our center, with higher estimated incidence than the general population. Here we report outcomes of provocative growth hormone testing in patients with 22q11.2DS and short stature. **Methods:** In a current IRB-approved chart review of electronic medical records, we identified unique patients with 22q11.2 DS seen during the years 2003 through 2023 who underwent provocative growth hormone testing at the Children's Hospital of Philadelphia (CHOP) and other institutions. **Results:** 51 patients (18 female, 33 male) underwent growth hormone testing. Height Standard Deviation Scores ranged from -0.73 to -4.95 (average -2.44) at the time of testing (n=29) and -0.04 to -4.89 (average -1.75) at final height (n=19). Maximum stimulated growth hormone levels ranged from 2.81 ng/mL to 95.6 ng/mL. 26 individuals had growth hormone levels below 10 ng/mL indicating growth hormone deficiency while 25 individuals had levels above 10 ng/mL, consistent with normal GH secretion. Furthermore, 10 individuals had levels below 7 ng/mL indicating severe growth hormone deficiency. **Conclusions:** Of those youth with chromosome 22q11.2DS seen at CHOP from 2003 through 2023, 51 had significant short stature that warranted provocative testing for growth hormone reserve. Twenty percent of those tested for growth hormone had evidence of severe growth hormone deficiency while nearly half were growth hormone sufficient, indicating other etiologies for their short stature.

041: Growth Hormone Treatment in Patients with 22q11.2 Deletion Syndrome and Short Stature

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Background: An estimated 39 to 67% of youth with chromosome 22q11.2 deletion syndrome (22q11.2DS) have short stature. The etiology of growth restriction is multifactorial, and we previously reported growth hormone deficiency (GHD) in 22q11.2 DS at our center. **Methods:** From an IRB-approved review of electronic medical records, we identified unique patients with 22q11.2DS seen from 2003 through 2023 who underwent treatment with human growth hormone (hGH) at the Children's Hospital of Philadelphia (CHOP) and other institutions. **Results:** Electronic medical records queried for the diagnosis and medication codes for GHD and hGH treatment identified 48 subjects (19 female, 29 male) who received treatment with human growth hormone (hGH). Height SDS values ranged from -0.73 to -3.95 (average -2.49) at the time of testing (n=14) and -0.04 to -3.70 (average -1.45) at final height (n= 18). Forty of these subjects were identified as having GHD (83%) by ICD9-10 codes. Of these, records of provocative GH testing at CHOP and other institutions were available for 25 subjects. From 2003 through 2023, maximum growth hormone levels ranged from 0.2 ng/mL to 25.8 ng/mL. Of these 25 subjects, 9 had levels below 7 ng/mL while 16 had levels above 7 ng/mL including 8 with levels above 10 ng/mL, consistent with normal GH secretion. **Conclusions:** Of those youth with chromosome 22q11.2DS seen at CHOP from 2003 through 2023, 48 had significant short stature warranting treatment with human growth hormone. Of those for whom results are available, 36% of those tested for growth hormone had evidence of severe growth hormone deficiency while 32% had stimulated levels in the borderline range for growth hormone deficiency. 17-32% of those receiving hGH treatment were growth hormone sufficient, indicating other etiologies for their short stature. This data is important in assessing and counseling families of children with 22q11.2DS and short stature.

042: Association Between Congenital Heart Defects and Growth in the 22q11.2 Deletion Syndrome

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Background: The 22q11.2 deletion syndrome (22q11DS) has a wide range of clinical features, including congenital heart defect (CHD, prevalence 60-80%), failure to thrive (30%), and short stature (15%). Nearly all potential causes of failure-to-thrive and short stature may apply to patients with 22q11DS. We aimed to study (i) to what extent CHD is associated with growth impairment in children with 22q11DS and (ii) whether these associations are age-independent. **Methods:** Detailed cardiologic phenotypes and heigsht and weight measurements from 379 Dutch children aged 0-18 years (52% female) with 22q11DS were obtained through retrospective medical record review. Classification of patients with CHD was carried out by a pediatric cardiologist; categories were based on whether cardiac interventions (cardiac surgery or interventional heart catheterization) were required (CHD-RI). Height and weight standard deviation scores (SDS) were evaluated in relation to the presence or absence of CHD-RI. **Results:** CHD was present in 200 patients (53%), of which 126 were clinically relevant and required cardiac intervention (e.g. ventricular septal defect n=63 (50%), tetralogy of Fallot n=30 (24%), interrupted aortic arch n=21 (17%)). Children with CHD-RI had a lower mean height and weight SDS than children without CHD-RI (height: -0,39 SDS ($p<.001$); weight: -0,49 SDS ($p<.001$)). Similar results were found using linear mixed models with random intercepts and random slopes for age; and after correction for potential confounders. **Conclusions:** We demonstrated that in children with 22q11DS CHD-RI is independently associated with diminished growth in both height and weight, corroborating the hypothesis that the syndromic manifestation of impaired growth is aggravated by the presence of CHD. A profound and lasting impact of CHD on baseline metabolism and growth potential can be assumed, possibly mediated by very vulnerable cardiorespiratory conditions before, during and after intervention.

043: Children and Young Adults with 22q11.2 Deletion Syndrome and Fractures: a Case Series

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Background: Up to 40-50% of children suffer at least one fracture by 18 years of age, the majority being forearm fractures. 22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome. Orthopedic manifestations including scoliosis, cervical anomalies, and club foot have been described in association with 22q11.2DS, however, data is limited regarding fractures. Here we present a case series of fractures in patients with 22q11DS from a large referral center. **Methods:** Under an IRB approved study, we retrospectively reviewed electronic health records cross referencing 22q11.2DS with fractures. **Results:** We identified 1558 patients with 22q11.2DS. Fifty-three (3.4%) ages 10 months to 26 years, had fractures, of whom, 3 had vertebral compression fractures and 9 had femoral fractures. The compression fractures were diagnosed at 18 years, 19 years, and 5 months respectively. Two were incidental findings and one was identified due to back pain. Two of 3 patients had early childhood feeding difficulties and transient neonatal hypoparathyroidism, one had cardiac disease. No other risk factors were identified. Of the 9 with femur fractures, most occurred following low impact trauma, two presented during young adulthood. All 9 patients had early feeding difficulties; 6 had transient hypoparathyroidism in the neonatal period and 1 developed permanent hypoparathyroidism. 56% had cardiac disease and 1 child had Crohn's disease treated with steroids; 3 were non ambulatory. Three of the patients with femur fractures had multiple fractures. Three additional patients had multiple fractures involving other long bones. **Conclusions:** In this series, we identified a subgroup of patients with 22q11.2DS who suffered low impact fractures including vertebral compression, femur, and multiple fractures. This suggests some patients with 22q11.2DS may be at higher risk for bone fragility. Further studies are needed to characterize skeletal health in this population to determine which subgroup of children with 22q11.2DS requires bone health evaluation.

044: Obesity and Metabolic Syndrome in Adults with 22q11.2 Deletion Syndrome

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Background: Despite recognition that life expectancy is reduced in 22q11.2 deletion syndrome (22q11.2DS), possibly partially relating to cardiovascular disease, research on cardiovascular risk factors in 22q11.2DS is scarce. In the current cohort study, we aimed to validate the previously reported findings on general obesity in adults with 22q11.2DS, while extending them with new data on abdominal obesity, and metabolic syndrome. **Methods:** We examined prevalence rates and related factors of obesity and metabolic syndrome in 93 adults confirmed to have a typical 22q11.2 deletion (median age 30.0 (range 17-72) years; 45.2% male). General obesity was defined by a body mass index (BMI) ≥30 kg/m^2, abdominal obesity as a waist circumference (WC) of ≥102 cm in males and ≥88 cm in females, and metabolic syndrome by standard Joint Interim Statement criteria. We used general linear models to examine the independent effect of age, sex, congenital heart defect (CHD), smoking, and anti-psychotic use on BMI, WC, and the presence of metabolic syndrome. **Results:** General and abdominal obesity were present in 28 (30.1%) and 46 (49.5%), and metabolic syndrome in 28 (30.1%) of the study participants. The regression models predicting BMI and WC were statistically significant (P=0.006; P<0.001). Only CHD made a statistically significant contribution to BMI, explaining 4.6% of the variance. Age explained 7.8%, and CHD 4.2%, of the variance in WC. History of CHD was associated with lower BMI and WC. The logistic regression model predicting metabolic syndrome was also significant (P=0.001), with higher age associated with the presence of metabolic syndrome. **Conclusions:** The study findings suggest that a large proportion of adults with 22q11.2DS have general and abdominal obesity, as well as metabolic syndrome. Hence, careful monitoring and management of obesity and metabolic derangements are needed to prevent cardiovascular disease, and to ultimately prolong life expectancy in 22q11.2DS.

045: Non-fasting Triglyceride-glucose Index as a Marker of Metabolic Syndrome in 22q11.2 Deletion Syndrome

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Objective*:* Early cardiovascular risk stratification is of increasing importance with rising metabolic syndrome prevalence among young adults. We aimed to evaluate metabolic syndrome, its individual components (low HDL-cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and obesity), and related risk factors, including elevated non-fasting triglyceride-glucose (TyG) index, in 22q11.2 deletion syndrome (22q11.2DS). **Methods**: We determined the presence of metabolic syndrome and related variables through comprehensive chart review in a well-characterized cohort of 439 adults with typical 22q11.2 microdeletions (median age 31.9, IQR 24.3-42.2, years; 52.2% female; median BMI 28.17, IQR 22.78-33.74, kg/m^2). We used multivariable logistic regression to identify possible risk factors for metabolic syndrome. **Results***:* Of the 416 adults with sufficient data, 144 (34.6%) had metabolic syndrome, including 63.3% (62/98) of individuals aged 40-59 years. Low HDL-cholesterol was the most common component of metabolic syndrome in adults aged 18-39 years (61.5%, 166/270), followed by obesity (44.4%, 120/270), hypertriglyceridemia (33.0%, 89/270), elevated HbA1c (24.1%, 65/270), and hypertension (4.4%, 12/270). Older age was associated with increasing HbA1c ($p < 0.0001$) and BMI ($p = 0.0011$). HDL-cholesterol ($p = 0.1916$) and triglycerides ($p = 0.1275$) were not significantly associated with age. Non-fasting TyG index was a significant independent predictor of metabolic syndrome (OR 2.49, 95% CI 1.87-3.32, $p < 0.0001$) in a logistic regression model accounting for age, sex, BMI, and hypothyroidism. **Conclusions**: The results demonstrate high prevalence of metabolic syndrome in a relatively young cohort of adults with 22q11.2DS. Preliminary findings suggest that low HDL-cholesterol and hypertriglyceridemia may precede hyperglycemia in the onset of metabolic syndrome and related insulin resistance. Non-fasting TyG index may serve as an inexpensive, accessible marker of metabolic syndrome and increased cardiovascular risk in 22q11.2DS. These findings highlight the importance of monitoring for metabolic syndrome in young adults with 22q11.2DS, particularly among those with high TyG index, to promote early intervention.

046: Trajectory of Cardiometabolic Conditions in Adults with 22q11.2 Deletion Syndrome

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Background: There is accumulating evidence that the adult phenotype of 22q11.2 deletion syndrome (22q11.2DS) includes cardiometabolic conditions. There is a need however to assess the adult burden of illness in the context of population-based norms. We have investigated 18-year health care costs for 22q11.2DS using health administrative data (HAD) available for 15 million people in Ontario with universal health care and now, aim to study the incidence of key cardiometabolic conditions. **Methods:** We linked a cohort of 365 adults with molecularly confirmed 22q11.2 microdeletion (median age 32 years, 51% females) to Ontario HAD, and matched them to 3,650 general population controls on date of birth, sex, and neighbourhood income. We assessed the first recorded instance of 8 cardiometabolic-related conditions, and a general multimorbidity (Charlson) index that included these conditions. We reported outcomes for individual conditions as incidence rate ratios (IRR) using Poisson regression and compared overall multimorbidity using standardized differences (SDs), with SD >0.1 indicating a meaningful difference. **Results:** The incidence of several conditions was significantly greater for the 22q11.2DS group, beginning at age 18-24 years for diabetes mellitus (IRR 3.21, 95% CI 1.42-7.24), hypertension (IRR 2.98, 95% CI 1.45-6.14), and renal failure (IRR 95% CI 1.06-5.28), and beginning at age 35-44 years for heart failure (IRR 95% CI 18.8-93.9). By study end (Aug/23), at average 32 years, the proportion of young adults with elevated (3+) Charlson comorbidity index scores was over 4-fold greater for those with 22q11.2DS than for controls (8.0% vs 1.6%, SD 0.3). **Conclusion:** Young adults with 22q11.2 microdeletion have significantly higher risk of new-onset common cardiometabolic conditions, and of extreme comorbidity scores, than matched population-based controls. The findings suggest a substantial health burden in early adulthood for individuals with 22q11.2DS, and the need for individualized care to optimally anticipate and manage increasing medical complexity over time.

047: Ophthalmologic Manifestations in Patients with 22q11.2 Copy Number Variants: An Update

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Background: In 2007 we reported ophthalmologic findings in 90 children with 22q11.2 deletion syndrome (22q11.2DS) identified by FISH who had been evaluated by pediatric ophthalmology. In 2008 we described sclerocornea in 7 patients with 22q11.2DS from several centers a blinding condition amenable to urgent intervention. In 2016, we catalogued ophthalmologic features in 19 children with 22q11.2 duplication syndrome (22q11.2DupS). Here we update our observations in a large cohort of children with 22q11.2 copy number variants (CNV) evaluated at a single center where additional information now includes CNV size. **Methods**: Under an IRB approved study, we retrospectively reviewed 1,690 ophthalmologic reports on 549 unique patients with 22q11.2CNVs. **Results**: 468 patients with 22q11.2DS and 81 patients with 22q11.2DupS had at least one eye exam at our institution. Findings associated with 22q11.2DS, included: astigmatism (36%), amblyopia (27%), myopia (18%), strabismus (16%), exotropia (14%), hyperopia (12%), esotropia (10%), nasolacrimal duct obstruction (7%), posterior embryotoxon (3%), iris or chorioretinal coloboma (3%), Duane syndrome (0.6%), sclerocornea in two children and microphthalmia in one. Forty-two (9.0%) patients had tortuous retinal vessels (TRV) including 1 with a nested LCR22B-LCR22D deletion, the remainder had a standard LCR22A-LCR22D deletion of whom 69% had congenital heart disease (CHD) including 23% with extracardiac anomalies, e.g., aberrant subclavian arteries. Findings associated with 22q11.2DupS included: esotropia (82%), astigmatism (30%), amblyopia (27%), myopia (26%), exotropia (25%), strabismus (22%), hyperopia (15%), nasolacrimal duct obstruction (5%), and posterior embryotoxon (1%). Two patients had iris colobomas and 1 had microphthalmia. None had TRV. 63% had a standard LCR22A-LCR22D deletion. **Conclusions**: Patients with 22q11.2CNVs have a variety of eye findings that may impact vision. Given the co-morbid developmental differences faced by children with 22q11.2CNVs, identifying sensory deficits followed by timely intervention is of utmost importance. Based on this data, all patients with 22q11.2CNVs will benefit from an eye exam at diagnosis and periodically thereafter. The impact of CNV size is under investigation.

048: Prevalence of Preterm Birth and Polyhydramnios in Association with 22q11.2 Deletion Syndrome

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Background: Preterm birth is defined as infants born alive before 37 weeks' gestation. In the US general population in 2022, 10.8% of all births, 8.7% of singleton births, and 62.2% of multiple births were categorized as preterm. Prematurity, known to be associated with polyhydramnios, has been reported in 18.5% of cases with mild polyhydramnios, 21.8% with moderate polyhydramnios, and 14.3% with severe polyhydramnios. Polyhydramnios can be isolated or associated with fetal abnormalities including palatal anomalies, laryngotracheoesophageal problems, and swallowing difficulties. Polyhydramnios has been reported in 0.2 to 2% of pregnancies and 15% of 52 pregnancies reported in 1998 with 22q11.2 deletion syndrome (22q11.2DS). The presence of polyhydramnios may provide a window into postnatal complications. Here we report the prevalence of prematurity, +/- related to polyhydramnios/congenital anomalies, in association with 22q11.2DS. **Methods:** We performed a retrospective chart review under an IRB approved protocol of 1,629 individuals with laboratory confirmed 22q11.2DS evaluated between 1992 and 2024. Gestational age, presence/absence of polyhydramnios, singleton or multiples, deletion breakpoints, and presence/absence of anomalies were abstracted and analyzed. **Results:** Twenty-six percent of all pregnancies affected by 22q11.2DS were preterm including 23% of singletons and 62% of multiples. Mean gestational age was 37 weeks 6 days (+/- 2 weeks). Polyhydramnios was reported in 20% of all pregnancies, and 28% of preterm births. Pregnancies with polyhydramnios were significantly more likely to deliver preterm (odds ratio 1.84; 95 % CI 1.29 to 2.66). Multivariate analysis to control for congenital anomalies is ongoing. **Conclusions:** Preterm birth and polyhydramnios are significantly more common in association with 22q11.2DS than in the general population, regardless of multiple births. Polyhydramnios may result in preterm birth complicating postnatal care by prematurity related issues and perhaps heralding postnatal complications. Further analyses to include examination of comorbidities and deletion size are ongoing.

049: Tracheoesophageal Anomalies in Association with the Chromosome 22q11.2 Deletion Syndrome *

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Background: Esophageal atresia (EA) and tracheoesophageal fistula (TEF) are rare anomalies (1/2500-4500 live births) more commonly observed in males. Tracheal atresia (TA) is even more rare (<1/50,000 live births). EA/TEF are associated with CHARGE, VACTERL, trisomy 13, 18, 21, and XXX. Digilio previously reported EA in a female with 22q11.2 deletion syndrome (22q11.2DS) in 1999. Here we contribute additional cases with tracheoesophageal abnormalities to support the association with 22q11.2DS. **Methods:** We retrospectively examined records on 1629 patients with 22q11.2DS under an IRB protocol to identify those with tracheoesophageal abnormalities. An additional patient was also identified in Rome. **Results:** 8/1629 (0.5%; 1/200) had EA/TEF including EA with TEF (5), EA without TEF (2), and TEF only. 7/8 (87%) were female. 2 expired in infancy. 4/8 (50%) had cardiac anomalies: vascular ring and VSD (2), TOF with MAPCAs, isolated VSD. 6/8 (75%) had a standard LCR22A-LCR22D deletion, 1 a nested LCR22C-LCR22D deletion, and 1 a nested LCR22B-LCR22D deletion and deletion of *CHD7*. We also identified an LCR22A-LCR22D deletion in a male fetus with tracheal agenesis who succumbed neonatally; and EA with TEF in a child with a familial LCR22C-LCR22D deletion. The additional patient from Rome had EA without TEF, small ASDs and a subaortic VSD. Resulting in a prevalence of ~2/500 Italian patients. **Conclusions:** We identified EA/TEF in ~1/200-250 patients with 22q11.2DS in Philadelphia and Rome. A >10-fold increase in prevalence compared with the general population, solidifying the association of tracheoesophageal abnormalities with 22q11.2DS and suggesting 22q11.2DS should be included in the first-tier differential diagnosis for such patients. Of note, most patients were female, in contrast to the general population, and 2 unrelated patients were found to have a nested LCR22C-LCR22D deletion - providing a potential window into identifying a developmental driver amongst the 11 genes within this region, such as *CRKL*.

050: Gastroesophageal Reflux Disease and Associated Comorbidities in Patients with 22q11.2 Deletion Syndrome

Asim Maqbool[1,2,3], T. Blaine Crowley[1,4], Victoria Giunta[1,4], Daniel E. McGinn[1,4], Bekah Wang[1,4], Audrey Green[1,4], Lydia Rockart[1,4], Lauren Lairson[1,4], Oanh Tran[1,4], Beverly S. Emanuel[1,3,4], Elaine H. Zackai[1,3,4], Ian Campbell[1,3,4], Donna M. McDonald-McGinn[1,3,4,5], Prasanna Kapavarapu[1,2,3] Maria Mascarenhas[1,2,3]

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Background: The overall incidence of gastroesophageal reflux disease in pediatric patients is 0.84 per 1000 person-years (95% confidence interval (CI): 0.80–0.89). After 1 year of age the incidence decreases till age 12 years and then increases to maximum at 16–17 years. We previously reported GERD in 34% of children with 22q11.2 deletion syndrome (22q11.2DS) at some point in their childhood (<18 years of age). Here we revisit the prevalence, age of onset, natural history, and potential confounders including comorbidities and deletion size. **Methods:** A retrospective chart review from 1,629 individuals with laboratory confirmed 22q11.2DS evaluated between 1992 and 2024 was conducted under an IRB approved protocol. Confirmation of GERD was obtained from electronic health records, our legacy database, and outside hospital records. Demographics, 22q11.2 deletion size, and medical comorbidities were catalogued, and analyzed via chi-square. **Results:** GERD was identified in 710 (43%) patients with 22q11.2DS; 54% male, 79% white, and 87% with standard LCR22A-LCR22D deletion. Mean age at onset was 2.2 years (+/- 4 months). No association was appreciated based on deletion size or familial v. *de novo* status. However, GERD was significantly associated with feeding difficulties ($p = 0.01$), asthma ($p = 0.02$), difficulty with sleep ($p = 0.04$), and failure to thrive (FTT) ($p = 0.05$). GERD was not significantly associated with congenital heart disease (CHD) ($p = 0.59$), chronic infection including recurrent otitis media, sinusitis, and other infectious histories ($p = 0.43$), or developmental delay ($p = 0.75$). **Conclusions:** GERD is frequently associated with the 22q11.2DS and is associated with feeding problems, FTT, asthma, and sleep difficulties. Conversely, GERD is not commonly associated with CHD, infection, or developmental differences. Given GERD is remediable, early identification and treatment are important to the patient's overall care, as well as the families wellbeing.

051: Prevalence of Enteral Feeding and Subsequent Intervention in Patients with 22q11.2 Deletion Syndrome

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Background: We previously noted chronic gastrointestinal symptoms in patients with 22q11.2 deletion syndrome (22q11.2DS) including a subset requiring enteral feeding due to persistent malnutrition, gastroesophageal reflux disease (GERD), and respiratory symptomatology. For severe cases of GERD, a Nissen fundoplication may be necessary. In 2022, we reported gastrostomy tube (G-tube) placement and Nissen fundoplication in 8% and 4% of patients respectively. Here, we provide an updated assessment of the prevalence of G-tube placement and fundoplication procedures in patients with 22q11.2DS. **Methods:** We retrospectively reviewed gastrointestinal findings in 1,629 patients with 22q11.2DS under an IRB-approved protocol specifically to identify those requiring tube feeds/Nissen fundoplication. **Results:** 234/1629 (14%) patients with 22q11.2DS required tube feeds, of whom 69 underwent a Nissen fundoplication (69/1629; 4%) (69/234; 29%). 156/234 (67%) began supplemental nutrition via nasogastric (NG) tube feeds. Of the 156 receiving NG feeds, 99 (99/234, 42%) went on to gastrostomy-tube (G) or gastrojejunostomy (GJ) tube placement. Specifics regarding age of onset and discontinuation of tube feeds was available for 85 patients. Mean age for the onset of tube feeds was 8.5 months. Mean duration of tube feeds was 3 years. Most patients requiring tube feeds had a standard LCR22A-LCR22D deletion (178/234; 76%). **Conclusions:** We identified an increase in prevalence of children with 22q11.2DS requiring enteral feeds from 8% to 14%. However, the number of patients requiring Nissen fundoplication remained stable at 4%. Most patients begin receiving supplemental nutrition within the first month of life and typically stop tube feeds before reaching school age. This data is of utmost importance to parents struggling to feed their infants and looking to 22q providers for reassurance that their children will ultimately PO feed.

052: Dysphagia in Children with 22q11.2 Deletion Syndrome and 22q Duplication Syndrome

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Background: Dysphagia is thought to occur commonly in children with 22q11.2 deletion syndrome (22q11.2DS) with few prior small studies noting dysphagia in 36%-41% of patients. No prior studies have looked at dysphagia in 22q duplication syndrome (22qDup). The purpose of this investigation is to more fully elucidate dysphagia in children with 22q11.2DS and 22qDup. **Methods:** Chart review was completed for one institution's 22q patient registry. Pediatric patients with a diagnosis of 22q11.2DS or 22qDup were included. Data extracted included genetic diagnosis, comorbidities, diagnosis of dysphagia, results of video fluoroscopic swallow studies(VFSS), and need for gastrostomy tube(g-tube). **Results:** 304 charts were reviewed, of which 289 met inclusion criteria. 235(81%) had 22q11.2DS and 54(19%) had 22qDup. Comorbidities included 63% cardiac defect, 25% cleft palate, 15% laryngomalacia, 8% laryngeal cleft, and 7% history of unilateral vocal fold paresis. Of the cohort, 43% had been evaluated by a feeding therapist, 23% underwent at least one VFSS, and 15% required a hospital admission due to feeding/swallowing concerns. G-tube insertion was required by 20% of patients. A total of 104 VFSS were reviewed, of which 92% were abnormal. VFSS results recommended 21% start on thickener and 10% advised no oral feeding. Twenty-six patients had multiple VFSS, of which 55% showed no change or worsened results over time. Differences between 22q11.2DS and 22qDup groups will be presented including the 22qDup with less frequent VFSS and fewer patients requiring G-tube. **Conclusions:** This data suggests dysphagia is common for children with 2q11.2DS and 22qDup although may be more less severe in 22qDup. Dysphagia may not always improve over time. VFSS can be helpful in diagnosing dysphagia and determining safe alternative feeding methods. G-tube was required by one in five patients in the cohort. Screening for swallowing/aspiration is important for children with 22q11.2DS and 22qDup to allow for accurate and timely diagnosis of dysphagia.

053: Exploring the Presentation and Mechanism of Dysphagia in Adults with 22q11.2 Deletion Syndrome

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Background: Features of 22q11.2 deletion syndrome (22q11.2DS) can include dysphagia, though little is known about the presentation and severity in adults. If unaddressed, dysphagia can lead to complications such as unintended weight loss and aspiration pneumonia. **Methods:** In this initial observational study in adults with 22q11.2DS, 40 patients were sequentially screened for dysphagia during regular clinical follow-up. If patients endorsed difficulty swallowing, a referral was made to speech language pathology for a formal swallowing assessment. A systematic search of historical clinical reports for the term "dysphagia" identified patients who had swallowing assessments done elsewhere. **Results:** All seven (3 M; 4 F, aged 21-54 years) patients who underwent videofluoroscopic swallowing studies were included, none with Parkinson's disease. Six were found to have some esophageal stage dysfunction, including slow esophageal transit, bolus retention and/or backflow. Five had oral pharyngeal dysphagia, most a mild form. Five patients were recommended dietary modification as part of treatment, most commonly soft/moist diet and thin liquids. One male patient aged 44 years was diagnosed with moderate-severe dysphagia due to previously undetected diffuse idiopathic skeletal hyperostosis (DISH) affecting the C3-C4 vertebrae. He was recommended a pureed diet, moderate thick liquids, and urgent surgical consultation. Unfortunately, he developed aspiration pneumonia before undergoing corpectomy to remove the vertebral projection. **Conclusions:** Adults with 22q11.2DS who report swallowing difficulties have evidence of underlying swallowing dysfunction, both in the oral-pharyngeal stage of swallowing and in the esophagus. The case due to DISH, a condition usually presenting in the elderly, is consistent with global vulnerability to age-related diseases in 22q11.2DS. Understanding the predictors of dysphagia in 22q11.2DS would help clinicians to develop screening specific to this population. Early identification could reduce the burden of illness on the patient, their caregivers and healthcare system.

054: Dental Caries and Malocclusion in Patients with 22q11.2 Deletion and Duplication Syndromes *

Shalin N. Shah[1], Cynthia Solot[2,4], Oksana Jackson[1,2,4], Audrey Green[4,5], Bekah Wang[4,5], Victoria Giunta[4,5], T. Blaine Crowley[4,5], Beverly S. Emanuel[4,5,6], Elaine H. Zackai[4,5,6], Lorraine L. Katz[4,6,7], L. Yap[1], Donna M. McDonald-McGinn[4,5,6,8], Hyun Duck Nah[1,2,3]

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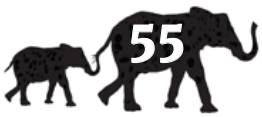
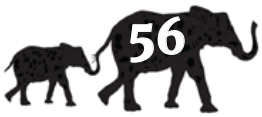
Background: 22q11.2 deletion syndrome (22q11.2DS) is a congenital disorder that occurs in 1 in 2,148 live births and 1 in 992 pregnancies. Reported oral characteristics include cleft palate, dental caries, enamel hypoplasia and malocclusion; however, little is known about the oral features of the 22q11.2 duplication syndrome (22q11.2DupS). The prevalence of 22q11.2DupS has been reported in 1 in 850 pregnancies. The primary objective of this study is to compare the orofacial and dental anomalies associated with 22q11.2DS and 22q11.2DupS. **Methods:** A retrospective chart review under an IRB approved study was conducted examining findings in patients with 22q11.2DS and 22q11.2DupS followed in the 22q and You Center at the Children's Hospital of Philadelphia. Recorded findings included orofacial and dental observations, as well as calcium supplementation. **Results:** Of the 125 patients evaluated in the Craniofacial and Orthodontics clinic, 108 had 22q11.2DS and 17 had 22q11.2DupS. Preliminary findings revealed: 24% caries, 24% overbite, 12% crowding, 6% missing teeth, and 6% cleft palate amongst those with 22q11.2DupS compared with 42% caries, 35% overbite, 32% crowding, 5% missing teeth, and 32% cleft palate in the 22q11.2DS group. Statistical analysis to compare these findings between groups is ongoing. **Conclusions:** Orofacial and dental anomalies appear to be more prevalent in patients with 22q11.2DS compared with 22q11.2 DupS. Further investigation regarding specific differences is in these groups, as well as contributions of comorbidities, CNV size, geocodes, etc. is ongoing, with a goal to aid in the inclusion of appropriate dental treatment in the multidisciplinary care of these complex patients.



055: Guidelines on the Dental Management of Individuals with 22q11.2DS *

Charlotte Lenes[1], Rohan Dasari[2], Michelle Scott[3]
[1]Penn Dental Medicine; [2]Drexel University; [3]Children's Hospital of Philadelphia

Background: The purpose of this report is to revise the dental management guidelines for treating individuals with 22q11.2 deletion syndrome (22q11.2DS). Our objective is to provide direction on the evaluation, prevention, observation, and management of the many dental and craniofacial presentations of 22q11.2DS. Based on a systematic review of the literature on manifestations of the syndrome, we fill gaps in knowledge and practice guidelines related to the identification and management of enamel developmental defects, high caries experience, aberrant tooth shape, tooth agenesis, delayed dental eruption, difficulties with speech, and cleft lip and palate. We update the current dental knowledge of 22q11.2DS, address the advantages and disadvantages of preventative and restorative interventions, and review specific recommendations. **Methods**: The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) analysis framework was used to conduct and report the results of our systematic review. This tool guided the systematic search, selection, and synthesis of relevant studies from both PubMed and Google Scholar in a structured manner, ensuring the application of appropriate inclusion criteria and study selection processes. **Results**: Given the wide phenotypic spectrum of this syndrome, multispecialty intervention is recommended as a best practice and reflects the dental field's evolving understanding of 22q11.2DS. Implementation requires the expertise of pediatric and general dentists, orthodontists, and oral and maxillofacial surgeons. **Conclusions**: This review discusses the diverse dental challenges associated with 22q11.2DS and provides comprehensive guidelines for appropriate management. Recognizing the need for a multidisciplinary approach, the recommendations underscore the importance of early diagnosis, preventive strategies, and tailored treatments to address the varied dental manifestations and associated craniofacial abnormalities. We encourage further prospective studies to enhance our understanding of dental interventions' efficacy and longevity in individuals with 22q11.2DS.



056: Surgical Decision Making for Patients with 22q11.2 Deletion Syndrome and Velopharyngeal Dysfunction: a Clinical Update

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Background: Velopharyngeal dysfunction (VPD) is one of the most common clinical features of 22q11.2 deletion syndrome (22q11.2DS) and often requires surgical intervention. Due to the multifactorial nature of VPD, these patients present unique and often complex surgical challenges. Patients with 22q11.2DS also have specific considerations both pre- and postoperatively that are crucial to the safety and success of speech surgery. The purpose for this presentation is to provide an update on current strategies and approaches in the evaluation, surgical management, and postoperative care for these patients. The goal is to help providers caring for children with 22q11.2DS optimize their VPD outcomes. **Methods**: This is a clinical update and not a data driven project. The author will present updates in the literature as well as her clinical experience treating patients with 22q11.2DS and VPD over the past 10 years. **Results**: We will highlight features seen in patients with 22q11.2DS that make this a unique and complex population for treating VPD. We will discuss the necessary steps in the preoperative surgical evaluation, including the assessment for medialized carotid arteries, when/if to obtain a sleep study, and the potential need for staged preoperative adenotonsillectomy. VPD surgical procedures will be examined including factors to consider when selecting the type of surgery to perform. Specifically, the surgeons' experience using buccal myomucosal flaps for VPD management in patients with 22q11.2DS will be discussed as this a relatively new surgical treatment option. Postoperatively, inpatient care will be reviewed as well as the importance of monitoring for postoperative hypocalcemia and sleep apnea. **Conclusion**: The surgical management of VPD in patients with 22q11.2DS is complex; specific factors need to be considered to optimize the success and safety of the surgery and the speech outcome. Buccal myomucosal flap appears to be a safe and effective procedure for certain patients with 22q11.2DS and VPD.

057: Long-term Changes in Post-operative Hypernasality Over Time in Patients with 22q11.2 Deletion Syndrome and Velopharyngeal Insufficiency

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Background: Velopharyngeal insufficiency (VPI) is well-documented in patients with 22q11.2 Deletion Syndrome (22q11.2DS). Treatment of VPI requires surgical intervention. Current best practice at our institution includes a Resonance Evaluation (RE) completed by a trained Speech-Language Pathologist pre-operatively and 2-3 months post-operatively, with subsequent annual follow-up. The goal of this study is to describe the time-course of improvement in hypernasality post-operatively to better inform clinical practice and adequately counsel patients and families. **Methods**: A retrospective chart review was completed for patients with 22q11.2DS who underwent surgical intervention for VPI between 2014-2022. We obtained demographic data, medical/surgical history, and scores from the Cleft Audit Protocol for Speech-Augmented Americleft Modification (CAPS-A-AM). Additional information regarding articulation characteristics, speech intelligibility, and impact of VPI on quality of life was collected. **Results**: Thirty-six patients were included. Average age at the time of surgery was 8.67 years, with an average pre-operative hypernasality score of 3.4. Thirty-three patients completed at least one post-operative RE. Eleven patients completed a RE within 90 days post-surgery with 7 of the 11 (63.6%) demonstrating minimal or no hypernasality (score of 0 or 1 on the CAPS-A-AM). Two reached 0 and 1 after 708 and 316 days respectively, and 2 were lost to follow-up. Overall, 14 of 33 (42.4%) patients had minimal or no hypernasality at their first post-operative RE, an average of 390 days after surgery. Twenty of 33 (60.6%) patients demonstrated minimal or no hypernasality an average of 939 days (range 70-3578) after surgery. **Conclusions**: Patients with 22q11.2DS may not demonstrate their maximum level of improvement of hypernasality after surgical intervention for VPI until long after our standard 2-3 month post-operative RE. Reduction in degree of hypernasality was noted up to 3 years post-operatively. Long-term follow-up and re-assessment of velopharyngeal function is warranted.

058: Prevalence of Permanent Hearing Loss and Ear Malformations in Children with Distal LCR22D-LCR22E 22q11.2 Deletions

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Background: Isolated preauricular tags and pits commonly occur in nonsyndromic children (1-3 %), thought to be related to fusion defects as the pinna forms. Associations with hearing loss have not been found, although children with standard 22q11.2 LCR22A-LCR22D deletions (22q11.2DS) have overfolded pinna/cupped ears, permanent hearing loss (~3%), or occasionally preauricular skin tags. Children with less common distal deletions involving LCRs C-E, D-E, and D-F (22qDistalDels), hearing loss and preauricular pits have been noted more commonly along with low birth weight, microcephaly, congenital heart disease, and developmental delay. Here we report a higher prevalence of permanent hearing loss (HL) including sensorineural HL (SNHL), conductive HL (CHL) and mixed HL (MHL) and whether this is associated with auricular anomalies (preauricular skin tags, microtia/atresia, canal stenosis) in children with distal deletions. **Methods:** Under an IRB approved protocol we examined records on 36 patients with 22q11.2DistalDels to identify the prevalence of SNHL/HL and anatomical ear malformations (skin tags, cupped ear, attached lobes/pinna differences/atresia/microtia/stenotic ear canals and inner ear anomalies). **Results:** 33/36 patients had data on ear differences. 17/33 (52%) had malformations of the pinna (primarily preauricular tags +/- cupped ears, attached lobes and less often microtia. 13/33 (39%) had permanent HL; 9/13 (69%) had preauricular tags +/- cupped ears; 2 had microtia/ear canal atresia. Of 5 with SNHL, 3 had unilateral SNHL with skin tags. Of 4 with CHL 2 had microtia and tags. **Conclusions:** Permanent HL is more common in children with 22q11.2DistalDels compared with 22q11.2DS (39 % vs 3%) and much greater than the general population (1-3/1000). Most patients with 22q11.2DistalDels (52 %) also had preauricular skin tags and other pinna malformations including microtia, cupped ears, and attached lobes compared with 22q11.2DS and nonsyndromic patients (1-3 %). Genotype-phenotype correlations are under investigation.

059: Factors Supporting Better Language Outcomes in Children with 22q11.2 Deletion Syndrome

Cynthia Solot[1,2], Victoria Giunta[2,3], Daniel E. McGinn[2,3], Lydia Rockart[2,3], Bekah Wang[2,3], Audrey Green[2,3], Oanh Tran[2,3], Beverly S. Emanuel[2,3,4], Elaine H. Zackai[2,3,4], Oksana Jackson[2,5,6], Katherine Baum[2,7], Edward Moss[2,7], T. Blaine Crowley[2,3], and Donna M. McDonald-McGinn[2,3,4,8]

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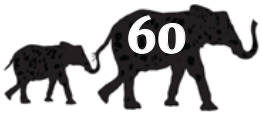
Background: 22q11.2 deletion syndrome (22q11.2DS) results in language deficits. We reported ~84% of children with 22q11.2DS score below average (+/- 1 SD) on the Clinical Evaluation of Language Fundamentals (CELF). Here, we aim to identify potential factors that may have supported better outcomes in those ~16% who performed well. **Methods:** We performed a retrospective chart review on records from 912 patients with 22q11.2DS who underwent a speech and language assessment onsite between 1994 and 2024 under an IRB approved protocol. Inclusion required a completed CELF yielding a Core Language Score (CLS) of ≥85. Demographics, deletion size, inheritance, medical comorbidities, and interventions were catalogued and analyzed via chi-square. **Results:** 332 children completed a CELF, of whom 76 (23%) scored ≥85. 52% were male, 84% white, and 89% had a standard LCR22A-LCR22D deletion. Mean age at evaluation was 9 years 5 months. Mean FSIQ was 88.5 v. 70.6 for those whose CLS was <85. Sex did not impact CLS scores. Parental level of education (LOE) was significantly associated with better outcomes on CLS ($p = 0.02$). FSIQ scores and CLS were closely associated. Medical comorbidities did not affect CLS scores. Enrollment in Early Intervention services, including speech therapy, trended towards significance ($p = 0.07$). Familial inheritance and deletion size were unable to be analyzed due to limited statistical power. **Conclusions:** While most children with 22q11.2DS exhibit language delays/deficits, and some demonstrate language decline, a small subset perform within the average or above average range on standardized language testing. Analysis of medical, demographic, genetic and therapeutic variables demonstrated a significant association with parental level of education and FSIQ, with early enrollment in Early Intervention trending toward significance. Additional investigation is needed to determine if early diagnosis with aggressive treatment, regardless of parental level of education/permissive background FSIQ genes, optimizes outcomes for all patients.



060: Language Abilities of School-aged Children with 22q11.2 Copy Number Variants (22q11.2 Deletion and 22q11.2 Duplication Syndromes): a Two-site Study *

Jente Verbesselt[1,2], Cynthia B. Solot[3], Ellen Van Den Heuvel[4], Jeroen Breckpot[1,5], Donna M. McDonald-McGinn[6,7,8], Inge Zink[2,9] and Ann Swillen[1,5]

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Background*:* Although it is known that copy number variants (CNVs) on chromosome 22, such as 22q11.2 deletion (22q11.2DS) and 22q11.2 duplication (22q11.2Dup) syndromes, are associated with higher risk for neurodevelopmental issues, few studies have examined the language skills across 22q11.2Dup nor compared them with the 22q11.2DS. **Methods**: The current study aims to characterise language abilities in school-aged children aged 6-16 years with 22q11.2Dup (n = 29), compared to age-matched children with 22q11.2DS (n = 29). Standardised language tests were administered, assessing receptive and expressive language skills across different language domains. **Results***:* Results indicate that children with 22q11.2Dup demonstrate significantly more language problems compared to the general population. Mean language skills were not significantly different among children with 22q11.2 CNVs in this cohort. While children with 22q11.2DS demonstrated language difficulties starting at the word level, the most common language problems in children with 22q11.2Dup started at the sentence level. Importantly, both expressive and receptive language as well as lexico-semantic and morphosyntactic domains were impaired in children with 22q11.2 CNVs. **Conclusion***:* Early identification, therapeutic intervention, and follow-up of language impairments in children with 22q11.2Dup are recommended to support language development and to reduce longitudinal impact of language and communicative deficits.

061: Linguistic Profile in Children and Adolescents with 22q11 Syndrome *

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22q11.2 syndrome is considered a rare disease that presents with a variable Intellectual Quotient and certain physical alterations. However, its manifestations also occur in other areas. At the linguistic level, there is mainly an alteration in the production of language and speech development. However, there are still few studies that delve into the specific linguistic characteristics of this group. Therefore, the objective of this research was to know the linguistic profile presented by children and adolescents with 22q11 syndrome. The sample was made up of 20 people between 6 and 16 years old belonging to the 22q11 Spain Association. To carry out the language evaluation, several linguistic tests were used: the Peabody test, the test BLOC-C and the CELF-5 evaluation test. The results show how people with 22q11 present linguistic difficulties in all areas of language, with a better level of comprehensive than expressive language. Furthermore, there appears to be some correlation between some of the areas evaluated. These results highlight the importance of linguistic intervention at all stages of development with the aim of maximizing their linguistic characteristics and improving their communicative level. In addition, a series of recommendations are included to improve intervention at all levels and to improve the quality of life of people with 22q11 Syndrome.

062: Serial Order Short-term Memory and Vocabulary in 22q11.2 Deletion Syndrome *

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Background: Many children with 22q11.2 deletion syndrome (22q11DS) have difficulties learning new words, resulting in a smaller vocabulary size relative to typically developing (TD) children. Vocabulary is essential for later academic skills, including learning to read; early interventions are thus of utmost importance. As of yet, it is however unknown why children with 22q11DS experience difficulties learning new words. In TD children, vocabulary size is known to be related to serial order short-term memory (STM), which is the ability to remember information in a certain order. As children with 22q11DS are reported to have weakened serial order STM skills, a similar relation may be hypothesized for children with 22q11DS. The present research was the first to test this hypothesis. **Methods**: A total of 43 children with 22q11DS and 43 TD children between the ages of 3 and 6,5 years ($M = 4;10$) participated. The groups were matched on age, with gender considered when possible. Vocabulary was tested with age-appropriate standardized tests. Serial order STM was measured with the Corsi block tapping task. **Results**: The results showed that children with 22q11DS have weaker serial order STM, receptive vocabulary and expressive vocabulary skills compared to matched TD controls. Serial order STM skills were found to be a significant predictor of vocabulary skills beyond age in children with 22q11DS, but not in TD children. **Conclusion**: The findings of this research have implications for diagnostics and treatment of language difficulties (in 22q11DS) in clinical practice. They show that difficulties learning new words in children with 22q11DS might not solely be a language problem, but may be connected to memory abilities. In Spring 2024, we will collect longitudinal data on the same children to evaluate these cross-sectional results. Preliminary results from these longitudinal data will be presented at the conference.

063: Early Development and Longitudinal Data in a Clinical Cohort of Children with 22q11.2 Duplication *

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Background:22q11.2 duplication (22q11.2Dup) has been linked to an increased susceptibility to neurodevelopmental challenges, including developmental delays, cognitive impairments and autism spectrum disorder. However, data characterising early developmental milestones, cognitive profiles and longitudinal cognitive trajectories remain limited. **Methods**: We reviewed and analysed in-person assessments, parental interviews and digital medical records regarding the developmental history of school-aged children (age 6-15 years) diagnosed with 22q11.2Dup. Specifically, we focused on early developmental milestones including motor skills, language development, and continence. Intelligence was assessed by standardised and age-appropriate instruments (Wechsler scales), with longitudinal IQ-data available for a subset. **Results***:* Our analysis revealed delayed attainment of language, motor, and continence milestones, while the average full-scale IQ (FSIQ) fell within the borderline range (FSIQ 70-84). Variability was observed within and between individuals across the five cognitive domains of the WISC-V, with notable discrepancies between verbal and non-verbal skills in some children. Longitudinal FSIQ-data showed that school-aged children with 22q11.2Dup exhibited significantly lower performance at the latest assessment point ($p<0.001$), with a subgroup demonstrating a pattern of growing into deficit. **Conclusion***:* Our findings highlight the frequent occurrence of delayed developmental milestones among clinically recruited individuals with 22q11.2Dup. Over time, school-aged children with 22q11.2Dup exhibit increasing cognitive deficits, underscoring the necessity for early diagnosis, regular cognitive monitoring and personalised intervention. The high proportion of disharmonic IQ-profiles emphasizes the importance of broadening the assessment beyond FSIQ outcomes. Future investigations in larger cohorts including carrier relatives are warranted to deepen our understanding of the penetrance and phenotypic heterogeneity associated with 22q11.2Dup.

064: A Comprehensive Overview of Neurodevelopmental Symptoms in Adolescents with 22q11.2 Deletion Syndrome – a Dimensional Perspective *

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Background: Neurodevelopmental symptom expression in 22q11.2 deletion syndrome (22q11DS) is mostly described by categorical prevalence rates of associated conditions, including intellectual disability, Autism Spectrum Disorder, and Schizophrenia. While useful for classification purposes, this approach insufficiently captures the high observed inter-individual variability in neurodevelopmental expression in individuals with 22q11DS. In the current study we adopt a dimensional approach to describe a wide range of neurodevelopmental domains associated with 22q11DS, to further our insight into the complex clinical presentation of adolescents with 22q11DS. **Methods:** Participants were 208 adolescents with 22q11DS, between 10-19 years. Semi-structured clinical interviews and IQ-tests were used to quantify symptom expression on neurodevelopmental dimensions, some reflecting DSM-IV diagnostic domains. We investigated symptom expression in those with and without formal DSM-IV classifications and examined between and within symptom dimensions. We explored associations between different symptom dimensions with correlation analyses. **Results:** We demonstrated inter-individual differences in symptom expression, both between and within neurodevelopmental symptom dimensions. On most dimensions, more than 50% of adolescents expressed one or more clinically relevant symptoms. A significant proportion of youth without formal DSM-IV diagnosis reported clinically relevant symptoms (e.g., >85% of those without an ADHD diagnosis reported ADHD symptoms). The exploratory correlation analysis indicated mostly positive correlations between various symptom dimensions. **Conclusions:** The finding that most adolescents with 22q11DS express clinical neurodevelopmental symptoms, even without a DSM-IV classification, has ramifications for guiding adequate support. It highlights the risk of overasking adolescents with 22q11DS, while underestimating the severity of their neurodevelopmental problems, that may frequently be inadvertently masked in absence of a formal psychiatric classification. Findings may also spur further research into the dimensional structure of neurodevelopmental symptoms in 22q11DS and aid in uncovering mechanisms that contribute to symptom expression. Ultimately, this provides leads to improve clinical care for 22q11DS and to understand phenotypical variation in high-risk genetic variants.

065: Irritability in Young People with Copy Number Variants Associated with Neurodevelopmental Disorders (ND-CNVs), Including 22q11.2 Deletion *

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Background: A range of rare copy number variants (CNVs), including 22q11.2 deletion, are associated with high risk of neurodevelopmental (ND) (ND-CNVs) and psychiatric conditions. Irritability is frequently observed in children with neurodevelopmental conditions, yet its aetiology remains largely unknown. Genetic variation may play a role, but there is a sparsity of studies investigating prevalence of irritability in young people with ND-CNVs, including 22q11.2 deletion. **Aims**: This study investigated whether: 1) young people with rare ND-CNVs are more likely to be irritable then their siblings without ND-CNVs (sibling controls); 2) the presence of psychiatric diagnoses or cognitive disability explains the presence of irritability. **Methods**: Irritability and broader psychopathology was assessed in 485 young people (mean age=9.8; range =6-17) with a range of ND-CNVs (including 150 with 22q11.2 deletion), and 164 sibling controls (mean age=10.8; range=6-17), using the child and adolescent psychiatric assessment (CAPA). The Social Communication Questionnaire (SCQ) was used to screen for autistic traits. Intelligence Quotient (IQ) was established using the Wechsler Abbreviated Scale of Intelligence (WASI). **Results**: Significantly more young people with ND-CNVs met the threshold for irritability compared to sibling controls (54% vs 20%, OR = 3.77, CI = 3.07-7.90, p= 5.31×10^{-11}). Notably, 50% of young people with 22q11.2 deletion met the threshold for irritability, compared to 20% of sibling controls (OR = 4.45, CI = 3.64-5.46, p= 1.5×10^{-5}). When controlling for the presence of psychiatric comorbidities, irritability was still associated with having a ND-CNV in the total sample and the subsample of young people with 22q11.2 deletion. There was no evidence for a relationship between irritability and IQ. **Conclusions**: Irritability is part of the clinical picture in young people with ND-CNVs, including those with 22q11.2 deletion, irrespective of whether they have psychiatric comorbidities or IQ impairment. Clinicians should take this increased risk into account when planning management and interventions.

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066: Polysomnography Findings of Patients with 22q11.2 Deletion Syndrome Related to Tonsillectomy

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Background: Prior studies suggest obstructive sleep apnea(OSA) is more common in patients with 22q11.2 deletion syndrome(22q11.2DS). While tonsillectomy is commonly pursued to ameliorate airway obstruction, there is limited data evaluating the success of tonsillectomy for treatment of OSA for these patients. Our goal was to investigate the efficacy of tonsillectomy for patients with 22q11.2DS based on polysomnography(PSG) results. **Methods:** Retrospective review was completed, and data combined for two large 22q Centers based in tertiary care children's hospitals in Kansas City and Philadelphia, USA. Inclusion criteria were a diagnosis of 22q11.2DS, history of tonsillectomy, and at least one PSG. Data extracted included genetic diagnosis, comorbidities, tonsillectomy details, and PSG results. **Results:** Sixty-six patients were included. Comorbidities included cardiac defect (71%), velopharyngeal dysfunction (67%) and ADHD (26%). Thirty-four patients (52%) underwent multiple PSGs. The cohort had a total of 116 PSGs. Median time between tonsillectomy and preoperative and postoperative PSG was 1 year (IQR: 0.4, 2.5 years) and 2.2 years (IQR: 0.8, 5) respectively. Only 9 individuals had both preoperative and postoperative PSG occurring within 1 year of tonsillectomy. These PSG results showed 1 individual improved to normal, 3 improved but had residual mild OSA, and 5 remained relatively unchanged. BMI did not seem to have an influence on any change in PSG results. For the presentation, we will have additional analysis on factors associated with PSG results. **Conclusions:** This data highlights the challenge of determining success of tonsillectomy for treating OSA in patients with 22q11.2DS. Despite 66 patients with both tonsillectomy and PSG data, few had both pre- and postoperative PSG data. Additionally, there was often a significant amount of time between the surgical procedure and PSG, making it difficult to attribute any change in OSA specifically to tonsillectomy. Our limited data does not show significant improvement in OSA with tonsillectomy for patients with 22q11.2DS.

067: Tonsillectomy in Children with 22q-related Disorders

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Background: Tonsillectomy is among the most frequent surgical procedures performed on children, with approximately 530,000 performed each year in America. With only one prior smaller study evaluating tonsillectomy in children with 22q11.2 deletion syndrome (22q11.2DS), our goal was to evaluate tonsillectomy indications, postoperative care, and complications for a larger cohort of pediatric patients with 22q- related disorders (22q). **Methods:** Retrospective chart review was completed for patients in our 22q Center's repository. Inclusion criteria were a diagnosis of a 22q-related genetic disorder, and a history of tonsillectomy. Data collected included: genetic diagnosis, demographics, indications for tonsillectomy, postoperative care, and complications. **Results:** 304 consecutive patients were reviewed, of which 67/304 (22%) had a tonsillectomy. 90% had 22q11.2DS, 9% had 22q duplication, and 1% had an atypical 22q distal triplication. For those with 22q11.2DS, the most common breakpoint was A-D. Among the cohort, 70% had history of cardiac defect and 63% had velopharyngeal dysfunction. Average age at tonsillectomy was 5.7 years; patients with 22q duplication were nearly 2 years older at time of surgery compared to 22q11.2DS. The most common indications for tonsillectomy were sleep-disordered breathing/obstructive sleep apnea(n=40) and facilitation of speech surgery(n=28). Average length of hospital stay was 1.03 days, and six patients were monitored overnight in the PICU. Complications occurred in 13% of patients and included airway obstruction and postoperative hypocalcemia. Five patients had post-tonsillectomy hemorrhage (PTH) of which 2 required additional operative treatment. **Conclusions:** Twenty-two percent of our 22q cohort underwent tonsillectomy; this is significantly higher than the incidence of tonsillectomy in the general population. Given this, providers caring for children with 22q should be familiar with the indications for tonsillectomy and understand when to refer to an otolaryngologist. Additionally, these data highlight the potential need for close postoperative calcium and respiratory monitoring. The rate of PTH was not increased compared to general population.

068: Sleep Difficulties Related to Psychopathology and Neurocognition in People with 22q11.2 Deletion Syndrome

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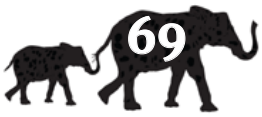
Background: The 22q11.2DS is associated with multiple medical conditions, neuropsychiatric disorders, and neurocognitive challenges. Individuals and parents often report insomnia impacting daytime functioning. Poor sleep can impede cognitive development, functioning and exacerbate psychiatric manifestations. Here we evaluate types and estimate prevalence of sleep disorders in a deeply phenotyped cohort with a comprehensive medical, sleep history and structured sleep interview; characterize sleep behaviors and sleep quality measured by a validated sleep questionnaire; examine relationships among sleep quality, psychosis and neurocognitive functioning. **Methods:** The observational cross-sectional study included 100 individuals from the "22q and You" Center. The Pittsburgh Sleep Quality Index (PSQI), and a comprehensive sleep history were obtained. The psychiatric evaluation and Penn Computerized Neurocognitive Battery (CNB) were completed independently for 92 participants. **Results:** Based on the comprehensive sleep interview and sleep questionnaire, 72% of participants had symptoms consistent with a sleep disorder, meeting criteria of the International Classification of Sleep Disorders. "Good Sleepers" (PSQI $\leq$5, 50% female, mean age 18.0$\pm$8.9, 48% of sample) were compared to "Poor Sleepers" (PSQI >5, 50% female, mean age 21.3$\pm$9.3, 52% of sample). Poor Sleepers had significantly lower global functioning (GAF; $p<0.001$), more positive psychotic symptoms ($p=0.048$) and more negative symptoms ($p<0.001$). For the CNB, the mixed model analysis showed a significant group X accuracy vs. speed interaction, $F=11.72$, $df=1,1886$, $p=0.0006$, indicating that Poor Sleepers were specifically impaired in accuracy more than speed across neurocognitive domains. Mediation analysis showed that the symptoms$\rightarrow$GAF relationships were mediated by sleep ($p< 0.001$), and conversely, the sleep$\rightarrow$GAF relationship was mediated by symptoms ($p < 0.05$). **Conclusions:** Sleep disorders are common in 22q11.2DS and create a vicious cycle whereby poor sleep exacerbates symptoms, impairing functioning and conversely, psychiatric symptomatology adversely affects sleep, which impact functioning. Interventions for improving sleep hygiene could improve functioning both directly and by reducing symptoms.



069: Sleep and Cognition in Individuals with 22q11.2 Deletion Syndrome *

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Background: Sleep disturbances are prevalent and associated with psychiatric symptoms in individuals with 22q11.2 Deletion Syndrome (22q11.2DS). Prior studies suggest that 22q11.2DS may be associated with non-restorative sleep, in which the quantity of sleep is sufficient, but without the daytime benefits of sleep. We test the hypothesis that individuals with 22q11.2DS exhibit non-restorative sleep, characterized by longer sleep duration, but worse sleep-dependent memory consolidation relative to typically developing (TD) controls. **Methods:** Participants with 22q11.2DS (n=15, M_{age}=18.7 years, Age range:7-41, 47% males) and TD controls (n=18; M_{age}=17.9 years, Age range: 10-22, 33.3% males) completed one week of wrist actigraphy. Mean sleep duration across the week was calculated for each subject. A subset of participants (22qDel: n=14, M_{age}=22.4 years, 42.9% male; TD: n=15, M_{age}= 19.5 years, 40% male) completed a well-validated motor sequence task (MST) to measure sleep-dependent memory consolidation. Participants completed a learning phase and a test phase across two days. Overnight improvement in performance was calculated for speed (number of correct sequences typed) and accuracy. Linear models controlling for age and sex were used to compare sleep duration and sleep-dependent memory consolidation (speed and accuracy) between 22q11.2DS and TD controls. **Results:** Subjects with 22q11.2DS exhibited increased sleep duration compared to TD controls (b=1.16, p<0.001). As expected, the TD group exhibited overnight improvements in speed (b=0.82, p=0.014) and accuracy (b=-0.66, p=0.040) on the MST. 22q11.2DS did not show these improvements (accuracy: b=-0.58, p=0.149; speed: b=0.42, p=0.312). The magnitude of overnight improvement was reduced in 22q11.2DS, relative to TD for speed (b=-0.87, p=0.011), but not accuracy (b=0.16, p=0.66). **Conclusions:** 22qDel carriers exhibit increased sleep duration and poor sleep-dependent memory consolidation. This supports our hypothesis of non-restorative sleep in 22q11.2DS. Next steps will involve examining thalamocortical sleep spindles as a canonical marker of overnight MST improvement.

070: Prospective Natural History Study of Idiopathic-like Scoliosis in Patients with 22q11.2 Deletion Syndrome, Starting Before its Pathological Onset *

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Background and Aim: 50% of 22q11.2DS-patients develop an idiopathic-like scoliosis. We screen 22q11.2DS-patients biennially with radiographs for scoliosis from age 6-18. Currently, important information about scoliosis development in 22q11.2DS is unknown. This study will use our longitudinal database to inventory the natural history of scoliosis in 22q11.2DS and to explore whether this can be used for predictive modelling. **Methods:** From the prospective registry, which includes radiographs before scoliosis onset, 722 full-spine standing radiographs of 292 patients with 22q11.2DS were included. Cobb-angles were measured, with scoliosis development defined as a curve ≥10°. Age of onset, risk of progression to >30° and need for surgical treatment were evaluated. **Results:** 116(40%) patients developed scoliosis ≥10°, 62(44%) of included girls and 55(36%) of included boys, 13(4%) progressed to >30°. Seven(2%) required surgical treatment. A total of 69 patients had radiographic follow-up until 16 years or older. In this group, 41(59%) had scoliosis with a Cobb angle ≥10°, 11(16%) >30° and 6(9%) required surgery. From all scoliosis patients, 31 had radiographs taken before the onset of scoliosis. In this group, the mean age of progression into a scoliosis was 11.3±2.6 years, 11.8 in girls and 11.0 in boys and ranged from 5.6 – 15.4 years. Before age 10, 50% of these patients already had a curve ≥10°, with more fluctuation (standard deviation compared to the predicted mean) in the curve angle values of future scoliosis patients. **Conclusions:** This prospective natural history study describes scoliosis development, starting before its onset. It appeared that many already have a minor scoliosis before age 10, often without progression, and that only a subset develops a severe progressive deformity. This dataset provides the opportunity for future risk-profiling to distinguish between mild, stable and progressive scoliosis, which possibly could be extended to the scoliosis population as a whole.

071: Tethered Spinal Cord in Association with 22q11.2 Deletion Syndrome

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Background: Tethered cord syndrome (TCS) is a neurologic disorder caused by tissue attachments that limit the movement of the spinal cord within the spinal column as it lengthens with growth. This causes an abnormal stretching of the spinal cord with resultant neurologic symptomatology such as leg pain/paresthesia/peripheral neuropathy, gait abnormalities, scoliosis, hammertoes, pes cavus, bowel and bladder problems including incontinence. TCS has been identified in 0.25 per 1,000 births in the general population and may occur in children with spina bifida which has been reported in patients with 22q11.2 deletion syndrome (22q11.2DS) including a child with a *SNAP29* mutation on the non-deleted allele (McDonald-McGinn 2014). It is estimated that 20-50% of children with neural tube defects repaired neonatally will require surgery at some point to untether the spinal cord. Here we report the association of TCS with 22q11.2DS, examining deletion size and potential genotype-phenotype correlations. **Methods:** We performed a retrospective chart review under an IRB approved protocol of findings reported in 1,629 individuals with 22q11.2DS evaluated between 1992 and 2024. Diagnostic confirmation of TCS was obtained from the electronic health record, legacy database records, and outside hospital records including imaging studies/surgical notes. **Results:** Sixty-three patients with 22q11.2DS were confirmed to have TCS (3.9%, 39 per 1,000 births), of whom 52% were male and 70% white, significantly less than our overall population where ~90% are white. 86% had a standard LCR22A-LCR22D deletion; three had an LCR22A-LCR22B deletion; one had a LCR22B-LCR22D deletion, and 4 had a LCR22C-LCR22D deletion. Surgical procedures to release TCS were performed in 73% of patients. **Conclusions:** Prevalence of TCS appears to be significantly higher in children with 22q11.2DS, with our center reporting a rate 156 times greater than the general population. Comorbidities and potential modifier genes are under investigation. TCS is a treatable condition, particularly when identified early, and a high index of suspicion should be maintained.

072: Possible Causes of Lower Extremity Pain in Children with 22q11.2 Deletion Syndrome - A Retrospective Cohort Study

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Background: Throughout childhood and adolescence many patients with 22q11.2 deletion syndrome (22q11DS) appear to suffer from lower extremity pain and / or exercise intolerance, with major impact on daily life activities and quality of life. Given the variety of somatic manifestations associated with the syndrome, several medical factors could be involved. We studied (i) the prevalence of lower extremity pain and exercise intolerance in youth with 22q11DS and (ii) to what extent medical factors congenital heart defects (CHD), hypocalcemia and / or orthopedic problems are associated. **Methods:** Data were extracted from medical records in the Dutch 22q11DS center in Utrecht. Out of 268 eligible patients (12-18yrs) matching inclusion criteria, 124 children were enrolled. Patient and family reports on standardized follow-up care questions on lower extremity pain and/or exercise intolerance and on the potential medical factors were recorded. **Results:** In total, 62/124 children (50%) reported lower extremity pain. Pain characteristics were: exercise-induced (44%), exercise-limiting (37%), need for analgetics (6%), and/or sleep-limiting (3%). Younger age was associated with lower extremity pain ($p<.01$). No associations were found between the presence of CHD ($p=.72$), hypocalcemia ($p=.13$), and/or orthopedic problems ($p=.08$) and lower extremity pain. Multivariable analysis, including potential confounders, did not show independent associations between CHD, hypocalcemia, and/or orthopedic problems and lower extremity pain. Sensitivity analyses with distinct CHD severities or pain categories yielded similar results. The presence of generally more prevalent orthopedic manifestations (scoliosis and/or pes planes) tended to be associated ($p=.05$). **Conclusions:** Lower extremity pain has a high prevalence in children aged 12-18yrs with 22q11DS, especially in those 12-14 years of age. The impact on daily life aspects like exercise and sleep are significant. No association was found between lower extremity pain and CHD, hypocalcemia and/or orthopedic problems, although the presence of scoliosis and/or pes planes showed a trend.

073: Occipital Frontal Circumference in 22q11.2 Deletion Versus 22q11.2 Duplication Syndromes

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Background: Microcephaly is defined as occipital frontal circumference (OFC), also known as head circumference, measuring below the age-adjusted 3rd percentile, estimated to occur in 1/800 to 1/5,000 children. Microcephaly can be described as congenital, present at birth or prenatally after 36 weeks' gestation; postnatal/secondary, developing after birth; isolated, when a small head is the only feature; syndromic, when associated with one of many conditions including other symptoms, such as seizures, motor/speech delay, cognitive deficits, feeding/swallowing problems, short stature, etc. Macrocephaly is OFC measuring two standard deviations above the 97th percentile. It is more common than microcephaly, occurring in 5% of children, and more common in males. It can be caused by genetic conditions, other disorders, or running in families The mean birth OFC, as reported by the World Health Organization, is 33.9 cm for females and 34.5 cm for males. **Methods:** We retrospectively reviewed our records on 1,859 individuals with 22q11.2 copy number variants (CNVs) under an IRB approved study to identify OFC <2% and >97%. Demographic information, CNV type/size, and growth parameters were also abstracted and analyzed. **Results:** Mean birth OFC for those with 22q11.2DS was 32.6 cm (+/- 3.4 cm) for females and 33.8 cm (+/- 1.8 cm) for males. Mean birth OFC for those with 22q11.2DupS was 34.8 cm (+/- 1.7 cm) for females and 34.0 cm (+/- 2.4 cm) for males. Of the 1629 patients with 22q11.2DS, 195 (12%) were microcephalic, while 72 (4%) were macrocephalic. Conversely, of the 230 patients with 22q11.2DupS, 19 (8%) were microcephalic and 68 (30%) were macrocephalic. Syndrome-specific OFC curves by sex and age were developed from this data. **Conclusions:** Microcephaly is relatively common in 22q11.2DS (12%) while macrocephaly is relatively common in 22q11.2DupS (30%). Sex, co-morbidities, and syndrome-specific changes over time will be discussed.

074: Neuroradiological Findings in a Large, Unselected Clinical Sample of Individuals with 22q11.2 Deletion Syndrome (22q11.2DS)

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Background: The functional neuroanatomy of 22q11DS has been extensively characterized using high-resolution MRI and quantitative neuroimaging. Although well-controlled prospective research studies have established a characteristic neuroanatomic profile, ascertainment biases owed to study exclusion criteria provide an incomplete picture of the 22q11DS endophenotype. Prior retrospective clinical neuroradiologic studies generally have had small samples (~N<20). **Methods:** Here we performed a systematic clinical review of all available (N=167) brain MRI in individuals with 22q11DS at the Children's Hospital of Philadelphia (CHOP), reinterpreted by a board certified neuroradiologist with expertise in 22q11DS. **Results:** The majority of individuals with 22q11DS had generalized cerebral volume loss relative to expectations for age (41% mild, 17% moderate, 6% severe), and prominent volume loss in the corpus callosum was seen in 3 patients. A large cavum septum pellucidum was present in 23%, and any sized cavum was observed in >37%; this frequency is substantially higher than the ~15% observed in the typically-developing population (p-value<0.0001). Polymicrogyria/pachygyria was observed in approximately 5% (p-value <0.0001), and gray matter heterotopia in ~2%. Although rare, Chiari I malformations (4%), cerebellar hypoplasia (2%), and possible rhombencephalosynapsis (1%) were significantly more prevalent relative to baseline expectations (p-value <0.0001). We also found probable basal ganglia mineralization (6%) and chronic microhemorrhages (6%) in a subset of individuals with 22q11DS, substantially above expectations for age and potentially related to systemic comorbidities and prior therapies. **Conclusions:** Although the current data also carries its own risk of ascertainment bias owed to clinical indications for MRI, it supports prior findings in smaller clinical samples and provides complementary information to larger but more selected research samples.

075: Neuroradiologic Findings in 22q11.2 Duplication Syndrome and Comparison to 22q11.2 Deletion Syndrome *

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Background: Chromosome 22q11.2 copy number variants (CNVs) result in duplication (22q11.2DupS) and deletion (22q11.2DS) syndromes with similarities in clinical neurologic presentations. These include developmental delay, cognitive deficits, ADHD, and seizures/epilepsy. However, while frequency of major brain malformations in patients with 22q11.2DS is estimated to be around 13%, the rate of major malformations and other neuroradiologic findings in those with 22q11.2DupS is currently unknown. Here we present neuroradiologic findings in patients with 22q11.2DupS compared with 22q11.2DS. **Methods:** Under IRB approval, we retrospectively reviewed electronic health records and MRI reports of all patients with a diagnosis of 22q11.2DupS followed in the 22q and You Center at the Children's Hospital of Philadelphia. **Results:** 149 individuals with 22q11.2DupS had records available for review. Of these, 62 had magnetic resonance imaging (MRI). Abnormalities were identified in 39 (63%). These included white matter abnormalities such as periventricular leukomalacia (n = 12, 19%), midline abnormalities of varying severity (n = 5, 8%) including one case of septo-optic dysplasia (SOD), and cerebellar differences (6, 10%). Compared with previous neuroimaging findings in patients with 22q11.2DS, where severe malformations such as hemispheric polymicrogyria and Chiari II malformation were observed, these abnormalities were rare in those with 22q11.2DupS, which was associated with midline defects, including holoprosencephaly and SOD as well as gray matter heterotopia. Of note, seizure frequency in 22qDupS was similar to that reported for 22q11.2DS. **Conclusions:** While total frequency of MRI brain abnormalities is similar across 22q11.2DupS and 22q11.2 DS, findings tended to be much more severe in 22q11.2DS, and midline abnormalities were more common in 22q11.2DupS. Potential correlations with CNV size, familial v. *de novo* occurrence, concomitant diagnoses, comorbidities, other malformations, gestational age, prenatal exposures, geocodes, risk factors, and impact on function will be discussed.

076: Local Cerebellar Dysplasia and Motor Learning Deficit in 22q11.2 Deletion Syndrome are Attributed to a Skeletal Deformity

Tae-Yeon Eom[1], J Eric Schmitt[2], Yiran Li[1], Audrey Bonnan[3], Christopher M. Davenport[1], Khaled Khairy[1], David R. Roalf[2], Raquel E. Gur[2], Beverly S. Emanuel[2], Donna M. McDonald-McGinn[2], Jason M. Christie[3], Paul A. Northcott[1], Stanislav S. Zakharenko[1]

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Background: The 22q11.2 deletion syndrome (22q11DS), also known as DiGeorge or velocardiofacial syndrome, is the most common microdeletion in humans. The syndrome is associated with multiple physical and neuropsychiatric morbidities. This led us to investigate the pathological and structural connectivity of 22q11DS brain abnormalities. Although meta-analyses show global and subcortical brain alterations in 22q11DS patients, the mechanisms underlying these structural and functional associations in 22q11DS are largely unknown. Herein, we used murine models of 22a11DS in combination with the 22q11DS study in humans to elucidate the mechanisms responsible for the neuroanatomical changes in 22q11DS, with a focus on the cerebellum. **Methods:** We used combinatorial methods to dissect the structural and functional changes in 22q11DS. These included *in vivo* and *ex vivo* magnetic resonance imaging, computerized tomography measurement, video-oculography and vestibulo-ocular reflex (VOR), patch clamp electrophysiology, generation and development of transgenic mouse models of 22q11DS, histologic analysis and immunohistochemistry, and single nuclear RNA sequencing (snRNA seq). **Results:** Our study found that volume of the vestibulocerebellum, especially paraflocculus/flocculus (PF/F), was considerably reduced (dysplasia) in mouse models and humans with schizophrenia-associated 22q11DS. This PF/F dysplasia was accompanied by impaired synaptic plasticity and motor learning and caused by haploinsufficiency of the *Tbx1* gene encoding a T-box transcription factor. PF/F dysplasia was not attributed to altered neural composition and neurogenesis but rather to malformation of the subarcuate fossa, a part of the petrous temporal bone (PTB), which encapsulates the PF/F in mice. snRNA seq revealed that *Tbx1* haploinsufficiency caused precocious differentiation of chondrocytes to osteoblasts in the PTB without affecting cell compositions in the PF/F. **Conclusions:** Our study suggest that skeletal abnormalities may lead to brain defects in schizophrenia-associated 22q11DS. Precocious chondrocyte-to-osteoblast differentiation in the PTB, triggered by *Tbx1* haploinsufficiency, specifically occludes the development of the vestibulo-cerebellar PF/F and results in deficient cerebellar function.

077: Presence, Severity, and Functional Associations of Incomplete Hippocampal Inversion in 22q11.2 Deletion Syndrome

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Background: Between gestational weeks 20-30 a morphologic inversion of the dentate gyrus and cornu ammonis occurs around the hippocampal sulcus. Failure to complete this inversion results in the incomplete hippocampal inversion (IHI). IHI incidence is higher in the left hemisphere (~17%) than right (~6%). While the hippocampus is smaller in patients with 22q11.2 deletion syndrome (22q11.2DS) the prevalence, severity, and functional consequences of IHI has not been assessed. Moreover, 22q11.2DS is known to increase individuals' risk for psychopathology. Investigating IHI in 22q11.2DS not only provides an opportunity to uncover features of a specific morphological abnormality but also offers the opportunity to link IHI to developmental origins of neurocognitive dysfunction and neuropsychiatric symptoms common in 22q11.2DS. **Methods**: Using MRI data, the presence (present/absent) and severity (0-10 scale) of IHI was measured in patients with 22q11.2DS (n=84) and typically developing (TD; n=663) individuals. Hippocampal volume, cognitive performance and psychopathology were assessed. **Results**: In 22q11.2DS the prevalence of IHI was significantly higher in both left (54%; $p<0.00001$) and right hemisphere (20%; $p<0.001$) as compared to TD (left: 23%, right: 8%). IHI severity was higher in 22q11.2DS compared with TD in both left (3.8 vs. 3.0; $p<.0001$) and right (2.9 vs 2.5, $p<0.001$) hippocampi. Left hemisphere IHI in 22q11.2DS was associated with a *smaller* hippocampal tail ($p<0.05$) and CA1 body ($p<0.01$) as compared to 22q11.2DS without IHI. Conversely, right hemisphere IHI in 22q11.2DS was associated with *larger* right hippocampal subfields encompassing the hippocampal body and head as compared to 22q11.2DS without IHI. Across 22q11.2DS, more severe left IHI was associated with lower educational attainment ($p=0.05$), poorer emotion recognition ($r(75)=-0.24$, $p<0.05$), face memory ($r(75)=-0.25$, $p<0.05$) and more impulsivity ($r(75)=0.24$, $p<0.05$), but fewer psychiatric symptoms ($ps<0.05$). **Conclusions**: These preliminary results indicate a high prevalence of morphological alterations of the hippocampus in 22q11.2DS that have functional correlates.

078: Synaptic-related Developmental Dysconnectivity in 22q11.2 Deletion Syndrome

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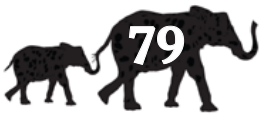
Chromosome 22q11.2 deletion is among the strongest known genetic risk factors for developmental disorders, including autism and schizophrenia. Brain imaging studies have reported atypical large-scale functional connectivity in people with 22q11 deletion syndrome (22q11DS). However, the significance and biological determinants of these functional alterations remain unclear. Here, we use a cross-species design to investigate the developmental trajectory and neural underpinnings of brain dysconnectivity in 22q11DS. We find that LgDel mice, an established mouse model of 22q11DS, exhibit age-specific patterns of functional MRI (fMRI) dysconnectivity, with widespread fMRI hyper-connectivity in juvenile mice reverting to focal hippocampal hypoconnectivity over puberty. These fMRI connectivity alterations are mirrored by co-occurring developmental alterations in dendritic spine density, and are both transiently normalized by pharmacological GSK3B inhibition, suggesting a synaptic origin for this phenomenon. Notably, an analogous hyper- to hypoconnectivity reconfiguration occurs also in human 22q11DS, where it affects cortico-hippocampal regions that are spatially enriched for autism-relevant transcripts and synaptic proteins that interact with GSK3β. This functional dysconnectivity is predictive of socio-behavioral alterations in 22q11 deletion carriers. Taken together, these findings suggest that synaptic-related mechanisms underlie developmentally mediated functional dysconnectivity in 22q11DS.



079: 22q11.2 Gene Dosage Effects on Cerebello-cortical Functional Connectivity

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Background: 22q11.2 copy number variations (CNVs) are among the most common genomic rearrangements in the human genome. Deletions(22qDel) and duplications (22qDup) at the 22q11.2 locus are associated with a range of developmental, psychiatric, and health outcomes. We have previously reported significant 22q11.2 gene dosage effects on cerebellar volumes. Here, we investigated whether these effects extend to cerebellar functional connectivity (FC). **Methods:** Following preprocessing, resting-state fMRI data from 179 participants (54% F; age M=16.4, SD=8.6; n=77 (22qDel), 74 (Control), 28 (22qDup)) were parcellated into 718 parcels using the Cole-Anticevic brain-wide network partition, where each parcel was assigned to one of 12 large-scale brain networks. Cerebello-cortical FCs were calculated as the Fisher z-transformed pairwise Pearson correlation between the cerebellar and cortical parcels. Linear regressions were employed to model the gene dosage effects on FC, with age, sex, and scanner included as covariates. Results were corrected with a false-discovery rate (FDR) threshold of q<.05. **Results:** Positive gene dosage effects (FDR q<.05) were observed in FC between bilateral cerebellar parcels of the somatomotor network (SMN) and bilateral cortical parcels of the visual network (VN): 1. Left-Cerebellum-SMN to Left-Cortex-VN (β=.05, p=.00012, 95% CI [.025, .075]), 2. Left-Cerebellum-SMN to Right-Cortex-VN (β=.046, p=.00032, 95%CI [.022, .071]), 3. Right-Cerebellum-SMN to Left-Cortex-VN (β=.066, p<.0001, 95% CI [.038, .092]), and 4. Right-Cerebellum-SMN to Right-Cortex-VN (β=.057, p<.0001, 95%CI [.030, .084]). **Conclusions:** Using a novel functional parcellation approach, our study revealed positive gene dosage effects on functional connectivity between the cerebellar parcels of the somatomotor network and cortical parcels of the visual network. To our knowledge, this is the first report of 22q11.2 gene dosage effects on resting-state functional connectivity in the brain. This prompts further investigation into how these functional neural disruptions may be linked to cognitive outcomes and psychiatric symptoms in 22q11.2 CNVs. **Funding Source:** This work was supported by the National Institute of Mental Health (Grant Nos. R01 MH085953 and U01MH101779 [to CEB]), Simons Foundation Autism Research Initiative Explorer Award (to CEB), and UCLA Training Program in Neurobehavioral Genetics (Grant No. T32NS048004 [to CHS]).

080: Neurite Orientation Dispersion and Density Imaging in 22q11.2 Deletion and Duplication Carriers *

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Background: Copy number variations (CNVs) at 22q11.2 are associated with elevated risk of neurodevelopmental disorders and atypical brain structure, including altered white matter microstructure. Previous diffusion tensor imaging findings indicate widespread higher fractional anisotropy (FA) in 22q11.2 deletion carriers (22qDel), while 22q11.2 duplication carriers (22qDup) display lower FA across white matter tracts. However, the underlying microstructural characteristics that contribute to group differences in FA remain largely unknown. Here, we applied novel multi-shell diffusion metrics, neurite orientation dispersion and density imaging (NODDI), to examine axonal density and fiber dispersion, which may contribute to the observed differences in FA. In addition, we explored age-related differences in NODDI measures for 22q11.2 CNV carriers relative to controls. **Methods:** The study includes site-harmonized NODDI-derived measures from individuals with 22qDel (N = 49, scans = 68, age range = 7.40–51.1), 22qDup (N = 23, scans = 33, age range = 8.33–49.4), and typically developing controls (N = 653, scans = 664, age range = 7.81–45.3). We used generalized additive mixed models to account for repeated measures and to examine non-linear age-related trajectories for NODDI measures. **Results:** Results showed widespread higher intracellular volume fraction (ICVF) for 22qDel and lower ICVF for 22qDup, relative to controls. Moreover, we observed regional differences using the orientation dispersion index (ODI) on white matter regions between 22q11.2 CNV carriers and controls, and atypical regional-specific age trajectories for ICVF and ODI measures across childhood and adolescence. **Conclusions:** These new diffusion methods reveal that altered FA in 22q11.2 CNV carriers appears to be primarily driven by altered axonal density, with opposing effects in 22q11.2 deletion and duplication carriers. Results also indicate regionally specific effects of fiber dispersion for 22q11.2 CNV carriers. Finally, atypical age trajectories may indicate that the altered white matter development in 22q11.2 CNV carriers extends into young adulthood.

081: Focal Volumetric Reductions in Subthalamic Nuclei in the 22.11.2 Deletion Syndrome (22q11DS)

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Background: The thalamus is an important relay station, with regionally-specific connectivity to most regions of the brain and a well-established role in sensory modulation. The thalamus is increasingly recognized for its role in higher-order functions including cognition, emotion, and consciousness. The thalamus has been implicated in the pathophysiology of schizophrenia. Prior studies have suggested that the thalamus is associated with the 22q11.2DS endophenotype, but to date there is no comprehensive analysis of subthalamic nuclei in this condition. Advances in machine-learning algorithms now facilitate volumetric measurements of thalamic subnuclei using high-resolution MRI. **Methods**: Sagittal T1-weighted MP-RAGE was acquired at 3.0 Tesla on N=73 individuals with 22q11DS and a matched typically-developing (TD) control group. Total thalamic and subthalamic nuclei volumes were calculated using THOMAS segmentation, resulting in 12 regions of interest (ROIs) per thalamic hemisphere. Group differences were assessed via regression models controlling for age, sex, race, and either total brain (TBV) or thalamic (TTV) volumes. Within-group brain-behavior associations between thalamic subregions and Computerized Neurocognitive Battery z-scores were assessed using canonical correlation analysis and multivariate regression. **Results**: Global thalamic volumes were slightly (~6.5%) smaller in 22q11DS (mean 11.1 cm^3) compared to TD controls (11.9 cm^3); differences were statistically significant (p-value=0.0090). After correction for multiple testing, six thalamic subnuclei were significantly smaller in 22q11DS regardless of covariates used (demographic covariates only; $p<0.0001$; +TBV ($p<0.05$); + TTV ($p<0.006$)); specifically, the bilateral antroventral (AV) nuclei, lateral geniculate nuclei (LGN), and bilateral pulvinar. Exploratory within-group brain-behavior analyses found significant associations between the pulvinar and social cognition ($p=0.0073$). Habenular and centromedian nuclei volumes were both significantly associated with processing speed ($p<0.010$). **Conclusions**: Individuals with 22q11DS have regionally-specific decreases in thalamic subnuclei, particularly nuclei with connectivity to the posterior cerebrum and limbic structures. Within-group neuroanatomic variation may be associated with differences in cognitive function. Further investigation is warranted.

082: Altered GABA-ergic short-term Synaptic Plasticity in Prefrontal Cortex of a Mouse Model of 22q11DS

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Background: There is a high incidence of psychotic disorders in patients with 22q11DS. Dysfunction in prefrontal cortex (PFC) is thought to critically underlie psychotic symptomology. The prevalence of dysfunctional gamma oscillations in patients with psychosis – including those with 22q11DS – points to likely L2/3 dysfunction. Given that short-term (ST) synaptic plasticity is a key regulator of network dynamics, here we explored possible PFC L2/3 synaptic dysfunction in a mouse model of 22q11DS. **Methods**: To assess synaptic function in the PFC of 22q11DS mice we employed recordings from acute coronal brain slices that encompassed the prelimbic and infralimbic regions. Whole-cell voltage-clamp recordings from PFC L2/3 pyramidal neurons were used to assess alterations in evoked synaptic responses and ST synaptic plasticity. **Results**: While most metrics of glutamatergic ST-plasticity were unaltered, we detected multiple alterations in GABA-ergic ST-plasticity. Specifically, we found alterations in GABA-ergic PPR and ST-depression during high-frequency stimulus trains in 22q11DS PFC. More detailed analysis revealed that the probablility of release and the replenishment rate of the readily releasable pool of GABA-ergic synaptic vesicles were altered. Given largely unaltered glutamatergic ST-plasticity, these GABA-ergic alterations predict that the ST dynamic regulation of local network excitatory-inhibitory balance may be significanlty compromised in 22q11DS PFC. **Conclusions**: Consistent with PFC dysfunction as a key contributor to psychotic symptomology, we found multiple alterations in synaptic dynamics in the PFC of 22q11DS mice. Our findings indicate that disruptions of GABA-ergic ST-plasticity are the predominant synaptic alterations. These disruptions in inhibitory transmission suggest possibly severe impairment of ST-plasticity mechanisms to dynamically modulate network excitatory-inhibitory balance. Thus our results indicate impaired GABA-ergic ST-plasticity may contibute to psychosis through dysregulated ST network control in PFC. Dissection of precise molecular mechanisms underlying GABA-ergic dysfunction will point to therapeutic strategies to restore well-regulated network function in psychotic disorders that share dysfunction with 22q11DS.

083: 7-Tesla in-vivo ^{1}H-magnetic Resonance Spectroscopy of Glutamate and GABA in 22q11.2 Copy Number Variants

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Introduction: Glutamate and GABA have been linked to psychosis and cognitive impairment. Therefore, investigating these neurotransmitter systems in 22q11.2 copy number variants (CNVs) can provide valuable insights into the predisposition to psychosis and cognitive dysfunction. People carrying the deletion (22q11.2DEL) are at increased risk of developing psychotic disorders and impaired cognitive functioning, whereas it has been suggested that those carrying the duplication (22q11.2DUP) may have a reduced risk of developing psychotic disorders. Here, we aimed to investigate alterations in glutamate and GABA concentrations in the anterior cingulate cortex (ACC) in individuals with 22q11.2 CNVs and healthy controls. **Methods:** We enrolled 11 22q11.2DEL (age = 33.73; M/F = 5/6) and five 22q11.2DUP participants (age = 35.20; M/F = 2/3) without a history of psychiatric illness and 22 matched healthy controls (age = 31.85; M/F = 12/10). Glutamate and GABA concentrations in the ACC were measured using 7-Tesla magnetic resonance spectroscopy (^{1}H-MRS). **Results:** Using one-way Analysis of Variance (ANOVA), we did not find significant differences in glutamate (F $(2,37)$ = 0.699; p = 0.504; η^2 = 0.038) or GABA (F (2,37) = 0.969; p = 0.389; η^2 = 0.052) concentrations between the three groups. **Conclusion:** No significant alterations in ACC glutamate and GABA concentrations in 22q11.2 CNVs were found. Patients included in this study did not have a history of psychosis. Possibly, altered glutamate and GABA levels are only present in those patients who develop psychosis and more severe cognitive impairments. These findings are in line with previous studies in 22q11.2DEL patients, showing no glutamatergic alterations in the ACC in 22q11.2DEL compared to controls. However, data collection for this study is still ongoing. It may also be relevant to investigate other cortical and subcortical brain regions.

084: Unique Functional Neuroimaging Signatures of Genetic versus Clinical High Risk for Psychosis

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Background: 22q11.2 Deletion Syndrome (22qDel) is a copy number variant (CNV) associated with schizophrenia and other neurodevelopmental disorders. Studying this population provides a framework for linking genes to neuropsychiatric phenotypes. Adolescents at clinical high risk for psychosis (CHR) have sub-threshold psychosis symptoms without a known genetic risk factor. Here we compared these high-risk populations on measures of functional connectivity and mapped these results to biological pathways with multi-modal data. **Methods**: Two large multi-site resting-state fMRI samples were analyzed: 1) 22qDel (n=164, 47% female) and typically developing (TD) controls (n=134, 56% female). 2) CHR individuals (n=244, 41% female) and matched TD controls (n=151, 46% female) from the North American Longitudinal Prodromal Study-2 (NAPLS2) at baseline. We computed fMRI measures of brain signal variability (BSV), local functional connectivity (LC) and global brain connectivity (GBC) across a whole-brain parcellation, and tested case-control differences for 22qDel and CHR separately. Group difference maps were related to previously published brain gradients using spin permutation. **Results**: BSV, LC, and GBC are significantly disrupted in 22qDel (False Discovery Rate $q<0.05$). Spatial maps of BSV and LC differences are highly similar, unlike GBC. In CHR, only LC is significantly altered, with a different spatial pattern compared with 22qDel. Group differences map onto multiple biological gradients, with 22qDel effects strongest in regions predicted to have high blood flow and metabolism. **Conclusion**: 22qDel and CHR are associated with divergent effects on fMRI temporal variability and multi-scale functional connectivity. 22qDel is associated with strong and convergent disruptions in BSV and LC not seen in CHR individuals.

085: Neuromelanin-sensitive Magnetic Resonance Imaging as a Proxy for Dopamine and Norepinephrine Dysfunction in 22q11.2 Deletion/Duplication Syndrome: Interim Results *

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Background: Investigating dopamine and norepinephrine systems in 22q11.2 copy number variants (CNVs) could provide valuable insights into the predisposition to psychosis and cognitive dysfunction. These systems are implicated in numerous cognitive processes, including executive function, salience, and working memory. In 22q11.2 CNVs, the catechol-*O*-methyl transferase (COMT) gene lies in the deleted/duplicated region. COMT degrades dopamine and norepinephrine, and variation in its activity has been shown to be related to cognition and psychopathology. **Methods**: 40 otherwise healthy 22q11.2 CNV carriers and 40 healthy controls (HC) will undergo 7 tesla neuromelanin-sensitive magnetic resonance imaging (NM-MRI) as a proxy for lifetime dopamine and norepinephrine metabolism in the substantia nigra (SN) and locus coeruleus (LC). They will also be assessed for psychiatric symptoms and cognitive function. **Results**: NM-MRI data is currently available for 25 participants (HC = 16; Deletion = 8; Duplication = 1). The duplication patient was therefore excluded from analyses. The age of the deletion carriers (Median = 34.50; IQR = 15.50) was not significantly different from HCs (Median = 25.00; IQR = 18.75)(Wilcoxon rank sum = 125, $p = 0.55$). A trend towards increased NM-MRI signal intensity in the left inferior SN of deletion carriers was observed relative to controls (Wilcoxon rank sum = 104, $p = 0.07$). Additionally, a significant positive correlation of NM-MRI signal intensity with (subclinical) negative symptoms of psychotic disorder was revealed in the combined and left inferior SN (Spearman's rho = 0.51, $p < 0.01$; Spearman's rho = 0.49, $p < 0.05$ respectively). The effect did not persist in carriers alone. **Conclusion**: Increased NM-MRI signal intensity in the SN of 22q11.2 deletion carriers aligns with the hypothesis that altered COMT copy number may lead to chronically increased dopamine level, which may be associated with (negative) symptoms of psychosis. However, final conclusions are pending ongoing data collection.

086: Transition from Youth to Adult Care, Most Recent Insights and Future Challenges

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The transition from adolescence to adulthood is a developmental process characterized by changes in legal status and social roles, which unfortunately often coincides with transfer of care from Child and Adolescent Mental Health Services (CAMHS) to Adult Mental Health Services (AMHS) in case of mental health problems. Adolescence constitutes a challenging time with profound physiological, psychological, and social-emotional changes. Adolescents and Young Adults (AYAs) are expected to take increased responsibility for their own lives and behavior. They try to find their meaningful and contributive role in society, become financially independent and make their own decisions. AYAs negotiate relationships with family, peers and networks in new ways. At the same time, adolescence is a high-risk period for the emergence of mental disorders and alcohol / substance abuse. Brain development is ongoing, and maturation won't be complete before age 25. Taken together, service provision for AYAs with mental health problems continuity of care, instead of the traditional disruption is crucial. In this presentation the gap between CAMHS and AMHS and the vulnerability for mental ill-health in AYA will be highlighted. Psychiatrists should be aware of the different aspects of the transition from adolescence into adulthood. In addition how to organize care i.e. how to prepare for transfer or how to provide continuity of care around age 18, how to meet the needs of young people and transdiagnostic psychiatry will be addressed. Recent guidelines for transition of care will be discussed. Special attention will be given to the impact of the transition of care for AYAs with intellectual disabilities and / or genetic syndromes, who are at increased risk for mental health problems.

087: Cognitive, Adaptive and Daily Life Functioning in Adults with 22q11.2 Deletion Syndrome

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Background: 22q11.2 deletion syndrome (22q11.2DS) is associated with cognitive impairments and an increased risk for psychopathology. Most of the research has been conducted in children and adolescents while the majority of affected individuals live well into adulthood. Hence, limited data is available on functional outcomes in adults. **Aims:** The aim of the present study was to provide more insight in cognitive and adaptive abilities, and daily life functioning (marital status, living situation and work situation) in adults with 22q11.2DS. **Methods:** This retrospective study included 250 Dutch speaking adults (16-69 years) with 22q11.2DS from 3 sites in the Netherlands and Belgium. Data on full scale intelligence quotient (FSIQ) scores (assessed with Wechsler adult intelligence scales, WAIS), adaptive functioning (assessed with the Vineland Adaptive Behavior Scale, VABS II), and functional outcomes including marital status, living and work situation, were systematically collected from clinical files. Additionally, we examined predictors of adaptive functioning. **Results:** The majority in our adult sample (65%) demonstrated a low level of adaptive functioning, mainly in the domain of communication/socialization. Unlike previous findings in children and adolescents, the majority functioned at an intellectual disability level (56%). Male sex, lower FSIQ and an autism spectrum disorder were predictors of lower adaptive functioning (P=.016, P<.001, P=0.16). **Conclusions:** These results suggest that low levels of cognitive and adaptive functioning are common in adults with 22q11.2DS. Future, longitudinal and multicenter studies including older patients (> 40 years) are needed to further investigate cognitive and adaptive trajectories, and their interaction with physical and psychiatric comorbidities.

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088: Global Burden of Clinical Conditions in 405 Canadian Adults with 22q11.2 Deletion Syndrome *

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Background: Advancements in pediatric care and genetic testing have led to greater numbers of adults with 22q11.2 deletion syndrome (22q11.2DS) living with increased medical complexity and multimorbidity, with higher associated healthcare costs compared to the general population. In this study, we sought to investigate the number of lifetime clinical features per individual for a well-characterized sample of Canadian adults with 22q11.2DS, and to identify predictors of those with greater clinical burden. **Methods:** We systematically assessed medical records for 405 adults aged ≥ 18 years with 22q11.2DS to identify lifetime clinical conditions present in ≥ 5% of the entire sample. Only those that represented a diagnosis and were (or ought to be) assessed by a specialist and/or required significant investigation and/or management were included. We used linear regression modeling to identify predictors of the number of features per individual, accounting for sex, ethnicity, age, major congenital heart disease (CHD), psychotic illness, and moderate to severe intellectual disability (ID). **Results:** There were 77 features present in ≥5% of the sample, 70 relevant to both sexes, involving 14 major systems. The median number of conditions per individual was 13 (range 2-34) at a mean age of 35.4 (SD 12.4) years. Age (p<0.0001), psychotic illness (p<0.0001), CHD (p=0.0007), and ID (p=0.02), but not sex or ancestry, were significant independent predictors of a greater total number of clinical features per individual (model R^2 0.23, p<0.0001). Post hoc analyses showed no evidence of significant effects of inherited deletions, or of ascertainment as a transmitting parent. **Conclusions:** By early adulthood, the global burden of multisystem conditions for individuals with 22q11.2DS is apparent, and though greater in those older and/or with major 22q11.2DS features, not confined to individuals with these characteristics. Most of these conditions are treatable, highlighting the importance of prompt identification, screening, and ongoing follow-up.

089: Secular and Other Trends in 22q11.2 Deletion Syndrome at Transition to Adult Care and Beyond

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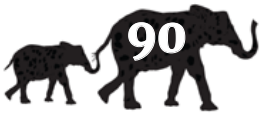
Background: Individuals presenting at transition for adult care at a specialized 22q11.2 deletion syndrome (22q11.2DS) clinic may differ from those referred at later ages, and there may be secular trends in features over time. We hypothesized that congenital complexity would be greater, and ethnicity more diverse, in those referred at transition, and that secular trends, and ever younger age at molecular diagnosis, would be noticeable over time. **Methods:** Within our cohort of 450 well-characterized adults with a typical 22q11.2 microdeletion, we compared the subgroup initially seen in the "transition" period (≤21 years) with the group >21 years on variables including major congenital heart disease (CHD), schizophrenia, moderate to severe intellectual disability (ID), ethnicity, and age at molecular diagnosis of the 22q11.2 deletion. **Results:** The transition group (n=226) was comparable in size to those seen initially at older ages (n=224). The transition group had a significantly greater proportion of individuals with major CHD (41.6% vs 26.8%, p=0.0009), and of non-European descent (34.5% vs 15.6%, p<0.0001), and a lower proportion of individuals with schizophrenia (21.7% vs 39.7%, p<0.0001) with a significantly younger median age at onset (18 vs 21 years, p<0.0001), but no difference in proportion with ID. There was no trend to younger age at molecular diagnosis within the transition group. There was however a trend to an increasing proportion with proximal nested 22q11.2 deletions over time. **Conclusions:** The findings suggest that a significant diagnostic odyssey remains for many patients, even amongst those recently transitioning to adult care. The results also indicate that population-based secular trends need to be considered as these can affect ascertainment, and thus clinical practice and research. Opportunities for preventive care await greater awareness and implementation of standard genetic diagnostics.



090: An Examination of Select Functional Outcomes in Adults with 22q11.2 Deletion Syndrome

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Background: Adults with 22q11.2 deletion syndrome (22q11.2DS) can have functional impairments in many areas of life, yet detailed information remains limited. **Methods:** We comprehensively examined select functional outcomes, including current living arrangements, education, employment history and financial supports received, in the 41 adults (median age 26.5, range 18.8–59.4 years; n=25 male) with a typical 22q11.2 deletion who were most recently assessed at our clinic for adults with 22q11.2DS. We assessed the relationship between functional outcomes and Global Assessment of Functioning (GAF) scores and level of support needed in instrumental activities of daily living (IADL), and possible effects of mild-moderate intellectual disability (ID, n=24) and psychotic illness (n=9). **Results:** The majority of individuals have received support from a provincial disability income support program (n=31, 75.6%), despite wide ranging GAF-scores (35–85). Many (n=24, 58.5%) individuals had attended some college/university, a substantial minority (n=15, 36.6%) have their driver's license, and most (n=29, 70.7%) have had some type of employment experience. There was no significant effect of ID, but adults with schizophrenia tended to require higher levels of supports with IADL (p<0.0001), and have lower GAF scores (median 53 vs 68.5, p=0.0002), than those with no psychotic illness. Excluding those with schizophrenia, there remained a significant relationship between no employment experience and need for IADL supports (p=0.0168). A minority (n=7, 17.1%) of this sample were living independently, all older than age 28.8 years. **Conclusions:** Employment and post-secondary educational experiences are common in adults with 22q11.2DS, yet widespread functional impairments are also common. Continued need for support in various areas of life is evident, regardless of presence or absence of ID, and particularly but not exclusively in individuals with psychotic illness. Further research is needed to illuminate the ever-evolving needs for supports at different life stages and transitions in adults with 22q11.2DS.

091: Systematic Genetic Dissection of 22q11.2-Linked Genes in vivo with AAV-Perturb-Seq

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The ever-growing compendium of genetic variants associated with human pathologies demands new methods to study genotype–phenotype relationships in complex tissues in a high-throughput manner. We created adeno-associated virus (AAV)-mediated direct in vivo single-cell CRISPR screening, termed AAV-Perturb-seq, a tuneable and broadly applicable method for transcriptional linkage analysis as well as high-throughput and high-resolution phenotyping of genetic perturbations in vivo. We applied AAV-Perturb-seq using gene editing and transcriptional inhibition to systematically dissect the phenotypic landscape underlying 22q11.2 deletion syndrome genes in the adult mouse brain prefrontal cortex. We identified three 22q11.2-linked genes involved in known and previously undescribed pathways orchestrating neuronal functions in vivo that explain approximately 40% of the transcriptional changes observed in a 22q11.2-deletion mouse model. Our findings suggest that the 22q11.2-deletion syndrome transcriptional phenotype found in mature neurons may in part be due to the broad dysregulation of a class of genes associated with disease susceptibility that are important for dysfunctional RNA processing and synaptic function. Our work establishes a flexible and scalable direct in vivo method to facilitate causal understanding of biological and disease mechanisms with potential applications to identify genetic interventions and therapeutic targets for treating disease.

092: Premature Neurogenesis Prefigures Loss of Upper Layer Cortical Neurons in 22q Model Mice

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Background: Diminished frequency of upper layer pyramidal neurons (L2/3 PNs) is likely central to cortical circuit dysfunction due to heterozygous 22q11 deletion in 22q11.2 Deletion Syndrome (22q11DS). It is not yet clear how 22q11 deletion compromises cortical stem cell development to selectively reduce L2/3 PN genesis. Previous work suggests that transit-amplifying basal progenitors (bPs) are impaired, but it is not known how 22q11 deletion impacts stem cell identity and proliferative capacity to preferentially disrupt L2/3 PNs production while sparing lower layer pyramidal cell populations. **Methods:** To assess bP identity and L2/3 PN genesis, we used multiple approaches in the *LgDel* 22q11DS mouse model: *in vitro* pair-cell assays to assess modes of bP division, EdU labeling followed by marker analysis to define bP proliferative and differentiation capacity *in vivo*, flow cytometry of bPs and other cortical stem cells, bulk RNAseq of sorted bPs, and single-cell RNAseq to determine stem cell identities and diversity. **Results:** *In vitro* pair-cell assays indicate that self-renewing capacity of individual bPs is significantly reduced. *LgDel* bPs undergo fewer symmetric or asymmetric divisions that yield stem cells, instead terminally dividing more frequently to produce neurons. In parallel, *in vivo* bP proliferative dynamics are altered so that *LgDel* L2/3 PNs are generated prematurely. Finally, transcriptional identities of *LgDel* bPs and other cortical stem cells diverges substantially from wild type. **Conclusions:** 22q11 deletion disrupts bP identity, along with proliferative and neurogenic capacity, leading to premature neurogenesis that diminishes the frequency of L2/3PNs, particularly those generated as cortical neurogenesis draws to a close. These changes not only yield fewer L2/3 PNs; they may alter the capacity of 22q11-deleted L2/3 PNs to differentiate and contribute to optimally functional cortical circuits.

093: Subtype-Specific Alterations in Interneuron Activity During Learning in The 22q11.2 Deletion CA1

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GABAergic interneurons in the hippocampus play critical roles in regulating activity and plasticity in excitatory circuits for encoding space and salient features in an environment. They play key roles in coordinating network activity, encode spatial information critical for navigation, and actively shape place fields through disinhibitory mechanisms. Individuals with the 22q11.2 deletion syndrome, one of the strongest genetic risk factors for schizophrenia, demonstrate cognitive impairments, including episodic memory dysfunction. Episodic memory and place cell stability in the hippocampus are impaired in a mouse model for the 22q11.2 deletion (*Df(16)A*$^{+/-}$), implicating dysfunctional inhibitory control. However there is no available information about functional alterations of inhibitory dynamics in mouse models for 22q11.2 deletion. To address this outstanding question we examined hippocampal interneuron subtype-specific activity in CA1 in *Df(16)A*$^{+/-}$ mice to examine both the individual and circuit-wide impact of interneuron activity in the model. Wild-type and *Df(16)A*$^{+/-}$ mice performed random foraging and goal-oriented learning on a spatially cued belt while undergoing large-scale, unbiased three-dimensional (3D) GCaMP-Ca^{2+} imaging of *in vivo* CA1 interneuron dynamics with *post hoc* molecular characterization of interneuron subtypes. We found that *Df(16)A*$^{+/-}$ interneuron activity carries remarkably reduced spatial information. Mutant mice perseverate in reward zones more than wildtype littermates. Interestingly, somatostatin-expressing (SomCs) interneurons exhibit a failure to extinguish old reward location enrichment activity when a reward zone is translocated. In addition to this altered reward response, Parvalbumin basket cells (PVBCs) and axo-axonic cells (AACs) exhibit aberrant responses to reward location. Overall we identify heterogeneous subtype-specific alterations in interneuron dynamics during learning depicting an inflexible microcircuitry in CA1.

094: Transcriptional Regulation of Basal Progenitor Cells in The Developing Cortex of 22q11DS Model *

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Background: Layer 2/3 projection neurons (L2/3 PNs) make cortico-cortical connections, especially between association cortices, and are key pathogenic targets in multiple neurodevelopmental disorders (NDDs) including Intellectual disability (ID), autistic spectrum disorder (ASD), and Schizophrenia (Scz). Aberrant regulation of cortical precursor proliferation, specifically basal progenitors (bPs) primary precursors of L2/3 PNs, has been proposed as a potential pathogenic mechanism underlying NDDs, altering L2/3 PN frequency as well as quantitative or qualitative changes in connectivity. Nevertheless, there is limited evidence for altered cortical progenitor proliferation in most NDDs. 22q11.2 Deletion Syndrome (22q11DS), is considered a model of polygenic risk associated with ID, ASD and Scz. Thus, we asked if bP transcriptional programs essential for L2/3 PN genesis were disrupted in the *LgDel* 22q11DS mouse model. **Methods**: We isolated bPs from the *LgDel* and WT embryonic cortex and performed transcriptional profiling using bulk RNAseq in 5 pooled biological replicates from each genotype. Sequence data was assembled using STAR and aligned reads were analysed for differential gene expression using EdgeR. Quantitive PCR as well as RNAscope *in situ* hybridization combined with cell class markers was used to validate RNAseq-predicted expression differences. **Results**: *LgDel* and WT bPs express most 22q11 deleted genes; however, in *LgDel* bPs these genes are uniformly downregulated, most by 50%. 74 additional genes are up regulated in *LgDel* bPs vs. WT. Most are associated with neuronal differentiation, paralleling our observations of premature neurogenesis from *LgDel* bPs. These expression differences were validated *in vivo* using RNAscope. Mean expression differences *in vivo*, however, reflect variation of expression per cell across the *LgDel* bP population. **Conclusion**: Dynamic regulation of gene expression levels in *LgDel* bPs prefigures diminished L2/3 PN frequency, likely contributing to association cortico-cortical under-connectivity. Apparently, 22q11 genes deletion targets bPs neurogenic capacity and transcriptional state resulting in suboptimal cortical development associated with NDD pathology.

095: Investigating Convergent Cellular Phenotypes of 22q11 and 3q29 Deletions

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Background: The two strongest known risk factors for schizophrenia are deletions at 22q11 and 3q29. While these variants result in hemizygosity of distinct sets of genes, they produce similar clinical phenotypic spectra. Therefore, we hypothesized that 22q11Del and 3q29Del disrupt similar cellular processes. **Methods**: We assembled an isogenic cohort of 22q11 and 3q29 deletion induced-pluripotent stem (iPS) cell lines by engineering either the 3Mb 22q11Del (N=3 clones) or 1.6Mb 3q29Del (N=3 clones) into an iPS cell line derived from a neurotypical individual (N=3 clones). We differentiated these iPSC lines to forebrain cortical organoids and performed quantitative TMT-proteomics at day 50, 100, and 150 in vitro (N=5/genotype/time point). We determined normalized protein abundances by genotype, compared the dysregulated proteome of 3q29Del to 22q11Del, and performed pathway analyses stratified by direction of change. **Results**: Principal component analysis indicated time point was a major factor distinguishing samples when all 8,221 proteins were considered. However, the differentially abundant proteins identified by genotype ($P<0.01$) were remarkably stable over time. Thus, subsequent genotype comparisons were performed across all three time points. Comparing the dysregulated proteomes of 3q29Del and 22q11Del, we found approximately 17-fold more overlap in differentially abundant proteins than would be expected by chance among both increased and decreased proteins (increased: 69 common proteins, 17.5-fold enriched, P=7.66e-72; decreased: 65 common proteins, 16.9-fold enriched, P=3.50e-66). The set of commonly decreased proteins was significantly enriched for mitochondrial function including oxidative phosphorylation whereas the set of commonly increased proteins was significantly enriched for mitochondrial translation and gene expression. Ongoing experiments are aimed at detailed validation of dysregulated proteins in independent cultures and an assessment of functional consequences. **Conclusions:** This quantitative proteomic study of human cortical organoids strongly indicated that the 22q11Del and 3q29Del similarly disrupt the mitochondrial proteome in developing human neural tissue.

096: Generation of Induced Pluripotent Stem Cells Carrying 22q11.2 CNVs as a Model System for Studying Neurodevelopmental Disorders

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Background: Copy number variations (CNVs) at 22q11.2 are associated with elevated risk for neurodevelopmental psychiatric disorders and they represent a powerful genetics-first approach to delineate molecular mechanisms underlying these disorders. Many clinical presentations are shared between 22q11.2 deletion and duplication carriers, including elevated risk for developmental delays, intellectual disability, and autism spectrum disorders. However, 22q11.2 microdeletion is a high-risk factor for schizophrenia, while 22q11.2 microduplication is less common in patients with this disorder than in the general population. Differences in brain structure between 22q11.2 deletion and duplication carriers are also reported. Although many animal models mimicking human diseases have been available for the research, only limited success has been achieved in revealing molecular mechanisms underlying human brain diseases. Thus, iPSCs derived from patients with specific disorders, such as neurodevelopmental disorders (NDDs), represent a powerful *in vitro* model system for studying molecular mechanisms underlying their pathophysiology. **Methods:** Control subjects and patients with 22q11.2 CNVs were recruited from the University Children's Hospital, and their peripheral blood mononuclear cells were reprogrammed using CytoTune™-iPS 2.0 Sendai Reprogramming Kit. The pluripotency of generated iPSCs was analyzed by immunofluorescence, qPCR, and trilineage differentiation using STEMdiff Trilineage Differentiation Kit. The iPSC lines were genotyped to identify any additional pathogenic CNVs. **Results:** We have generated iPSC cell lines from five patients with 22q11.2 microdeletion, six patients carrying 22q11.2 microduplication, and three healthy individuals. Pluripotency was confirmed by the expression analysis of pluripotency markers, while the capacity of generated iPSCs to differentiate into all three germ layers was revealed by STEMdiff Trilineage Differentiation Kit. **Conclusions:** Generated patient-specific iPSCs carrying 22q11.2 CNVs represent a model system that will enable further studies on molecular mechanisms underlying NDDs.

097: Protein and RNA Levels in 22q11.2DS Ipsc Derived Neurons Compared to Controls Over a 100-Day Time Course *

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Neuroscience and Mental Health Innovation Institute, Cardiff University

22q11.2 Deletion Syndrome (22q11.2DS) also called DiGeorge Syndrome involves the deletion of a section of DNA on one of the pairs of Chromosome 22. 22q11.2DS is a rare neurodevelopmental disorder with a range of presentations including heart defects and learning disabilities amongst others. Individuals diagnosed with 22q11.2DS have approximately 25 times higher likelihood of developing schizophrenia than the general population. We are investigating the action of the gene DiGeorge Syndrome Critical Region 8 (DGCR8), which is lost on one of the chromosomes pairs on the long arm of chromosome 22 in 22q11.2DS carriers. This gene encodes a protein component of the "microprocessor complex", which is required for production of molecules called microRNAs which are essential for normal development and function. In this work cortical neurons were generated from induced Pluripotent Stem Cells (iPSC) from biopsies taken from 22q11.2 patients and controls. The research focused on expression of DGCR8 and associated miRNAs in 22q11.2DS patient cell lines compared to controls over a 100-day developmental time-course specifically in stem cells, neuronal precursor cells, immature neurons, and mature neurons. Initial results have shown that the levels of DGCR8 change across development and are reduced in the 22q11.2DS line compared to controls. The fact that the DGCR8 levels change across neuronal differentiation suggests that there may be specific time points which are key to development and function. Future work aims to look at the downstream targets of the micro- RNAs identified in this research as a means of better understanding biological mechanisms underlying brain and behavioural changes, and vulnerability to psychiatric problems, seen in 22q11.2DS.

098: Multi-Modality Functional Genomics Analysis of the Effects of The 22q11.2 Deletion in Multiple Cell Types, Obtained with Multiple Cell-Reprogramming Methods

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We generated relevant cell types using three alternative reprogramming approaches: fibroblast to induced neuron (iN), fibroblast to iPSC to NPC to neuron, and fibroblast to iPSC to neural organoid (containing neurons and astrocytes). These approaches were applied to the same 22q11DS fibroblasts and controls, which had also been analyzed with whole-genome sequencing. We carried out multi-modal functional genomics analyses in these reprogramming systems, across the different cell types. The assays include RNA-Seq (also single-cell RNA-Seq, in the organoids) for all systems, and various combinations of microRNA-Seq, DNA-methylation analysis, ATAC-Seq chromatin openness, and HiChIP for chromosome folding. We observe that across the systems, gene expression within the CNV boundaries follows copy number of genomic sequence, while outside of the CNV, and genome-wide, there is widespread, and cell type specific, alteration of gene expression patterns. Across the other functional genomics data modalities, we observe again genome-wide and cell-type specific epigenomic reprogramming. Pathway analyses make it possible to observe disease relevant effects, e.g. on synapse formation and function, while integrative analysis across the functional genomics modalities are beginning to reveal how, on the molecular level, epigenomic levels of control are affected by the presence of the 22q11.2 deletion and in turn mediate these effects towards distal interacting factors across the genome.

099: Generation and Characterization of Human Induced Pluripotent Stem Cell Derived Neuronal Models from Patients with Microdeletion Syndrome and Microduplication Syndrome 22q11.2

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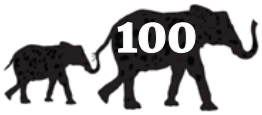
Background: Microdeletion syndrome and microduplication syndrome 22q11.2 are high-risk syndromes for the development of mental morbidity. In the case of deletion, the lifetime prevalence of psychotic disorders is up to 30% (Schneider et al., 2014). Compared to the general population, both syndromes are associated with a significantly increased risk of autism spectrum disorders, affective disorders, ADHD and anxiety disorders (Olsen et al., 2018). Induced pluripotent stem cells are cells reprogrammed from adult somatic cells by transferring transcription factors, from which early development can be modeled in vitro by differentiation, for example into cortical neurons (reviewed in McNeill et al., 2020). **Methods:** We reprogrammed human induced pluripotent stem cells from fibroblasts of 3 patients with microduplication syndrome and 2 patients with microdeletion syndrome by Sendai virus-mediated transfer of the Yamanaka transcription factors c-Myc, Klf-4, Oct-4 and Sox-2. We next differentiated them into neuronal progenitor cells and cortical neurons. **Results:** We demonstrate the presence of bona fide human pluripotent induced stem cells. Two clones each were generated from fibroblasts of 3 patients with microduplication syndrome and 2 patient with microdeletion syndrome. Our cell lines show morphology typical for human pluripotent induced stem cells, expression of pluripotency markers and differentiation capacity into all three germ layers (mesoderm, ectoderm and endoderm). We successfully differentiated neuronal progenitor cells and compared proliferation to wildtype. We also showed correct differentiation into cortical neurons. **Conclusion:** We successfully generated bona fide human pluripotent induced stem cells and used them to generate a model of neuronal development in patients with 22q11.2 syndromes.



100: The 22q and You Center – A Model for Comprehensive Multidisciplinary Coordinated Care

T. Blaine Crowley[1,2], Victoria Giunta[1,2], Daniel E. McGinn[1,2], Bekah Wang[1,2], Audrey Green[1,2], Lydia Rockart[1,2], Oanh Tran[1,2], Ryan LaPointe[1,2], Conner Weinberg[1], Sam Alperin[1,3,4], Sarah Hopkins[1,3,4], Madeline Chadehumbe[5], Vaneeta Bamba[1,3,6], Lorraine Katz[1,3,6], Katherine Baum[7], Ed Moss[7], Malcolm Ecker[1,8,9], John Flynn[1,8,9], Lisa Elden[1,9,10], Steven Handler[1,9,10], Brian Forbes[1,9,11], Elizabeth Goldmuntz[1,3,12], Oksana Jackson[1,9,13], Cynthia Solot[1,14], Thomas Kolon[1,9,15], Asim Maqbool[1,3,16], Maria Mascarenhas[1,3,16], Michael Nance[1,9,17], Kathleen Sullivan[1,3,18], Beverly S. Emanuel[1,2,3], Ian Campbell[1,2,3], Elaine H. Zackai[1,2,3], and Donna M. McDonald-McGinn[1,2,3,19]

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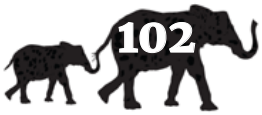
Background: 22q11.2DS is identified in 1/992 pregnancies, 1/1497 miscarriages, and 1/2148 livebirths. Most deletions are *de novo*. Conversely, 22q11.2DupS, reported in 1/850 pregnancies, is often familial. Both have significant morbidity and some mortality, with wide inter and intrafamilial variability. With a 1/2000 prevalence, ~326,000 Americans should be affected. Therefore, we should consider how we will deliver comprehensive multidisciplinary coordinated care once detection is improved. Here we provide guidance based on our 22q and You Center experience. **Methods:** We evaluated 1,893 patients between 1992-2024, including 1,667 with 22q11.2DS, 226 with 22q11.2DupS, and 89 with distal deletions or duplications. **Results:** Examining our 22q11.2DS and 22q11.2 DupS cohorts, 50% and 54% were male respectively, currently aged 0-77 years with a mean of 19 years. Most patients had standard LCR22A-LCR22D CNV's but 22 had CNVs not mediated by LCRs. 61% resided within 100 miles of CHOP and 2% traveled internationally. Centralized coordinated care occurred for local and out-of-town families alike, considering previous evaluations/imaging/laboratory studies, subspecialists availability across up to 35 disciplines, a single blood draw at the conclusion of visits, and sedated procedures arranged independent of neuro-cognitive/developmental/behavioral assessments. Unlike cleft/craniofacial clinic models, given the number of evaluations, assessments were coordinated over several days rather than on a single day. In total, our Center accounted for ~3,500 annual visits with 248,052 encounters completed since 2001, when EHR data was available for analysis, including 82,949 visits of which 67,250 were subspecialty appointments and 3,019 were surgical procedures. Visits were associated with 46,782 unique diagnoses including ~25/patient, with GERD being the most common indicator followed by language and developmental delay. Top visit box scores included Cardiology (14,997), Craniofacial (14,856), and Gastroenterology (5,706). Importantly, families valued the coordination. **Conclusions:** Recognizing the need for sufficient evaluation time and centralized organization, we will share our Center's model for coordinated care.

101: Characterizing the Spectrum of Clinical Manifestations in 22q11.2 Duplication Syndrome: Insights from an Institutional Experience *

Gail Budhu, MD[1]; Kristen Facey, MD[1]; Raghuram Reddy[2], BS; Karla Santoyo[2], BS; Raul Escobar[3], MD; Brian Cauff[4], MD; Hanadys Ale, MD[5]

[1]Pediatric Residency Program, Joe DiMaggio Children's Hospital, Memorial Healthcare System; [2]Florida International University Herbert Wertheim College of Medicine; [3]Hospital Universitario Clínico Quirúrjico Manuel Fajardo; [4]Center for Cancer and Blood Disorders, Joe DiMaggio Children's Hospital; [5]Division of Immunology, Allergy and Rheumatology, Joe DiMaggio Children's Hospital, Memorial Healthcare System.

Background: Duplication of chromosome 22q11.2 is a genetic syndrome associated with a spectrum of clinical manifestations. While there is some overlap with the more widely recognized 22q11.2 deletion syndrome, the duplication variant presents unique diagnostic challenges due to oftentimes subtler manifestations. Further characterization of this syndrome is therefore imperative for timely identification and intervention. **Methods:** A retrospective analysis of patient records from Joe DiMaggio Children's Hospital (USA) with genetically confirmed 22q11.2 duplication was performed. Data on clinical history and laboratory results was compiled, aiming to identify shared patterns and trends. **Results:** A cohort of 14 patients, 8 females and 6 males, of various ethnicities and ages was assessed. Most prevalent among them were developmental delays/learning difficulties, affecting 85.7% of the group. Dysmorphic features of varying severity were observed in 78.6%. Cardiac anomalies were present in 50% of the cases. Feeding challenges in infancy occurred in 50% of cases. Recurrent infections were noted in 42.9%, with a minority (14.3%) experiencing severe infections, despite immunoglobulins being within normal ranges. Of 7 patients evaluated for vaccine responsiveness, 71.4% showed inadequate responses. The disease appeared sporadically in families, with the exception in a family with 2 siblings who both had the typical and an atypical locus on chromosome 22 affected, a novel observation not previously reported. The siblings exhibited profound developmental and learning impairments. **Conclusions:** Our cohort highlights a broad spectrum of clinical manifestations in 22q11.2 duplication syndrome, underscoring need for a high index of suspicion when patients present with some of the predominant characteristics, together or in isolation. Genetic testing has emerged as a key modality that has facilitated identification of these patients in our community. A multidisciplinary clinic has since been established at our institution to address these patients' needs which often extend beyond the scope of a primary care provider.



102: Clinical Review of a Large 22q11.2 Cohort at a Tertiary Centre *

Megan Dunlop, Alice Roueché, Julia Kenny
Evelina London Children's Hospital

Introduction: The 22q11.2 service at Evelina London Children's Hospital has been running in its current form since approximately 2015. Over this time, the clinic has had around 200 patients under its care at any one time, composed of children with both 22q11.2 deletion syndrome (22q11.2DS), and 22q duplication. The clinic is led by General Paediatrics and Immunology, has its own clinical nurse specialist, and works closely with the wider multidisciplinary team, including psychiatry. This is the first time a large review of this nature has been undertaken by the service. 22q11.2DS is a complex disorder with an incredibly variable phenotype and expressivity. The cohort at this centre provides a unique opportunity to explore the numerous clinical manifestations across a variety of organ systems.

Aims:

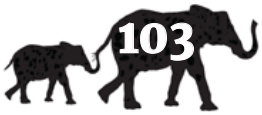
- To describe the cohort of patients under the 22q11.2DS specialist clinic at Evelina London Children's Hospital. This will include a particular focus on:
  - Immunity and vaccinations.
  - Educational support and child psychiatry.
  - Thrombocytopenia.
  - Prevalence of leg pain symptoms.
- To add to the current knowledge around 22q11.2DS.

Methods:

This is a review currently being undertaken of 194 active patients under the 22q11.2DS specialist clinic at Evelina London Children's Hospital in February 2024. Retrospective data analysis of these patients is being collected from Electronic Patient Records (EPR), superseded by EPIC. Information collected includes:

1) Deletion or duplication,
2) Age at diagnosis/ referral acceptance/ clinic appointments,
3) Lymphocyte sub-sets and immunoglobulins,
4) Vaccine response,
5) Platelet count,
6) Patient, family, or carer reported legs pains,
7) Education, Health and Care Plan (EHCP) status,
8) Diagnosis of Autism Spectrum Disorder (ASD) and/ or Attention Deficit Hyperactivity Disorder (ADHD).

Results: Full cohort analysis will be ready for presentation prior to the conference.



103: An Overview of 22q11.2 Diagnostic and Research Facilities in the Countries of The Western Balkan Region

Goran Cuturilo[1,2], Danijela Drakulic[3], Natasa Kovacevic-Grujicic[3], Mina Peric[3], Milena Stevanovic[3]

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Background: 22q11.2 deletion syndrome is the most common microdeletion disorder in humans, with the incidence of approximately 1 in 2000 newborns. The Balkan region is characterized by many social and language interconnections, intense people and services' flow, but also diversity of health systems. The aim of the study was to analyze current state of diagnostic and research programs in the Balkan region. Methods: A survey using 6-item-questionnaire was conducted among clinical/medical geneticists of university clinical centers in Bosnia and Herzegovina, Montenegro, Croatia and Serbia, and Macedonian Academy of Sciences and Arts in North Macedonia. Results: The study showed that all countries involved in the survey provide diagnostic testing for 22q11.2 CNVs either in domestic laboratories or by sending samples abroad. The survey's results range from not having domestic 22q11.2 diagnostic or research programs in Montenegro to having several domestic diagnostic centers in Serbia and Croatia. Regarding research activities, domestic and international research programs dedicated specifically to investigation of the 22q11.2 chromosomal region exist only in Serbia. **Conclusions**: This survey's results point to significant variations in 22q11.2 diagnostic and research facilities among Balkan countries. It seems that diagnostic services of the countries positively correlate not only with a size of population, but also with existence of well-established and long-term research programs. Additionally, diagnostic and research programs in Serbia seem to be successfully integrated with the local 22q11.2 patient organizations' activities.

104: Overview of 22q11.2 Deletion Syndrome: a First Moroccan Pediatric Series

Asmaa Gaadi[1], Said Trhanint[2], Laila Boughenouch[3], Karim Ouldim[3], Ahmed Aziz Bousfiha[1,4], Mouna Lehlimi[5]

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Background: The 22q11.2 deletion syndrome (22q11DS) is an autosomal dominant genetic syndrome, frequently due to a microdeletion located on chromosome 22, presenting a wide variety of clinical manifestations. Cytogenetic methods are used to identify chromosomal deletions specific to the 22q11 region. This study aimed to describe the first serie of pediatric patients in Morocco, selected for their strong suspicion of Digeorge syndrome. **Methods**: The inclusion criteria were the presence of at least two or three major symptoms, including facial dysmorphia, congenital heart disease, hypoplasia or aplasia thymia and/or hypocalcemia, and allowed the inclusion of 30 patients. To confirm 22q11DS, all patients in our series were diagnosed by fluorescence in situ hybridization (FISH), of which only 5 patients were also diagnosed by MLPA (multiplex ligation-dependent probe amplification). **Results**: 22 patients were confirmed. The majority exhibited facial dysmorphia, hypocalcemia (77%), thymic anomalies (50%), and various cardiac malformations (86%). Specific biological examinations revealed recurrent infections, hematological disorders, oral/dental issues, skeletal anomalies, and urological/gastrointestinal anomalies. Immune profile analysis in 14 cases indicated varied CD3, CD4, CD8, IgA, and IgG levels. The study provides comprehensive insights into the clinical and genetic aspects of 22q11DS. **Conclusion**: Advances in molecular cytogenetics have enabled precise detection of microdeletions associated with 22q11DS, highlighting its global importance, but also revealing regional diagnostic challenges. Studies with larger cohorts are emphasized to strengthen the validity of findings and improve clinical management approaches.

105: Establishing a Support Framework for Children with 22q11.2DS in School Settings in Japan

Simon Elderton[1], Chiaki Kitamura[2], Ai Muro[2], Yuma Chino[2], Hiroki Ishiguro[3], Yasue Horiuchi[4], Nobuhiko Hayashi[5,6], Satoko Nakagomi[7]

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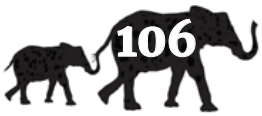
Background: Awareness and early diagnosis of 22q11.2DS are increasing in Japan, due to genetic testing protocols for newborns with congenital heart disease, thymic hypoplasia, or hypocalcemia (Nakagomi et al., 2021). A phased approach including early engagement with counselors and psychiatrists throughout childhood to adulthood, and interactions with educators at entry into elementary, middle, and high school can help remediate cognitive deficits and adaptive functioning (Óskarsdóttir et al., 2023). Teachers play a crucial role in understanding and supporting the diverse needs and characteristics of children with 22q11.2DS during their school years. However, lack of awareness is a barrier to the provision of tailored education according to individual characteristics and strengths. **Methods:** We have established a multidisciplinary team comprising individuals from various professions such as nurses, educators, certified genetic counselors, genetics specialists, psychiatrists, clinical psychologists, speech therapists, and university faculty to provide a support framework for children with 22q11.2 DS in school settings. **Results:** Our team holds social gatherings for children with 22q11.2DS and their families which include workshops conducted by psychiatrists, clinical psychologists, and speech therapists focusing on support for individuals with 22q11.2DS. Families can be directed towards further appropriate support services such as genetic counseling, or consultations with psychiatrists. We have developed a support guide booklet aimed at helping school teachers of children with 22q11.2DS in their understanding of the disorder and supporting known effective educational practices. Members of our support team visit the school with the parents and use these guides to explain the child's condition, strengths and weaknesses. **Conclusions:** Involvement of healthcare professionals alongside educators in school settings facilitates appropriate evaluation of the abilities and characteristics of children with 22q11.2DS. Tailored support at school leads to experiences of recognition of success and participation in school life which bolsters children's confidence, social skills, and subsequent adaptive ability.



106: No-Show Clinic Appointments and The Social Determinants of Health in Pediatric Patients with 22q11.2 Deletion Syndrome and 22q Duplication Syndrome

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Background: 22q11.2 deletion syndrome (22q11.2DS) and 22q duplication syndrome present a wide range of medical challenges. The health and well-being of pediatric patients with 22q11.2DS may be influenced by socioeconomic factors, which can significantly shape their healthcare experiences, access to services, and overall quality of life. The objective of this study is to identify what factors are correlated with no-show clinic visits for children with 22q11.2DS. **Methods:** Retrospective chart review was completed for pediatric patients in a 22q center's registry. Genetic diagnosis, demographic data, appointment attendance, comorbidities, and patient specific outcomes were collected. The patient's home address was cross-referenced with the GeoMarker database to define corresponding socioeconomic contextual variables. **Results:** 236 patients were included in the study including 198 patients (83.9%) with 22q11.2DS and 38 patients (16.1%) with 22q duplication syndrome. Collectively, these patients were scheduled for a total of 9,734 hospital clinic visits and 2,347 visits with the institution's 22q multidisciplinary clinic. The overall mean rate of no-show clinic visits was 7.69% ± 10.90. Factors associated with clinic no-show included lower median household income (OR (95% CI) 1.43 (1.25-1.64), $p < .001$), lower fraction of population with high school diploma (OR (95% CI) 2.33 2.04-2.67), higher fraction of population below the poverty line (OR (95% CI) 1.52 (1.32-1.73), $p < .001$), and higher fraction of population that required assisted income (OR (95% CI) 1.38 (1.21-1.58), $p < .001$). Interestingly, farther distance from the hospital was associated with lower no-show rate (OR (95% CI) 0.71 (0.60-0.85), $p < .001$). **Conclusions:** These findings highlight the potential influence of socioeconomic factors on no-show clinic appointments in pediatric patients with 22q11.2DS and 22q duplication syndrome. These factors can be used to help identify patients at risk of no-show clinic appointments and be used to develop targeted interventions aimed at improving clinic attendance and ultimately elevating patient outcomes.

107: Parent Acceptability of a 22q Multidisciplinary Infant Assessment Clinic to Assess Motor and Cognition in Infants with 22q *

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Background: Children with 22q are at an increased risk for neurodevelopmental delays in cognitive, gross/fine and neuromotor difficulties. These developmental areas are often not assessed early enough to allow for infants with 22q to benefit from early intervention services (EI). We will describe the development of a multidisciplinary 22q infant assessment clinic to assess motor and cognition in infants with 22q and describe parent acceptability of this clinic model. *Methods:* Parents of infants (0-12months) are referred to the 22q infant assessment clinic for concerns with developmental delays. They participate in a 2-hour assessment with a psychologist and occupational therapist using the Bayley Scales of Infant Development, 4th Edition (BSID) to assess cognition and fine and gross motor skills. Parents receive test results, actionable recommendations to support their child's development, and psychoeducation and information of how to establish EI services. Parents complete a survey following their clinic appointment asking about their level of satisfaction, feasibility, and usability of recommendations. *Results: 13 parent-infant dyads have participated in the multidisciplinary 22q infant assessment clinic (M_{age} = 11 months; range 7 – 15 months). 92% of children had a 22q deletion and were in a primarily English-speaking household. 62% of infants were receiving EI services at the time of the assessment. We recommended establishing or continuing with EI services for 92% of infants evaluated. Qualitatively, parents shared having a positive* experience participating in the developmental assessment clinic and in receiving guidance and direction about their infant's development. *Challenges included establishing care coordination between EI service providers and assessment team and coordinating billing between providers. Conclusions:* Few 22q centers have an established assessment clinic to identify early neurodevelopmental risks in infants with 22q. This abstract will describe a multidisciplinary 22q infant assessment clinic to identify early neurodevelopmental risks and to support families in establishing EI services to promote positive neurodevelopmental outcomes. We will discuss future directions for extending assessments to 12–24-month-olds and incorporating a speech-language pathologist.

108: Animation Genetic Counselling Aid for Adults with 22q11.2DS and their Caregivers

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Background: To our knowledge there are no genetic counselling aids for adults with 22q11.2DS. We aimed to develop an aid to facilitate genetic counselling that would be attractive, informative, and comprehensible to adults with 22q11.2DS. **Methods:** Together with a graduate student in Biomedical Communications at the University of Toronto, we developed an animation to aid in genetic counselling of adults with 22q11.2 deletion syndrome (22q11.2DS). The process involved discussing the needs of adult patients with 22q11.2DS, developing a formal needs assessment survey, deciding on the medium, then developing and modifying a narrative script and respective animation. An experienced biomedical communications professor supervised the technical components. **Results:** After informing the student and Biomedical Communications supervisor about 22q11.2DS and our aims, we provided opinions about what would form a most appropriate visual aid for adults with 22q11.2DS. These included the necessity and desire for the aid to be attractive, adult and intellectual level-appropriate (e.g., grade 6 level language), concrete, accurate to get major points across, and brief. Feedback from patients and caregivers concurred, suggesting a brief (e.g., 3-5 minutes) video, and further value if this could also help educate an extended community, including family and friends, and include the need for guidance in behavioural/functioning areas. An extensive iterative process, involving our entire clinic staff, ensued to develop and modify a narrative script, and draft a storyboard and the subsequent animation. Patients and caregivers provided feedback at a beta-testing stage. The final genetic counselling animation video (4 minutes, 32 seconds) focuses on background about 22q11.2DS and associated microdeletion, health affects, and management principles. **Conclusions:** While not meant to be a substitute for in-person genetic counselling, the animation video created may be a helpful adjunct. We are in the process of assessing its accessibility, likeability and utility in the clinical setting.

109: Neurobiological Insights from Human Cellular Models of the 22q11 DS

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The 22q11.2 deletion (22q11.2del) confers significant risk of developing schizophrenia (SCZ), intellectual disability, autism, and many other neuropsychiatric and medical conditions. The 22q11.2del is SCZ's most statistically significant genetic association, yet its extraordinary developmental, medical, and psychiatric outcome heterogeneity is not well understood. As a result, the pathways through which it contributes to SCZ, and broader neuropsychiatric risk remain unclear. We studied gene expression changes imposed by 22q11.2del using induced pluripotent stem cell (iPSC) lines from a case control cohort of 50 control and 22q11.2del samples, along with isogenic lines with 22q11.2del. We found that 22q11.2del significantly altered the expression of many genes with established genetic associations with neurodevelopmental disorders and SCZ. In neural progenitor cells, we found the deletion altered the abundance of transcripts associated with risk for autism, and in more differentiated excitatory neurons, transcripts encoding presynaptic factors associated with genetic risk for SCZ. To identify morphological signatures associated with the deletion in different cell types, we developed "NeuroPainting", an adaptation of Cell Painting, a high-content imaging assay, tailored to neural cells, and applied it to our 22q11.2del case-control cohort. We used high resolution imaging data to quantify cellular traits in stem cells, neuronal progenitors, excitatory neurons, and astrocytes derived from our cohort. Finally, we developed a fully human neuron-astrocyte co-culture system and used it to interrogate synaptic phenotypes linked to 22q11.2 deletion. Overall, we hope that our multi-modal analyses of neural phenotypes linked to 22q11.2del will facilitate the identification of genetic or pharmacological manipulations that can reverse the cellular defects.

110: A Report from the International 22q11.2 Brain and Behavior Consortium (IBBC) and Genes 2 Mental Health Network (G2MH)

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Background: Progress in advancing the understanding and care of individuals with rare neurogenetic conditions builds upon global collaborations of investigators, research teams, affected persons, and their families. Such ongoing efforts, exemplified in the Biennial International 22q11.2 Meeting, enabled the formation of the International 22q11.2 Brain and Behavior Consortium (IBBC) that successfully obtained funding from the National Institute of Mental Health (NIMH). As NIMH expanded the research to include additional copy number variants (CNVs), IBBC members contributed to the formation of the Genes to Mental Health Network (G2MH), adding to the previously collected samples and phenotypic and genomic data from patients with 22q11.2DS, while expanding to include the 22q11.2DupS, 16p11.2DS and 16p11.2DupS. This presentation will highlight the major goals of these projects, the process of establishing procedures, monitoring data collection, data analyses, reporting requirements, and the challenges and rewards in our efforts to make a difference that will improve the lives of individuals and families affected by CNVs. **Methods:** The IBBC represented 22 clinical and 5 genomic sites across 5 continents collaboratively responding to a request for application (RFA) from NIMH where we delineated our goals and planned our analytic approach. G2MH was also a response to an RFA, ultimately integrated into three existing projects forming a CNV network. **Results:** The large sample of individuals with 22q11.2DS in the IBBC's five-year project provided a rich dataset for examining neuropsychiatric, cognitive, and genomic findings. In the G2MH project, which is still ongoing, we established a prospective phenotypic dataset across multiple CNVs with quality control and genomic and phenomic analyses underway. **Conclusions:** Global collaborative efforts, in partnership with patients and families impacted by CNVs, particularly 22q11.2DS, create critical opportunities to examine developmental trajectories, contribute to our understanding of risk and resilience factors, develop novel therapeutics, and ultimately improve function while facilitating genomic discoveries.

111: CNVs Elucidate Rare-Variant Associations and Genotype-Phenotype Relationships across 6 Major Psychiatric Disorders

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Background: Rare variants are a key component of the genetic basis of psychiatric disorders. Much of the evidence is from studies of rare copy number variants (CNVs). However, the risk loci are unknown for most disorders; and for those that are known, the relationship of genotype to phenotype is unclear. **Methods:** To characterize rare genetic influences on mental health, we performed analysis of CNVs in 6 psychiatric disorders from large GWAS datasets on autism (ASD), ADHD, schizophrenia (SCZ), post-traumatic stress disorder (PTSD), major depression (MDD) and bipolar disorder (BD) (N = 537,466). **Results:** Analysis of CNV burden and genome-wide association demonstrated that rare variants contribute in all disorders, with relative effect sizes that were proportional to estimates of twin/SNP-based heritability. We identified 36 genome-wide significant associations at 18 loci, including novel associations in SCZ (*SMYD3*), MDD (Del16p13.11 and *IMMP2L*) and the combined cross-disorder (XD) cohort (*ASTN2*, *DLG2*). Despite highly overlapping etiologies of psychiatric disorders, rare CNVs show distinct genotype-phenotype relationships with psychiatric diagnosis. Salient examples include reciprocal deletion and duplication that have positive and negative associations with SCZ (22q11.2) or alleles that show opposing associations with SCZ and BD (Del15q11.2 and Dup16p13.11) or MDD (Dup22q11.2). **Conclusions:** These results expand our knowledge of the rare genetic influences on psychiatric traits. Opposing associations of multiple variants with psychosis and mood disorders suggest that, for some molecular pathways, (susceptibility to) different disorders may lie at opposite extremes of gene function

112: The Clinical Course of Individuals with 22q11.2 Deletion Syndrome Converting to Psychotic Disorders: A Long-Term Multi-Center Retrospective Follow-Up

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Background: This retrospective study aims to investigate the evolution and clinical course of psychotic disorders from three large international cohorts of individuals with 22q11.2 deletion syndrome (22q11.2DS) (Tel Aviv, Philadelphia, and Geneva). **Methods***:* We followed 118 individuals with 22q11.2DS and comorbid psychotic disorders from years prior to years following the onset of psychotic disorders. Data from structured baseline assessment of psychiatric disorders, symptoms of prodrome, indicators and types of psychotic disorders were collected. Additionally, cognitive evaluation was conducted using the age-appropriate Wechsler Intelligence Scale. Electronic medical records were reviewed for medication usage, occupational status, living situation, and psychiatric hospitalizations. **Results:** At baseline evaluation, the most common psychiatric disorders were anxiety disorder (80%) and attention/deficit hyperactivity disorder (33%). The age of onset of prodromal symptoms and conversion to psychotic disorders were 17.8 ± 2.1 and 20.4 ± 1.8, respectively. The most common prodromal symptoms were exacerbation of anxiety symptoms and social isolation. Of the psychotic disorders, schizophrenia/schizoaffective disorders occur in 61%. History of at least one psychiatric hospitalization was present in 43% of participants, and the number of psychiatric hospitalizations was 2.3 ± 0.8. Compared to the normalized chart, IQ scores in our cohort were lower after vs. before conversion to psychosis. Following conversion there was a decrease in the use of stimulants and antidepressants and an increase in antipsychotics use, and most individuals with 22q11.2DS were unemployed and lived with their parents. **Conclusions:** Here we present for the first-time data on hospitalizations, treatment and functioning of individuals with 22q11.2DS and psychotic disorders from three large centers. Our results indicate that 22q11.2DS psychosis is like non-22q11.2DS in its course, symptoms, and cognitive and functional impairments.

113: The Core PsychoPathology Summary (C2PS): A Novel Tool to Harmonize Large Scale Neuropsychiatric Phenotype Collection for Genomic Studies

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Objective*:* Large cohorts are required for genetic studies of neuropsychiatric traits. Reliable, yet pragmatic phenotype harmonization procedures can enable meaningful analysis of data from multinational collaborations, furthering the study of psychopathology in individuals with rare genetic disorders. **Methods***:* We developed the Core PsychoPathology Summary (C2PS) to facilitate harmonization of neuropsychiatric data across studies and sites for the purpose of downstream genetic analyses. The C2PS has been employed across 14 institutions and 7 countries, participating in the National Institute of Mental Health funded Genes to Mental Health (G2MH) Network. Here, we describe the development and structure of the C2PS and its inter-rater reliability. **Results***:* Ten core neuropsychiatric/developmental domains were agreed upon by network investigators. Investigators complete the C2PS by specifying lifetime presence or absence of a diagnosis, subthreshold trait-level symptomatology, and source of diagnosis/phenotype (e.g., standardized assessment, surveys) by domain. Inter-rater reliability (seven case vignettes describing individuals with deletions or duplications of genomic regions 16p11.2 or 22q11.2, each scored by six investigator raters from four different countries) indicated fair to excellent agreement across most domains (Light's Kappa: psychotic disorders: 1 (0.86 to 1.0); bipolar disorder: 0.76 (0.62 to 0.89); depressive symptoms: 0.83 (0.70 to 0.97); obsessive compulsive traits: 0.60 (0.47 to 0.72); anxiety symptoms: 0.58 (0.47 to 0.68); attention-deficit/hyperactivity disorder: 0.73 (0.60 to 0.87); oppositional 0.48 (0.30 to 0.61) and defiant 0.52 (0.35 to 0.66) behaviours; autism spectrum disorders: 0.85 (0.71 to 0.99); learning disability: 0.76 (0.65 to 0.85); intellectual disability: 0.69 (0.56 to 0.83). **Conclusion***:* Our initial experience and empirical data indicate that the C2PS presents a pragmatic and reliable way of harmonizing heterogeneous phenotypic data, and as such contribute to the multi-site collection of much needed observations in individuals with rare variants associated with neuropsychiatric phenotypes.

114: Neuropsychiatric Presentation in de novo and Inherited 22q11.2 Deletion Syndrome

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Background: The 22q11.2 deletion commonly occurs as a *de novo* event, yet in about 7-10% of impacted individuals the deletion is inherited from an affected parent, with maternally inherited deletions apparently more deleterious on IQ. The burden of this multi-system genetic condition on families with two members affected is significant. The role of multifaceted environmental exposures as contributory to neuropsychiatric presentation in the general population has been increasingly recognized, with intergenerational effects, adversity, and neighborhood mediating clinical presentation and course. Here we evaluate the presentation and course of well phenotyped groups with *de novo* and inherited 22q11.2 deletions with a comprehensive neuropsychiatric and neurocognitive assessment. **Methods:** The sample included 70 individuals with 22q11.2 deletion from the "22q and You" Center: *de novo* (N=35) and inherited (N=35). Probands in the two groups were demographically matched: Mean age (SD) 16.3 (7.30) and 16.5 (7.63); 16 females per group (45.5%) and 10 males (54.3%); race – White (62.9%, 60%), Black (31.4% per group), Other (5.7%, 7.1%). The standardized psychiatric evaluation and Penn Computerized Neurocognitive Battery (CNB) were completed for all participants. **Results:** There were no overall differences between the groups on either accuracy or speed, except for working memory accuracy, where those with inherited deletions performed more poorly than those with *de novo* deletions ($p < 0.05$). Psychiatric comorbidity was similar in the two groups. The effects of maternal compared to paternal transmissions will be examined. **Conclusions:** The effects of 22q11.2 deletion on neurocognitive functioning is overall similar in those who inherited the deletion compared to *de novo* deletions, except for working memory where those with inherited deletions performed more poorly. No differences were seen in psychiatric comorbidity rates. Larger samples are needed to replicate this finding and compare potential maternal to paternal transmission effects.

115: Integrative health and 22q11.2 Copy Number Variants: Results of a Patient-Family Survey *

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Background: Individuals with chromosome 22q11.2 copy number variants (CNV) may have difficulty managing associated conditions, such as pain and anxiety, via medical interventions alone. Integrative health (IH) approaches offer additional support for symptom management. Here we explore existing IH knowledge to determine interest and barriers to accessing care. **Methods**: A REDCap survey was distributed to 820 families where at least one family member was affected by a 22q11.2CNV. **Results:** 82 respondents completed the entire survey, including 77 caretakers of an individual with a 22q11.2CNV and 5 individuals with a 22q11.2CNV. 70% reported knowledge of IH. Of individuals with a college or graduate school degree, 78.1% reported knowledge of IH and of individuals with at most a high school diploma, 27.8% reported knowledge of IH. 59.8% reported using an IH therapy, 89.8% of whom had a college or graduate degree. 64.6% sought IH therapies for more effective symptom management and 93.9% found IH therapies helpful. Respondents primarily sought IH therapy for stress (71.4%), relaxation (63.3%), and back pain (51%). Most helpful therapies included massage (53.1%), breathing techniques (44.9%), and chiropractic therapy (36.73%). Overall, 51.2% felt cost was a primary barrier to seeking complementary therapies, as well as being unsure of where to find a good provider (47.6%). **Conclusions**: This survey demonstrates that IH is considered a beneficial resource for individuals and families affected by 22q11.2CNVs in managing symptoms, particularly anxiety and pain. It is also clear that those with a higher level of education were more likely to be aware of IH and to seek IH therapies. To provide holistic care for our patients and families affected by 22q11.2CNVs, it behooves us to further explore such complementary therapies and to educate our families about the possible benefits of IH regardless of educational backgrounds, as well as to address the barriers to finding experienced, affordable providers.

116: Use of Auricular Acupressure for Symptom Control in a Child with 22q11.2 Deletion Syndrome

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Background: Disorders of gut-brain interaction (DGBI), e.g., irritable bowel syndrome, are related to impaired gut and brain communication via the nervous system. Acupuncture/acupressure, key components of traditional Chinese medicine can be used to treat health problems such as pain and nausea. Little is known about employing integrative therapies (IT) in patients with 22q11.DS. **Methods:** Here we report outcomes in an 11-year-old boy with 22q11.2DS and DGBI using IT. **Results:** The patient presented in infancy with club feet, laryngeal web, and dysphagia leading to the diagnosis of a standard 22q11.2 LCR22A-LCR22D deletion. During early childhood he had wheat, soy and oat allergies, constipation, GERD, and frequent infections, necessitating frequent antibiotics. At 8 years following his second foot surgery he reported disabling nausea, odynophagia, and abdominal pain. Normal studies included inflammatory markers, CBC, celiac panel, thyroid function tests, upper GI with small bowel follow, and glucose and lactulose breath tests for bacterial overgrowth (SIBO) x 2. Upper and lower endoscopy with esophageal biopsies were positive for fungal esophagitis (*Candida albicans/dubliniensis)*. Symptoms improved with fluconazole but ongoing abdominal pain and nausea remained resulting in a diagnosis of DGBI. Symptoms flared again one year later. Repeat upper endoscopy was negative for fungus. Over the two years rifaximin for SIBO had minimal benefit. Amitriptyline increased constipation. Psychological interventions were not helpful. Cyproheptadine and magnesium were partially effective. IT was initiated, specifically his mother was trained in placing and removing auricular acupressure seeds. Points used included Shen Men, tranquilizer, small intestine, stomach and sympathetic. Symptoms are currently well managed with cyproheptadine, magnesium, lactase enzymes, and auricular acupressure. He has not missed school since the addition of auricular seeds. **Conclusions:** We present positive outcomes in a child with DGBI and 22q11.2DS using IT, specifically auricular acupressure, which may be a useful approach to other patients with 22q11.2DS.

117: Evaluating The Impact of an Online Coaching Intervention for Parents of Children Diagnosed with the 22q11.2 Deletion Syndrome *

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Background: 22q11.2 deletion syndrome (22q11DS) affects 1 in 2,000 people and is associated with both psychological and physical challenges which may significantly impact the well-being of affected individuals and their families. Parents of children with 22q11DS often report strained familial relationships, financial burdens and struggles with their child's behaviour, which may result in poor parental mental health. Previous work suggests that parenting skills can mediate the relationship between parent mental health and the affected child's behavioural issues. Improving parenting skills and parent mental health could improve the child's behaviour. While psychological online interventions have proven effective for parents of children with other chronic illnesses, their efficacy for 22q11DS remains unknown. This pilot study aims to assess the impact of an online coaching intervention on the mental health and parenting skills of parents of children with 22q11DS. **Method:** The online intervention offers evidence-based strategies provided in 12 online modules. Parents work through the modules on their own and attend a weekly coached self-help group to facilitate further skill acquisition and successful implementation using problem-solving and role-playing techniques with 5-8 parents. Eligible participants with children aged 3-15 diagnosed with 22q11DS are randomized to receive either the online coaching intervention or services as usual. Parents rate their mental health using the Depression Anxiety & Stress Scale Short Form (DASS-21) and their parenting skills in the Parenting and Family Adjustment Scales (PAFAS) at three timepoints. The effect of the intervention on DASS-21 and PAFAS scores across time will be examined. **Conclusions:** If the results of this pilot study demonstrate that the intervention is effective in improving mental health and parenting skills, it could configure an accessible and cost-effective early intervention for families living with 22q1DS, and stipulate further validation on a larger scale.

118: Assessing the Dietary Impact of an Online Nutrition Program for Adults with 22q11.2 Deletion Syndrome

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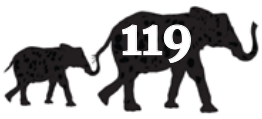
Background: Adults with 22q11.2 deletion syndrome (22q11.2DS) may be at higher risk of metabolic disorders such as dyslipidemia, elevated blood sugars and obesity, and would benefit from preventive measures such as a higher intake of fruits and vegetables, whole grains, and plant-based proteins. However, barriers to healthy eating such as impulsivity and low food literacy may make sustained behaviour change difficult for this population. An online group nutrition program with regular follow-ups could provide the structure to support this change. **Methods:** Over three rounds of the program, a total of 21 adults with 22q11.2DS attended online meetings comprising 7 sessions: 4 weekly gatherings, 2 monthly follow-ups, and a final follow-up 3 months after that. At each of the weekly sessions, participants received nutrition education and participated in a facilitated group discussion. Participants chose a goal meal to make and were instructed to take a picture of the meal to review the following week. We measured eating habits by comparing pictures of goal meals with Canada's Food Guide visual of a healthy plate. **Results:** The average attendance was 59% across the three rounds of the program. Of the 21 participants, 62% were female, and 62% had mild intellectual disability. A median of 91% of participants included fruits and vegetables, 88% included grains and 100% included proteins (animal and plant-based) in their meals, week by week. Qualitative feedback from participants identified increased social interaction as an unintended benefit of the program. **Conclusions:** A structured online nutrition group program can help improve understanding of participants' dietary intake. Increased social support was an unintended benefit of the program. Improving attendance was identified as an important area for future investigation. Implementing mechanisms to encourage dietary behavioural changes will have important implications for overall health and quality of life for adults with 22q11.2DS.



119: Maternal Diet as a Modifier of Congenital Heart Defects in 22q11.2 Deletion Syndrome

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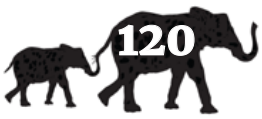
Conotruncal defects represent a subset of congenital heart defects (CHDs) that impact the outflow tract and ventricular septum. These defects occur in some, but not all, individuals with 22q11.2 deletion syndrome (22q11DS). Variability is likely due to the influence of unknown genetic and/or environmental modifiers. Identifying these modifiers and understanding how they interact with 22q11DS is a key question in the field. Maternal diet, an important environmental factor, can significantly influence CHDs. For instance, maternal consumption of too much or too little vitamin A can cause conotruncal defects. Depending on diet and supplement usage, pregnant women may ingest varying amounts of vitamin A, which the embryo must buffer to ensure proper cardiac development. We propose that these buffering mechanisms are defective in the developing 22q11DS embryo, resulting in increased sensitivity to vitamin A exposures. Retinoic acid is the biologically active metabolite of vitamin A and is produced in a gradient across the developing heart field. Formation of this precise gradient is critical for the proper specification and development of the cardiac progenitors and neural crest cells that contribute to the conotruncus. This gradient is established by regulated expression of retinoic acid synthesis and degradation enzymes that locally transform vitamin A into retinoic acid and is modulated by positive and negative feedback loops. Using a mouse model of 22q11DS, we found that the impaired ability of the embryo to rapidly engage negative feedback mechanisms to buffer slight increases in retinoic acid exposure may contribute to the variability in incidence and severity of conotruncal defects in 22q11DS. Thus, maternal diet may be an important modifier of CHDs in 22q11DS.



120: Tbx1 Haploinsufficiency Causes Brain Metabolic and Behavioral Anomalies in Adult Mice which are Corrected by Vitamin B12 Treatment

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Introduction: The brain-related phenotypes observed in 22q11.2 deletion syndrome (22q11.2DS) are highly variable and their origin is poorly understood. Changes in brain metabolism may cause or contribute to the phenotypes, given that many of the deleted genes (approx. 10%) are implicated in metabolic processes, but this is currently unknown. It is clearly important to address this knowledge gap, but in humans, the primary material required for studying brain metabolism is inaccessible. For this reason, we sought to address the issue using two mouse models of 22q11.2DS. **Methods:** We used three independent approaches to investigate brain metabolism in young adult mice, namely, mass spectrometry, nuclear magnetic resonance spectroscopy and transcriptomics. We selected to study primarily *Tbx1* single gene mutants because it is the primary candidate disease gene. We then confirmed key findings in the multi-gene deletion mutant *Df1/+*. **Results:** We found that *Tbx1* mutants have alterations of specific brain metabolites, including methylmalonic acid, which is highly brain-toxic, as well as a more general metabolomic imbalance. We provide transcriptomic evidence of an interaction genotype-vB12 treatment, and behavioural evidence of a response to vB12 treatment, which rescued some of the behavioural anomaly observed in *Tbx1* mutants. We conclude that *Tbx1* haploinsufficiency causes extensive brain metabolic anomalies, which are partially responsive to vB12 treatment. We suggest that alterations of glutamine-glutamate metabolism and fatty acid metabolism are key components of the metabolic phenotype in these mutants.

121: Exploring the Epigenetic Impact of Vitamin B12 Supplementation on Cardiac Phenotypes in a 22q11.2DS Mouse Model *

Llull-Albertí, M.V[1], Ventayol-Guirado, M[1], Amengual-Cladera, E[1], Hernández-Rodríguez, J[1,2], Merkel, A[6]; Asensio, VJ[1,2], Muncunill, J[3], Rocha, J[4], Torres-Juan, L[1,2], Santos-Simarro, F[1,2], Martínez, I[1,2], Baldini, A[5], Illingworth, E[7], Lania, G[5], Esteller, M[6], Heine-Suñer, D[1,2]

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Our study explored Vitamin B12's potential epigenetic impact on 22q11.2 deletion syndrome (22q11.2DS), following its success in reversing cardiac anomalies in a Tbx1 knockout mouse model. We extended this inquiry to the Df1/+ mouse, more closely resembling human 22q11.2DS due to its deletion of 1.2 Mb encompassing multiple genes. Both wild type (WT) and Df1/+ females received dietary Vitamin B12 supplementation for six weeks from weaning (VitB12 0.16mg/kg). They were subsequently mated with Df1/+ or WT males, and experimental groups were categorized based on embryo genotype and diet: WT and Df1/+ embryos without Aortic Arch Defects (AAD), and Df1/+ embryos with AAD from both WT and Df1/+ mothers fed either a Vitamin B12 supplemented or a control diet. Cardiac phenotypes were assessed at embryonic day 18.5, and genomic methylation analysis was conducted using DNA from embryonic hearts and placenta with Illumina Infinium Mouse Methylation BeadChip arrays. Contrary to expectations, Vitamin B12 supplementation did not reverse the cardiac phenotype observed in Tbx1/+ mice. Notably, Df1/+ mothers on a Vitamin B12-supplemented diet exhibited a 2.5-fold rise (66%) in AADs in their Df1/+ offspring compared to all other groups. Methylome analysis showed significant methylation changes exclusive to the group with higher AAD prevalence, with minimal differences among the remaining groups. Enrichment analysis revealed that differentially methylated genes were predominantly involved in pathways associated with aortic arch formation and development, including cell-matrix adhesion, blood vessel development, and morphogenesis. In summary, our study did not demonstrate a reversal of the cardiac phenotype through dietary Vitamin B12 supplementation in a 22q11DS mouse model. However, it highlighted the role of Vitamin B12 as an epigenetic modifier and revealed the influence of maternal genotype on the phenotypic manifestations and methylation patterns induced by Vitamin B12 supplementation, as well as differences in the phenotypic effects between the Df1/+ model and Tbx1/+ mice.

122: Changes in Dietary Vitamin A Dosage Disrupt Compensatory Mechanisms in the Cardiac Phenotype of a 22q11.2 Deletion Syndrome Mouse Model *

Llull-Albertí, M.V[1]; Amengual-Cladera, E1, Ventayol-Guirado, M[1]; Hernández-Rodríguez, J[1,2]; Asensio, VJ[1,2]; Muncunill, J;[3] Rocha, J[4]; Torres-Juan, L[1,2]; Santos-Simarro, F[1,2]; Martínez, I[1,2]; Baldini, A[5]; Illingworth, E[6]; Lania, G[5]; Heine-Suñer, D[1,2]

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The 22q11.2 deletion syndrome (22q11.2DS) exhibits considerable phenotypic variability. Mouse models of 22q11.2DS commonly manifest hypoplasia of the 4th Pharyngeal Arch Artery (PAA) at embryonic day E10.5, progressing to aortic arch defects (AAD) in later stages. Intriguingly, the incidence of PAA associated anomalies decreases between E10.5 and later fetal stages suggesting compensatory mechanisms leading to phenotypic recovery. Deficiency of retinoic acid (RA), a metabolite of vitamin A (VitA) has been shown to accelerate recovery from arterial growth delay in Tbx1+/- but not in 22q11.2 deletion mouse models (LgDel). Our study aimed to assess the impact of dietary VitA dosage changes on the incidence of great artery anomalies in the 22q11.2DS Df1 mouse model, aiming to identify potential therapies for the cardiac phenotype. Experimental groups consisted of Df1 and Wt mothers fed with a VitA-supplemented diet (200 IU vitamin A/Kg), control diet (20 IU vitamin A/Kg), and deficient diet (0 IU vitamin A/Kg) for 10 weeks. Subsequently, they were mated with males of opposite genotypes, and embryos were phenotyped and genotyped on gestational day E18.5.All experimental Df1/+ embryo groups exhibited an incidence of approximately 30% of embryos with AADs, except for two groups with 51% and 45% of embryos with AADs. The two groups with low recovery capacity (LRC) from PAA hypoplasia displayed different diets and maternal genotypes (Df1/+ embryos from WT mothers fed VitA-supplemented diet and Df1/+ embryos from Df1/+ mothers fed VitA-deficient diet). These results indicate that although no therapeutic effect was observed, dietary VitA doses interacting with the maternal genotype can disrupt compensatory mechanisms that reverse the cardiac phenotype. Through transcriptomic studies we identified 210 differentially expressed genes shared between the two LRCs, primarily involved in biological processes such as energy metabolism, angiogenesis, oxygen homeostasis, and epigenetic modifications of histones.

123: Real-World Treatment of Schizophrenia in Adults with a 22q11.2 Microdeletion

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Background: Individuals presenting at transition for adult care at a specialized 22q11.2 deletion syndrome (22q11.2DS) clinic may differ from those referred at later ages, and there may be secular trends in features over time. We hypothesized that congenital complexity would be greater, and ethnicity more diverse, in those referred at transition, and that secular trends, and ever younger age at molecular diagnosis, would be noticeable over time. **Methods:** Within our cohort of 450 well-characterized adults with a typical 22q11.2 microdeletion, we compared the subgroup initially seen in the "transition" period (≤21 years) with the group ≥22 years on variables including major congenital heart disease (CHD), schizophrenia, moderate to severe intellectual disability (ID), ethnicity, and age at molecular diagnosis of the 22q11.2 deletion. **Results:** The transition group (n=211) was comparable in size to those seen initially at older ages (n=239), with younger median current age of the transition group (25.3 y, range 17.4–47.8 y vs 41.1 y, range 21.8–76.3 y, $p<0.0001$). The transition group had a significantly greater proportion of individuals with major CHD (42.2% vs 27.2%, $p=0.0008$), and of non-European descent (53.6% vs 16.3%, $p<0.0001$), but no difference in proportion with ID. The transition group had a significantly lower proportion of individuals with schizophrenia (22.8% vs 37.7%, $p=0.0006$), with a significantly younger age at onset (18 vs 21 years, $p<0.0001$). There was no trend to younger age at molecular diagnosis within the transition group. There was however an increasing proportion with proximal nested 22q11.2 deletions over time. **Conclusions:** The findings suggest that a significant diagnostic odyssey remains for many patients, even amongst those recently transitioning to adult care. Secular trends need to be considered as these can affect ascertainment, and thus clinical practice and research. Opportunities for preventive care await greater awareness and implementation of standard genetic diagnostics.

124: Historical Perspective of the Role of Fasoracetam in Neurodevelopmental Disorders

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Background: Fasoracetam, a novel nootropic and a member of the racetam family of drugs, is garnering attention for its potential therapeutic applications in neurodevelopmental (ND) and neuropsychiatric (NP) disorders. This compound has been studied for its effects on certain neurodevelopmental conditions, including ADHD, autism, anxiety, and ND symptoms in 22q11.2 Deletion Syndrome (22qDS). **Methods:** Fasoracetam´s mechanism of action involves modulation of neurotransmitters in the brain, including metabotropic glutamatergic receptor (mGluR) signaling involved with learning, memory and attention, the GABA(B) receptors involved with anxiety and emotional regulation, and the cholinergic system, which plays critical roles in cognitive processes, all domains that are affected in patients with 22qDS and related NDs. **Results:** In clinical trials, fasoracetam showed promise improving symptoms of ADHD in children with comorbid ND symptoms, demonstrating significant improvement in the Clinical Global Impression Improvement scale and sub-scales (Elia et al, *Nat Comm*, 2018; P<0.001), supporting fasoracetam as treatment option for patients with ND, including those who are non-responsive or intolerant to other medications given fasoracetam´s favorable side effect profile. Its effects on enhancing attention and reducing impulsivity underscore its relevance in managing ADHD's core symptoms. Fasoracetam also improved social behavior and communication skills in ASD, with anxiolytic effects reported by some parents as being transformative for their children. **Conclusions:** The genetic and neurobiological complexities of 22qDS, a condition marked by a wide range of psychiatric and developmental issues, pose significant treatment challenges, where fasoracetam´s neuroprotective properties and its ability to rectify dysregulated neurotransmitter signaling suggest a potential therapeutic avenue worth exploring for individuals with 22qDS. This is supported by a recent clinical trial in patients with 22qDS – as presented separately at this meeting. Collectively, fasoracetam offers a multi-faceted approach addressing the intricate web of ND and NP disorders, highlighting the importance of innovative pharmacological interventions in improving patient outcomes.

125: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial of Nb-001 (Fasoracetam) for Neuropsychiatric Symptoms in Children and Adolescents with 22q11 Deletion Syndrome (22q11DS)

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Objective: This Phase 2 trial was designed to evaluate the safety and efficacy of NB-001 (fasoracetam), a non-stimulant mGluR activator, as a novel treatment for non-psychotic psychiatric symptoms of 22q11DS. **Methods:** Eligible subjects included children and adolescents (ages 6-17) with 22q11DS, a CGI-S score ≥4 (scale of 1-7), and psychiatric symptoms of anxiety and/or ADHD-inattention and/or ASD. Subjects with a history/current symptoms of psychosis were excluded. Endpoints were safety/tolerability (primary), and improvement on CGI-I per central rater and targeted symptom improvement per PARS, ADHD-RS-5, and SRS-2 scales (secondary). Mixed-effect models were used to examine CGI-I with NB-001 vs placebo at 6 weeks. **Results:** 37 participants were randomized; 32 completed the trial. Median age was 12 years (range, 6–17), 67% were male. Overall, 35 subjects had full length 22q11DS A-D deletions and 2 had partial deletions. NB-001 was well tolerated; all adverse events (AEs) were mild/moderate (54.5% during treatment vs 70.6% during placebo), with no treatment-related severe or serious events. Only one subject discontinued from the trial due to an AE (insomnia while on placebo). For the full analysis set (N=33), CGI-I per central rater showed improvement with NB-001 vs placebo with least squares mean (SE) at Day 42 for the treatment group of 3.31 (0.16) vs 3.68 (0.16) for the placebo group (delta = -0.37 (0.20), p=0.07). Subgroup analyses showed improvement in CGI-I for subjects with subclinical/clinical ADHD (p=0.03), anxiety (p=0.07) and autistic traits (p=0.09). CGI-I responders (defined as very much, much, or minimally improved) at Day 42 were 61% for the treatment group vs 39% for the placebo group (p=0.071). **Conclusion:** NB-001 was safe, well tolerated, and had clear clinical efficacy trends for the predominant psychiatric symptoms associated with 22q11DS in pediatrics. These promising results support further evaluation in a more robustly powered Phase 3 setting.

126: Riluzole as Cognitive Enhancer in 22q11.2 Deletion Syndrome?

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Background: 22q11.2 deletion syndrome (22q11.2DS) is associated with an increased risk of developing psychotic disorders, and cognitive dysfunction. Genetically mediated alterations in glutamate and GABA function, and consequential disruption of neural excitation/inhibition balance, are implicated in the occurrence of psychiatric and cognitive symptoms in 22q11.2DS. In this study we examined the effects of riluzole, a glutamate/GABA modulating compound, on psychiatric symptoms and cognitive functioning. **Methods:** This study had a placebo-controlled, partially blinded fixed order cross-over design. At time of writing, 14 participants (4 male, 10 female) completed the study (mean age 25 years). All participants received 8-week treatment with placebo and 8-weeks of oral riluzole treatment (100 mg daily). Cognition was assessed with the computerized neurocognitive battery (CNB). Additionally, glutamate and GABA levels in the anterior cingulate cortex (ACC) were measured using ^{1}H-MRS. **Results:** We did not find significant effects of riluzole on psychotic symptom severity, anxiety, or social functioning in 22q11.2DS. We found a significant effect of condition on depression severity (BDI scores, p=0.041). Post-hoc analyses revealed a significant decrease in depression symptoms between baseline and placebo (p=0.010). No significant differences were found between baseline and riluzole (p=0.698) and placebo and riluzole conditions (p=0.85). We also found significant differences between treatment conditions on a sensorimotor task (p=0.012, η^2=.325). Post-hoc analyses demonstrated that riluzole significantly decreased reaction time compared to baseline (p=0.013) and placebo (p=0.007). Additionally, compared to baseline, riluzole decreased reaction time on a test for emotion differentiation (p=0.008) and visual memory (p=0.014). Riluzole did not significantly alter ACC glutamate (p= 0.98) and GABA (p=0.23) concentrations. **Conclusion**: The current results suggest that riluzole may improve sensorimotor abilities and speed of processing in 22q11.2DS subjects. However, these results should be considered preliminary due to the small sample size. Final conclusions are pending ongoing data collection.

127: TANGO2: What's it to You?

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Background: The chromosome 22q11.2 deletion syndrome (22q11.2DS) is associated with significant morbidity and some mortality, with wide inter and intrafamilial variability. We previously reported patients with atypical features due to dual diagnoses related to a deletion one chromosome 22q11.2 and a variant on the remaining non-deleted chromosome 22 allele, unmasking autosomal recessive conditions, including Bernard-Soulier due to mutations in *GP1BB*, CEDNIK syndrome due to variants in *SNAP29*, Autosomal Recessive Noonan syndrome due to variants in *LZTR1*, and CGS syndrome (also known as Meier-Gorlin syndrome) due to mutations in *CDC45*. Other such conditions include proline dehydrogenase deficiency (*PRODH*), van den Edne Gupta syndrome (*SCARF1*), and *TANGO2* related disease (*TANGO2*). *TANGO2* related disease is an autosomal recessive mitochondrially mediated condition associated with dystonia, hypoglycemia, thyroid disease, rhabdomyolysis, metabolic crises, hearing loss, developmental delay, arrhythmia, and sudden death. Here we report the association of 22q11.2 deletion syndrome and variants in *TANGO2* on the intact allele. **Methods:** We identified a *TANGO2* variant in a single patient with 22q11.2DS in 2018, following his sudden death in 2015 prior to the description of *TANGO2* related disease in 2016. We subsequently identified variants in additional patients due to clinical suspicion or as part of whole genome sequencing on a research basis. **Results:** Eight patients were identified in total, 6 in Philadelphia and 2 in Leuven. Genomic studies were performed in Warsaw. Two patients had deletions in Exons 3-9, 3 had variants resulting in premature stop codons, and 3 had missense mutations. Those with deletions including *TANGO2* on the intact allele had the most significant findings. Some patients exhibited no related features to date, making the diagnosis particularly challenging. **Conclusions:** *TANGO2* related disease is an important diagnosis for the 22q community to consider including associated features, prevalence, variability, and mortality related risk.

128: Prevention, Recognition, and Life Saving Treatment: TANGO2 Deficiency Disorder and Life-Threatening Cardiac Risks among 22q11.2 Patients

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TANGO2 deficiency disorder (TDD) is an autosomal recessive condition (a child has defects in 2 copies of the TANGO2 gene) characterized by progressive neurocognitive and developmental and speech delays, seizures, hypothyroidism, and episodic metabolic crisis. Up to 1 in 300 individuals are carrying a defective TANGO2 gene. Because TANGO2 resides in the 22q11.2 region and all children with 22q11.2 deletion syndrome are missing one TANGO2 gene copy, all 22q11.2 children are at risk for also having TDD. TDD symptoms can be difficult to distinguish from 22q11.2 spectrum but there are some distinct features that are important to note for both families and physicians. In this talk, we will discuss the importance of recognizing the symptoms of TDD and we will discuss the heart related problems that can occur. We will review the risks of life-threatening arrhtyhmias, heart failure, cardiac arrest and death and when children are at risk. Data regarding treatment options and potential life-saving interventions will be discussed. At the end of this talk, learners should know symptoms that may indicate TDD, when to worry about heart related problems, and life saving interventions that can be helpful to prevent life threatening events.

129: Episodic Dystonia, Ataxia, and Weakness in Children with 22q11.21 Deletion Syndrome Should Prompt Consideration of Co-Morbid TANGO2 Deficiency Disorder

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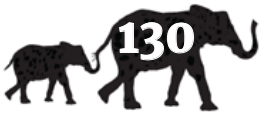
TANGO2 deficiency disorder (TDD) is an autosomal recessive neurodegenerative disease characterized by movement disorders, epilepsy, hypothyroidism, and life-threatening metabolic crises. Accumulating evidence suggests that supplementation with pantothenic acid (vitamin B5), and potentially other B-vitamins, is beneficial for patients with TDD, underscoring the need for early diagnosis. As the *TANGO2* gene resides within the 22q11.21 locus, patients with 22q11.21 deletion syndrome are at significantly increased risk for TDD (~1:350 based on aggregate population-level pathogenic allele frequencies) relative to the general population. In this talk, I will first review the neurological features of TDD, specifically the characteristic movement disorders that frequently precede metabolic crisis events. Based on video-based assessments of 26 patients with TDD, we found that nearly all patients studied experienced episodic abnormal movements, which our team identified as dystonia, ataxia, and weakness. Over half of the patients we studied experienced a full cessation of these events after initiation of B-vitamin supplementation. Second, I will review our work using symptom-based screening methods for TDD trialed across two institutional patient cohorts (total N=435). Of the 21 living patients meeting consensus criteria for *TANGO2* sequencing, 9 underwent genetic testing, and 0 were found to have comorbid TDD. However, we also observed 12 deaths in the suspected comorbid TDD cohort. Collectively, our findings highlight the need for robust prospective screening tools, inclusive of movement disorder assessments, in the 22q11.21 deletion syndrome population. Given the favorable risk-benefit profile of B-vitamins, the utility of broader prophylactic supplementation also warrants further exploration.



130: Using Zebrafish to Functionally Define Unique and Overlapping Developmental and Behavioral Roles of Genes Deleted in 22q11.2

Michael Granato
University of Pennsylvania, Perelman School of Medicine

Microdeletions of a 3Mb region encompassing 45 protein-coding genes at chromosome 22q11.2 (22qDS) predisposes individuals to multiple neurodevelopmental disorders and is one of the greatest genetic risk factors for schizophrenia. To systematically test 22qDS genes for their individual roles in neurodevelopment and behavior, we generated genetic null mutants for each of the 37 conserved zebrafish orthologs. We then subjected each of these mutants to seven previously validated behavioral assays using visual and acoustic tumuli, recorded behavioral responses at millisecond resolution and then performed observer independent analyses. Using this unbiased approach, we identified five single-gene mutants with partially overlapping behavioral phenotypes, two of which, mrpl40 and prodha respectively, encode mitochondrial proteins, further supporting the hypothesis that defective mitochondrial function might contribute to 22qDS pathogenesis. Furthermore, we find that both mrpl40 and prodha mutants exhibit partially overlapping changes in brain volume and display aberrant neural stem and progenitor cell proliferation, with each gene regulating distinct cell populations. Intriguingly, double mutant analysis reveals a partially redundant role for mrpl40 and prodha in regulating radial glia-like cell proliferation (Campbell et all 2023). We will present data to support our conclusions and will discuss ongoing work to further define molecular roles for 22qDS genes in regulating neural developmental and behavior.

131: Neurovascular Mitochondrial Susceptibility in the 22q11.2 Deletion Syndrome Impacts Blood-Brain Barrier Function and Behavior

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Background: Maintaining the integrity of the blood-brain barrier (BBB) is crucial for optimal brain function. A distinctive characteristic of the BBB is its heightened mitochondrial content compared to peripheral endothelial cells, yet the functional implications of this phenomenon remain elusive. In this study, we investigated BBB mitochondrial function in the 22q11.2 deletion syndrome (22q11.2DS), a condition associated with a significantly elevated risk of neuropsychiatric diseases. As the 22q11.2 deletion encompasses six mitochondrial genes, and considering our prior identification of BBB impairment, we hypothesized that mitochondrial deficits contribute to BBB dysfunction, impacting behavior in 22q11.2DS. **Methods and results**: Our findings reveal mitochondrial impairment in human induced pluripotent stem cell (iPSC)-derived BBB endothelial cells from individuals with 22q11.2DS, as well as in BBB endothelial cells from a mouse model of 22q11.2DS. Notably, interventions aimed at enhancing mitochondrial function successfully alleviate mitochondrial deficits and improve BBB function in both the iPSC and mouse 22q11.2DS models. Significantly, this treatment also ameliorates social memory deficits, a previously identified impairment associated with BBB dysfunction. **Conclusions:** Given the correlation between BBB integrity and social memory performance, our collective results suggest that mitochondrial dysfunction within the BBB plays a pivotal role in influencing both barrier integrity and behavior in individuals with 22q11.2DS.

132: Synaptic Energetics in Schizophrenia Risk and Treatment in the Context of 22q11.2 Deletion Syndrome

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The Children's Hospital of Philadelphia and The University of Pennsylvania Perelman School of Medicine

People with 22q11.2 deletion syndrome (22q11DS) have an elevated rate (25%; 25x that of the general population) of developing schizophrenia (SZ) before young adulthood. We found that human stem cell-derived neurons from people with 22q11DS+SZ have reduced oxidative phosphorylation (OXPHOS) capacity relative to both 22q11DS without SZ and to controls. Moreover, the no-SZ 22q11DS group had altered gene expression relative to the 22q11DS+SZ group *and controls*, with elevated nuclear and mitochondrial-encoded components of the electron transport chain/OXPHOS pathways, as well as key transcriptional activators of these genes. These findings are being followed up by three lines of study: 1) How might reduced neuronal OXPHOS increase the risk of developing SZ? We have developed the capacity to simultaneously image both presynaptic vesicle cycling and synaptic glutamate release. This live imaging of single synapses in vitro also identifies whether mitochondria are localized to a given presynaptic terminal. We find that synaptic vesicle re-acidification following glutamate release occurs more rapidly at synapses with attendant mitochondria. In addition, glutamate release probability is reduced by inhibitors of OXPHOS. These studies are being extended to stem-cell derived neurons from controls, and from people with 22q11DS with or without SZ. Weaker glutamate release in the +SZ group would be consistent with extensive evidence that SZ largely results from reduced cortical connectivity. 2) Inspired by our gene expression studies, do stem-cell derived neurons from the 22q11DS NO SZ group have increased mitochondrial genesis and turnover relative to 22q11DS+SZ and controls? We have evidence supporting this contention, and also find that the 22q+SZ group have defective lysosomal function and mitophagy. 3) We are using the experimental systems above to test new approaches for improving neuronal health in the 22q11+SZ neurons, in model mice, and ultimately in affected people with this debilitating and difficult to treat neurodevelopmental challenge.

133: Transcriptional Response to Mitochondrial Dysfunction, and Treatment, in Developing Cortical Projection Neurons

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Background: Mitochondrial dysfunction, including reactive oxygen species (ROS) dysregulation, is a key contributor to altered cortical circuit differentiation and function in 22q11DS. Several 22q11 mitochondrial genes, including *Txnrd2*, have been associated with this disruption. Using 22q11DS mouse models, we previously showed that the ROS- scavenging drug, N-Acetylcysteine (NAC), restores cortical layer 2/3 (L2/3) projection neuron (PN) growth during early post-natal life, leading to improved cortical circuit function and behavioral performance. However, molecular pathways that disrupt 22q11 gene-dependent L2/3 PN growth or restore it in response to NAC remain unclear. **Methods:** We generated *Txnrd2*$^{+/-}$, *LgDel*, and wild-type (WT) L2/3 PN cultures, including a subset of *LgDel* and WT cultures treated with NAC. Neurite growth was measured and bulk RNAseq performed for each genotype/treatment. RNAscope quantitative *in situ* hybridization was used for *in vivo* validation of differentially expressed (DE) genes in L2/3 PNs in the cerebral cortex of early postnatal *LgDel*, WT and *LgDel*+NAC mice. **Results:** *Txnrd2*$^{+/-}$ and *LgDel* L2/3 PN *in vitro* neurite growth was similarly compromised; however, there was no significant overlap of DE genes for these two genotypes. In contrast, a subset of *LgDel* L2/3 PN *in vitro* DE genes were partially restored toward WT levels in *LgDel*+NAC L2/3 PNs; however, this subset did not include any 22q11 genes. In addition, there are several novel DE genes, including ROS-responsive genes, in *LgDel*+NAC L2/3PNs *in vitro*. These "restored" and "novel" NAC-regulated genes were validated by RNAscope in L2/3 PNs *in vivo* in *LgDel*, *LgDel*+NAC and WT postnatal mice. **Conclusions:** Mitochondrial/ROS-sensitive regulation of dendritic and axonal differentiation in *Txnrd2*$^{+/-}$, *LgDel* and *LgDel* +NAC L2/3 PNs relies upon mostly divergent transcriptional states despite related phenotypes in each genotype. Transcriptional responses to NAC could highlight downstream molecular pathways that represent new, selective, targets to optimize therapeutic intervention via circuit growth in 22q11DS.

134: Prevalence of Parkinson's Disease in 22q11.2 Deletion Syndrome: A Multicenter Study

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Background: 22q11.2 deletion syndrome (22q11.2DS) has been associated with an increased risk of early-onset Parkinson's disease (PD). However, there is uncertainty about the prevalence of PD in 22q11.2DS, and the effects of age and sex. **Methods:** We conducted an international multicenter study including 856 adults (median age 28.1 (range 16–76) years; 47% male) confirmed to have a typical 22q11.2 deletion. We calculated 95% confidence intervals for the prevalence of PD, defined as a clinical diagnosis by a neurologist, including bradykinesia and at least one of either rest tremor or rigidity, and suspected PD as a clinical diagnosis or suspicion of PD but failure to meet all above criteria for PD. We used logistic regression to test a model predicting PD. **Results:** PD was found in 1.8% (95% CI: 0.9-2.6%) of the study sample, and 3.4% (95% CI: 2.2-4.6%) when individuals with suspected PD were also included. A sharp increase in PD prevalence was seen in adults aged 50 years and older; 14.0% (95%CI: 6.9-21.0%) of them had PD. The regression model predicting PD was significant ($P<0.001$), indicating that age ($P<0.001$), but not sex ($P=0.62$), was associated with the presence of PD. **Conclusions:** The study findings suggest an increased prevalence of PD in 22q11.2DS in comparison to the general population, especially in adults aged 50 years and older. We propose periodic neurological evaluation in all adults with 22q11.2DS aged 40 years and older in order to enable early diagnosis and treatment.

135: Increased Striatal Dopamine Transporter Binding in 22q11Del versus 22q11Dup Individuals

Therese van Amelsvoort[1], Carmen van Hooijdonk[1], Rik Schalbroeck[1,4], Erik Boot[1,2,3], Claudia Vingerhoets[1,2], en Jan Booij[4].
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Introduction: 22q11.2 deletion syndrome (22q11Del) is associated with an increased risk of developing early-onset Parkinson's disease (PD). It is unknown whether individuals with 22q11.2 duplication syndrome (22q11Dup) have an altered risk of PD. As PD is characterized by loss of striatal dopamine transporter (DAT) binding, we explored striatal DAT binding in non-psychotic individuals with 22q11Del, 22q11Dup and in healthy controls (HC). We hypothesized that striatal DAT binding ratios would be highest in 22q11Del and lowest in 22q11Dup, since previous studies suggest higher striatal DAT expression in subjects at risk to develop PD. **Methods**: Six individuals with 22q11Del (mean age 36.5 years, 4F/2M), four individuals with 22q11Dup (mean age 37.3 years, 2F/2M), and eight HC (mean age 39.1 years, 4F/4M) were included. None of the study participants took any psychopharmacological medication. [^{123}I]FP-CIT single photon emission computed tomography was administered for determination of striatal DAT binding ratios. **Results**: After correction for age and sex, we found statistically significant overall group differences in mean DAT binding ratios in left and right putamen (p=0.025 and p=0.014, respectively), and left and right caudate (p=0.014 and p=0.010, respectively). Post-hoc analyses revealed significantly increased mean DAT binding ratios in 22qDel versus 22q11Dup in all four subregions (left putamen p=0.02, right putamen p=0.012, left caudate p=0.026, right caudate p=0.005). Effect sizes were large (> η_p^2=0.577) in all regions. **Conclusion**: Our study findings are in line with a previously reported hyperdopaminergic state in 22q11Del, that may be driven by COMT haplo-insufficiency. This hyperdopaminergic state might eventually cause auto-neurotoxicity with subsequent dopaminergic loss, that could partially explain the increased occurrence of PD in 22q11Del. Our preliminary results support further exploration of DAT imaging as a potential predictor of PD in individuals with 22q11Del.

136: Expanding the Phenotypic Spectrum of Movement Disorders in 22q11.2 Deletion Syndrome: A Retrospective Study *

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Introduction: Emerging evidence suggests that a wide range of movement disorders occur in 22q11.2 deletion syndrome (22q11.2DS). However, formal phenotypic characterization of the spectrum of these problems is largely lacking. **Materials and methods:** We conducted a retrospective study of 31 adults (mean ± SD age: 45.9 ± 13.0 years) with molecularly confirmed 22q11.2 microdeletion who were referred to the Toronto Western Hospital Movement Disorders Centre. We performed extensive phenotyping through review of patient records to collect clinical, laboratory, radiologic, and electrophysiologic information relevant to movement disorder characterization. Descriptive statistics were used to summarize the data. **Results:** The mean ± SD age of onset of any movement disorder was 33.1 ± 12.5 years, with a median (IQR) duration of symptom of 3.5 (7) years prior to evaluation by a movement disorder specialist. The majority (71.0%) of cases had two or more movement disorders on examination. The most frequent findings were non-parkinsonian tremor (71.0%), parkinsonism (48.4%), dystonia (36.7%), and myoclonus (32.1%). In 19 unpublished cases, we found additional cases of tics and functional movement disorder (FMD), and identified novel phenotypes including stereotypies as well as electrophysiologically confirmed cortical myoclonus and slow orthostatic tremor. The presence of multiple (≥ 2) movement disorders did not significantly differ between antipsychotic-naïve individuals and those with a history of antipsychotic use (70.0% vs. 71.4%, $p > 0.99$). **Conclusion:** The majority of individuals with 22q11.2DS evaluated for a movement disorder by experts in this field exhibit multiple movement disorders, which can occur irrespective of antipsychotic use. Although parkinsonism is common, as previously reported, clinicians should be aware that other movement disorder phenotypes can exist along with or independent of parkinsonism, including non-parkinsonian tremor, dystonia, myoclonus, tics, stereotypies, and FMD. Electrophysiologic studies may support the presence of and help in further characterizing 22q11.2DS-associated movement disorders.

137: Proteomic Analysis of Plasma in 22q11.2DS

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Background: The most commonly identified immunologic features in 22q11.2DS relates to diminished T cell production due to thymic hypoplasia. The consequences of the T cell lymphopenia include infections, atopy, and autoimmunity. Studies of limited sets of cytokines have generally revealed increased levels of mediators in 22q11.2DS, suggesting that the landscape in 22q11.2DS is altered. This landscape might contribute to autoimmunity and inflammatory diseases. Psychosis, seizures, and other behavioral differences may be related to immune dysfunction and/or inflammation. To better understand the features in 22q11.2DS, we performed an unbiased analysis. **Methods:** We undertook an unbiased proteomic analysis of adults with 22q11.2DS and unaffected relatives and controls to better understand the landscape that might contribute to inflammation. We utilized the Olink Target 96 Inflammation panel (Uppsala, Sweden) using 49 adult patients with 22q11.2DS and 62 healthy adult controls. **Results:** TNF, IL-6, MCP-3, CCL-19, IL-17C, and TRAIL were all significantly elevated in patients with 22q11.2DS. These mediators are connected through their induction by bacterial products or TNF. An unexpected finding was increased FGF5, GDNF, NT-3, and bNGF. Altered levels of these mediators have been identified as associated with depression or anxiety. We additionally found elevated IL-24, IL-33, LIF and IL-4. Increased Th2 cytokines have been previously described. **Conclusions:** The inflammatory milieu is altered in 22q11.2DS, possibly contributing to the increase in autoimmunity in this syndrome. The findings of increased neuronal markers requires additional study to define source and ramifications.

138: A Follow-up Study Indicates Inflammatory Factors as Predictors to Cognitive Decline and Psychosis in Individuals With 22q11.2 Deletion Syndrome

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Background: We have previously investigated the involvement of inflammation in cognition and psychosis in 22q11.2 Deletion Syndrome (22q11.2DS). In a study, conducted between 2014-2015, we found that 22q11.2DS participants had elevated levels of CRP, IL-6, TNFα and IL-10 compared to controls. Furthermore, the psychotic 22q11.2DS participants had higher levels of IL-6 compared to the nonpsychotic 22q11.2DS individuals. IL-6 levels correlated with the severity of the cognitive deficits in the 22q11.2DS participants. In this follow-up study, we recruited the same individuals who participated in the study eight years ago and assessed their cognitive and psychiatric status. **Methods**: Thirty three individuals from the original cohort (2014 -2015) participated in the current follow-up study (2022-2023). All 22q11.2DS psychotic and non-psychotic underwent cognitive assessments using the Penn Computerized Neurocognitive Battery (CNB) and psychiatric assessments using the Hebrew version of the structured Interview for Psychosis-Risk Syndromes (SIPS). **Results:** We found in our cohort a sub-group of six participants that had converted to psychosis between the two studies (named converted-group). Those individuals, when compared to other non-psychotics in the first study, had higher scores in their positive and disorganized symptoms. When analyzing the whole cohort, we found a negative correlation between the change in cognitive abilities at the follow-up study and the levels of IL-6 at first detection, and a positive correlation between the changes in positive symptoms in the follow-up study and the levels of IL-10 and IL-1Ra in the first study. **Conclusions:** To the best of our knowledge this is the first study that found inflammatory parameters as predictors of deterioration in cognitive abilities and psychiatric symptoms when analyzing twice the same individuals with 22q11.2DS. In addition, we found that there were psychiatric symptoms that were detected eight years before the arousal of full-blown psychosis in some of the participants (converted group).

139: Altered Metabolomic and Proteomic Profiles in Individuals with 22q11.2 Deletion Syndrome

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Background: Clinical picture of chromosome 22q11.2 deletion syndrome (22q) displays extreme phenotypic heterogeneity and represents the strongest known molecular genetic risk factor for psychosis and schizophrenia. Thus, it is a strong and unique model for prospective study of risk and protective factors for psychosis, as many at-risk youths can be studied even before symptoms appear. The well-defined microdeletion contains multiple genes which haploinsufficiency has the potential of altering protein and metabolic profiles which could identify endophenotypes among those with 22q and represent predictors of psychosis diagnosis before symptoms are evident. **Methods**: Leveraging on the unique data and specimens collected from individuals with 22q followed longitudinally in a previous study and on a currently Uytengsu-Hamilton 22q11 Neuropsychiatry Research funded award, we performed untargeted metabolic and proteomic analysis in plasma samples derived from 30 subjects (22q n=16, TD n=14) with and without medical involvement, psychiatric conditions, and ASD. Deletion size was characterized by ddPCR. **Results**: We observed a large number of metabolites and proteins showing significant changes in expression levels in 22q as compared to TD, including those involved in several pathways such as gene expression, the PI3K-Akt signaling pathway and of the complement and coagulation cascade and cytokines involved in immunoregulatory functions. Analysis of the correlation of the observed molecular dysregulation with clinical phenotypes is in progress. **Conclusions**: This is the first report on the identification of plasma metabolic and protein signature and on the identification of unique biomarkers in 22q which may play a potential role for the onset of comorbid conditions in 22q. Ultimately, the altered protein pathways in 22q may provide insights of the biological mechanisms underlying the neurodevelopmental phenotype and could be used as markers of prognosis, disease development and progression and for the development of future pharmacological interventions.

140: The Contribution of Genome-Wide Tandem Repeat Expansions to Schizophrenia in 22q11.2 Deletion Syndrome

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Background: Individuals with 22q11.2DS are at elevated risk of developing schizophrenia. This may be attributed to the 22q11.2 deletion coupled with additional genetic factors, including common risk SNPs (in aggregate as polygenic risk score; PRS) and rare copy number variants (CNVs). However, these variants only account for part of the phenotypic heterogeneity. We hypothesize that tandem repeat expansions (TREs), which we have established as being involved in schizophrenia in the general population, also contribute to the outcome of schizophrenia in 22q11.2DS. **Methods**: We have sequenced 88 *de novo* trio families of European-Canadian background (i.e., adult proband with typical 22q11.2 deletion and both unaffected parents), using Illumina HiSeqX genome sequencing (>30x depth). We detect SNPs and CNVs with standard GATK pipelines, and use ExpansionHunter denovo followed by DBScan to detect any TREs in the genomes. We use a multiple regression model to evaluate and compare the burden of different genetic variants between individuals with and without schizophrenia. **Results**: We have identified a significant contribution of genome-wide rare (<0.1% population frequency) TREs to schizophrenia risk in 22q11.2DS ($p<5x10^{-3}$). Most of the TREs in the probands are expanded from the parental TRE. The effect size of these TREs, collectively, is on par with that conferred by PRS, but their effects are not correlated to each other. The contributions of other rare genetic variants are non-significant in this cohort. The TREs are mostly located within genes, in the intronic regions. The TREs identified in 22q11.2DS with schizophrenia significantly overlap with those from our previous study of a community-based schizophrenia cohort without 22q11.2DS ($p<5x10^{-7}$), suggesting potential shared disease-modulating mechanisms. **Conclusions**: Our results suggest that TRE is one of the major genetic modifiers for schizophrenia in 22q11.2DS, which broadens the scope by which this psychiatric condition may be detected and managed.

141: The Future is Now

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The ex-British Prime Minister Harold Wilson once said, “A week is a long time in politics”, and certainly the two years since Split is a long time in science. The rationale for this presentation given by the organizers is to highlight some advancements that might impinge upon our specific lines of inquiry over the next two. So, there are no data, and soothsaying doesn’t have a great track record! Of course, most of us will peruse Nature, Science, New England Journal etc for biological and medical insights, as well as be generally aware of the burgeoning impact of AI, so I will refrain from aiming at comprehensiveness. I will attempt to draw out some broad themes I hope will interest you, very much a personal opinion of what has piqued my interest. While clinical, educational and psychological interventions continue to make hard won progress for our patients and families the major issue for 22q11.2DS, in common with many other congenital disorders, is how to overcome the developmental disruption that means problems are “hard wired” into the patient during embryogenesis. The question for future 22q11.2DS research therefore: is there any prospect of undoing this?

142: Implementation of a 22q Tracker to Improve Efficiency of Clinic Visits

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Seattle Children's Hospital

Background: Patients with 22q11.2 related disorders require multispecialty care coordination and collaboration throughout their lives. This level of complex care can be difficult for providers and families to manage over time as many electronic health systems do not allow for a comprehensive view of the patients' entire care plan while also providing a collaborative approach to tracking care and highlighting unique social and/or communication needs. Lack of such a system can result in missed opportunities for 22q team members to address patient needs during the various touchpoints they have with patients between visits. This can be especially burdensome with families coming from great distance. **Methods**: Seattle Children's Hospital has implemented a collaborative 22q Tracker for tracking all 300+ active patients at our center. In addition to communicating each patient's scheduling needs and plan of care, the spreadsheet functions to highlight high risk patients, prioritize patients for upcoming clinics and track patients transitioning to adult care as well as waitlists for 22q sub clinics such as Developmental Assessment Clinic. The 22q Clinic RN, Scheduler and MA update this tool with every patient interaction and use it to inform just in time scheduling and phone triage. **Results**: In the 3 years we have been using the 22q Tracker, we have gained the ability to answer calls live with instant access to every patient's comprehensive plan of care. When a patient/family calls, they are informed of all the visits they need, whether that be in 22q Clinic or with another service, and the scheduler, MA or nurse offer to assist with transferring them to the correct department or assisting with coordinating future visits within our own clinic. This has increased patient compliance with care recommendations and has helped keep our more vulnerable patients from "falling through the cracks". **Conclusion**: Careful consideration and management of each patient's plan of care using our 22q Tracker has improved the efficiency of our team's care coordination, increased access to care for our vulnerable patients and resulted in positive family feedback.

143: Implementation of RN Clinic Prep for Pediatrician visits using a 22q Focused Assessment Checklist

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Background: In the Seattle Children's 22q Program, patients with 22q11.2 related disorders are seen by one of 3 pediatricians as part of their team visits. The role of the pediatrician is to cover all aspects of the child's physical and mental health and make sure additional needs are met. Because of the complex needs of patients with 22q-related disorders, medical, psychological, and social needs often change between visits. When these changes are not anticipated, communicated and planned for, clinics visit become less efficient and helpful. **Methods**: Seattle Children's Hospital 22q Clinic has 3 pediatricians and one primary RN who follow 300+ patients. To prepare families and providers for pediatrician visits, the RN reaches out to each family seeing a pediatrician 1-2 weeks prior to clinic to document an in-depth review of their overall care. We have been using this process for about 2 years now and have created a documentation tool we use for this based upon the "Recommendations for periodic assessments and management of children and adolescents with 22q11.2 deletion syndrome". **Results**: The use of our 22q patient call template has improved clinic efficiency and utilization of health care for patients. Bringing awareness to medical concerns prior to clinic visits gives providers time to communicate with other members of the care team, obtain labs or other studies as needed, and to coordinate adding in other providers such as social work, child psychology, or nutrition when needed. This call also gives families time to consider their questions and concerns they want to discuss with the pediatrician or other members of the care team prior to the visit. **Conclusion**: Careful consideration of each patient's care using the 22q patient call has improved efficiency of pediatrician clinic visits and the quality-of-care coordination our patients receive.

144: Bridging the Care Gap: A Multidisciplinary Approach for Adults with 22q11.2 Deletion Syndrome in Florida *

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Background: The transition from pediatric to adult healthcare for individuals with 22q11.2 Deletion Syndrome (22qDS) is globally challenging. Patients frequently lose follow-up when they transition out of pediatric care. Recognizing the need for continuous, specialized care, the 22q Multidisciplinary Program at Joe DiMaggio Children's Hospital/Memorial Healthcare System in Florida has innovatively expanded to include adult services. In April 2023, we celebrated a major milestone by launching our first adult 22q Multidisciplinary Clinic, marking a significant step towards lifelong, comprehensive care for the 22qDS community. **Methods:** Conducted quarterly, this pioneering clinic, is spearheaded by a core team comprising specialists in Cardiology, Genetics, Endocrinology, Immunology, and Social Work, ensuring a comprehensive approach to the unique needs of adults with 22qDS, a demographic historically underserved in the transition from pediatric to adult healthcare. It supports both transitioning pediatric patients and newly diagnosed adults, often identified through genetic testing of parents at our pediatric 22q multidisciplinary clinic. **Results:** Our group has identified 54 adult patients within our healthcare system, 24 males and 30 females, ages 18-41 years old, with the confirmed genetic diagnosis of 22qDS. The team has successfully conducted 3 multidisciplinary clinics serving approximately 3 patients per session. This initiative has not only filled a critical care gap but also provided valuable insights into the unique challenges and healthcare issues of adults with 22qDS. **Conclusions:** The establishment of this adult 22q clinic represents a significant advancement in our mission to offer exceptional, lifelong care to individuals with 22qDS. We aim to share our initiative, hoping to inspire colleagues in the US and overseas on the creation of similar 22q adult multidisciplinary clinics around the world, not only to close the care gap that exists in the adult 22q age group, but also to contribute to the global understanding of 22qDS across the lifespan.

145: Co-producing a Healthcare Passport to Improve Quality of Care and Communication Engagement for Young People Living with 22q11DS

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Background: Participatory research conducted with young people living with 22q11.2ds in Ireland revealed the significant mental health distress experienced due to navigating multiple health providers. There is a need for communication tools, which indicate the needs and preferences of people with complex conditions. A grant application was successful, supporting the project. Using a Co-production ethos, qualitative methods using purposeful sampling aimed to identify the perspectives of affected young people– and co-create a solution. The creation of a disease specific passport should include input from all key stakeholders**. Methods**: A 'Body Mapping' workshop was undertaken with affected young people and a digital focus group with parents. Body mapping is a collection of activities that involve drawing full-sized body images, which tell the story of the body with drawings, symbols, words and painting (de Jager *et al.,* 2016). Visual representations of semi-structured interview questions were used to facilitate engagement. Thematic analysis methods were undertaken. **Results:** Affected young people relayed constant recalling their medical history was stressful; they had poor understanding of specialist care and medical staff roles; and they required printed feedback and information, which they did not always receive. They felt their care at times, 'lacked humanity'. These insights are supported by parental feedback. A communication passport was developed in conjunction with the same young people, with meaningful and regular feedback sought. Each pack has tabs to individualise each journey, with information leaflets from point of diagnosis to adulthood developed. **Conclusion:** This co-produced patient-held communication tools may be helpful to some people living with 22q11 but will require future auditing. This innovative approach captures co-production in its context: '*a meeting of minds coming together to find shared solutions and involves people who use services working together with staff, from the start to the end of any project that affects them'* (HSE Ireland 2023)

146: Transition to Adult Care from a Pediatric 22q Center: Midway Through a Pilot Project

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Background: Patients with 22q11.2-related disorders require multidisciplinary care, including in adulthood. Historically, our team has struggled to identify primary, subspecialty, and mental health care for our adult patients. Consequently, we continue to care for many adult patients, despite a lack of adult healthcare providers on our team. **Methods**: We have developed a pilot project based on Got Transition (gottransition.org), a standard of care for transition to adult care, endorsed by the American Academy of Pediatrics. Our program employs Got Transition's six core elements of healthcare transition:

1. Policy
2. Tracking & Monitoring
3. Readiness
4. Planning
5. Transfer of Care
6. Transition Completion

We leverage our electronic medical record (EMR) software's capabilities wherever possible to ensure reproducibility. We also collaborate with other subspecialty clinics, including recently connecting with an adult-focused clinic that can offer multidisciplinary care after transition from our system. **Results**: We share a transition policy with all patients 14 years and older. We discuss transition at every pediatrician's visit for patients 16 years and older (goal of 14 years in the future) and we track this in the EMR. We are developing an EMR-integrated version of the TRAQ, a validated assessment of transition readiness. We are surveying families for their input on what materials to include in a transition planning packet. Our collaboration with the adult-focused clinic is so new that we have not completed transition of a patient to them yet but are excited to do so! **Conclusions**: Patients with 22q11.2-related disorders are experiencing improved quality of life and life expectancy. Focusing on their transition to adult care is essential to ensuring ongoing trust in the healthcare system at a time of vulnerability. By addressing this issue early in adolescence and providing options for trusted adult-focused resources, we can ensure that adult patients maintain trust in healthcare.

147: Genetic Breakthroughs in Neonatal Medicine: Advancements Transforming Newborn Care

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Background: Congenital anomalies, affecting 1-3% of all births, pose a significant global public health challenge, contributing to neonatal and infant morbidity and mortality. This study underscores the importance of early and accurate diagnosis in guiding medical interventions, detecting complications, and understanding prognosis in dysmorphic cases. With a particular focus on antenatal diagnosis, this research highlights the crucial importance of early identification of congenital anomalies before birth. The ability to detect these anomalies from the antenatal period offers significant advantages in guiding parents, healthcare professionals and management strategies from the earliest stages of fetal development. **Methods:** Collaboratively conducted between the neonatal intensive care unit and the medical genetics department from June 2015 to February 2024, the research centers on newborns and infants with dysmorphic syndromes. Pediatricians conducted thorough physical examinations, classifying cases with internal or external organ abnormalities as genetic disorders (GD). Those without apparent physical defects but suspected malformations were referred to the medical genetics department for further investigation. The study delves into ten subjects, each representing a distinct syndrome with a confirmed genetic etiological diagnosis. **Results:** Among 70 babies, the study explores 36 cases under investigation, 25 confirmed cases, and 09 suspected cases, with a detailed focus on 10 subjects, unveiling diverse conditions like Prader-Willi syndrome, chromosomal deletions, and Wolf-Hirschhorn syndrome. Comprehensive genetic, clinical, and neurological examinations offer crucial insights into each case, enriching our understanding of congenital anomalies. **Conclusion:** The imperative search for associated malformations underlines the importance of thorough genetic testing. This study contributes not only to establishing accurate genetic diagnoses, but also to guiding subsequent care strategies. The emphasis on a multidisciplinary approach underscores the complexity of neonatal anomalies and highlights the importance of ongoing follow-up for a comprehensive understanding of the patient.

148: Integrated Care for Young People with 22q.11.21 Deletion Syndrome – a Patient, Provider Initiative

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Background: A disease specific 22q.11 Deletion Syndrome clinic was established in Children's Health Ireland (CHI) to meet the needs of families living with this rare disease, with the following objectives: A 'Patient and Public Involvement' ethos underpins this initiative, completed in conjunction with 22qIreland, a parent support group. Families reported significant difficulty in coordinating care for their children, and many are linked with multiple hospital sub-specialities, community based disability and mental health services. **Methods**: A Consultant Paediatrician with the support of a Complex Care Coordinator (CCC) leads a fortnightly, disease-specific clinic. The chairperson from 22qIreland also attends the clinic, and provides disease specific information and support. The team collaborated with an adult physician in St. James Hospital, who attends the adolescent clinics in CHI, and the transition pathway and process is commenced. Transition clinics are undertaken in SJH with the same team in CHI, to ensure continuity and reduce the gathering of medical information. The CCC and adult physician provide support related to disability related needs, mental health and transition. **Results**: Parents report improved coordination of care, and less self-management of communication between services; improved access across specialities, with same day access facilitated. Parents have support from diagnosis to adulthood, with a transferable model of care. Clinic establishment objectives were met: 1) Patient provider Collaboration – involve users in healthcare; 2) Establishing a disease specific 22q.11 Clinic and 3) Improve Transition for young people with 22q11.DS. **Conclusion:** It is difficult to put a value and measurement on integrated care but families report significant improvement in their healthcare experience and navigating the complex web of specialities and services. Innovative collaborations are one of the key factors in achieving integrated care, and this project highlights the need to collaborate with people and organisations that provide services for families living with 22q.

149: Surgical Needs of Patients with 22q11.2 Deletion or Velocardiofacial Syndrome

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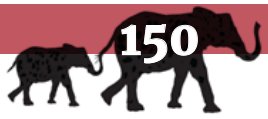
Background: The phenotype of 22q11.2 Deletion Syndrome varies widely. Patients may present to an otolaryngology practice with airway anomalies, hearing loss, and/or velopharyngeal insufficiency (VPI) requiring surgical intervention. The perioperative care of these patients may be complicated by congenital heart disease, immune deficiency, and platelet dysfunction. The complexity of these patients often necessitates coordination of care between services. The purpose of this study was to delineate the quantity and types of procedures required by pediatric patients with 22q11.2 Deletion Syndrome in order to assist the otolaryngologist with pre-operative planning and counseling. **Methods**: All procedures under general anesthesia recorded in the electronic medical record between 2007 and 2022 for patients with a diagnosis code of Q93.81 and/or D82.1 (Velocardiofacial Syndrome/22q11.2 Deletion Syndrome and DiGeorge Syndrome) were included. Descriptive content analysis was performed. **Results**: 253 patients with ages ranging from 1 day to 18 years underwent 2289 procedures. The number of procedures per patient ranged from 1 to 62, with a mean of 9.04 procedures. 87.8% (222) of patients underwent more than 1 procedure. Otolaryngology procedures were most common at 29.2% (670) of total procedures performed, followed by diagnostic radiology at 19.9% (457), cardiovascular surgery at 14.4% (331), cardiology at 7.3% (168), and pediatric surgery at 5.3% (122). The most common procedures were microlaryngoscopy with bronchoscopy (226), MRI (188), echocardiogram (171), cardiac catheterization (168), and myringotomy with tympanostomy tube placement (116). **Conclusions**: Many patients with 22q11.2 Deletion Syndrome undergo multiple procedures during childhood, most commonly with otolaryngology. The otolaryngologist should be aware that these patients often also require diagnostic imaging under anesthesia, as this presents a potential opportunity to coordinate care and thereby reduce the number of times these patients undergo general anesthesia. This data can also assist the otolaryngologist in pre-operative counseling and the formation of perioperative protocols.



150: Prevalences of Comorbid Cardiovascular, Psychiatric, Orthopedic, Endocrinologic and Development-related Diseases in Patients with 22q11.2 Duplication Syndrome – a Systematic Review *

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Background: The 22q11.2 duplication syndrome (22q11.2Dup) is a relatively rare genetic variation (1:1600) that leads to increased risk for multiple diseases. Concrete prevalence figures for comorbid diseases in 22q11.2Dup remain unclear. **Methods:** Literature in English and German was searched between August 2022 and August 2023 in the databases Pubmed, Web of Science and Cochrane. Studies focusing on 22q11.2Dup were considered in the fields of cardiology, psychiatry, orthopedics, growth and development, immunology, hematology/oncology, otolaryngology, oral and maxillofacial surgery and endocrinology. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to further assess the quality of evidence, taking into account Risk of Bias (RoB), inconsistency, indirectness, lack of precision, and publication bias. **Results:** 20955 studies were identified in the systematic searches, of which 10 were included. Congenital heart defects were increased in comparison to those without 22q11.2Dup, and high prevalence numbers were found for psychiatric diseases such as anxiety (7-30%), autism (7-30%) and ADHD (9-44%). Development-related diseases such as growth disturbance (33.3-36.7%), speech and language problems (12.5-68%) and motor delay (57.7-81.8%), or variations in IQ scores were also observable. Reported orthopedic and endocrinologic diseases were hypotension and hypocalcemia. The majority of the studies showed a low or moderate RoB. The total quality of evidence according to GRADE was very low. **Conclusion:** This study to our knowledge represents the first systematic review of disease prevalence in individuals with 22q11.2Dup, with elevated rates noted in psychiatric disease, as well as disorders of growth and development. Even though quality of evidence according to GRADE was low, it is recommended to offer early routine check-ups to individuals in this population and genetic screening for 22q11.2Dup.

151: Examining Parent of Origin in Patients with *de novo* 22q11.2 Duplication Syndrome *

Oanh Tran[1,2], Ryan Lapointe[1,2], Victoria Guinta[1,2], T. Blaine Crowley[1,2], Audrey Green[1,2], Lydia Rockart[1,2], Bekah Wang[1,2], Daniel E. McGinn[1,2], Steven Pastor[3], Elaine H. Zackai[1,2,4], Donna M. McDonald-McGinn[1,2,4,5], and Beverly S. Emanuel[1,2,4]

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Background: 22q11.2 duplication syndrome (22q11.2DupS) is common, occurring in 1/850 pregnancies. Most duplications are inherited, but *de novo* occurrences have been observed assumed to be due to non-allelic homologous recombination mediated by low copy repeats, like the reciprocal 22q11.2 deletion syndrome (22q11.2DS). While parent-of-origin studies have been performed on patients with *de novo* 22q11.2DS, no such data exists for *de novo* 22q11.2DupS. Here we report the first such analysis. **Methods:** Under an IRB approved protocol, samples from patients with *de novo* 22q11.2DupS underwent parent-of-origin studies using PCR amplified microsatellite biomarkers located between the duplication breakpoints. Fragment analysis was performed on biomarkers using GeneMarker software (Version 3.0). An informative biomarker consisted of an affected child exhibiting three unique fragments; two of which had a clear delineation to one parent. Duplications were also sized using MLPA SALSA P250 DiGeorge diagnostic probe kit (MRC-Holland). **Results:** Of the 158 probands with 22q11.2DupS, 25 were confirmed to be *de novo* clinically or by parental research studies, 75 were inherited (75%), and 58 remained unknown due to lack of parental samples. Within the *de novo* sub-cohort, 7/25 had informative markers/parental DNA available for analysis, of whom 6 were found to be maternal in origin (86%). Of note, one of these 6 patients was an identical twin whose co-twin was also affected but not included in the proband analysis; and an additional family was identified where the proband was diagnosed with a standard *de novo* 22q11.2 deletion of maternal origin and the younger brother was subsequently found to have a *de novo* 22q11.2 duplication of paternal origin. Thus, in total, 2/8 (25%) duplications were paternal in origin. **Conclusions:** We found 75% of our sub-cohort with *de novo* 22q11.2 duplications to be maternal in origin, even higher than what we have observed in patients with 22q11.2 deletions (59%).

152: Supernumerary Nipple in Association with 22q11.2 Deletion Syndrome *

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Background: A supernumerary nipple (SN) is a minor malformation of mammary tissue resulting in extra nipple/s. Also known as an accessory nipple, third nipple, ectopic nipple, or extra nipple, SN is the aborted beginning of an additional nipple. The hyperpigmented macule may have features like a fully formed nipple. They usually occur anywhere along the two vertical milk lines that originate in the axilla, descend through the region where nipples are typically situated, and terminate at the groin. About 5% form outside the milk lines on the skin of the neck, back, vulva or thigh. SN are congenital, and usually harmless. However, they are influenced by hormones and susceptible to other disease processes. They present as either isolated findings or as features of genetic conditions, such as Ruvalcaba-Myhre syndrome and Hay-Wells ectodermal dysplasia. SN are associated with an increased risk of urinary tract abnormalities. They are familial in ~6% of cases, thought to be autosomal dominant with incomplete penetrance and more common in males. ~6% of people in the general population have a SN. We previously noted supernumerary nipples on physical exam in patients with chromosome 22q11.2 deletion (22q11.2DS) and therefore wished to explore the prevalence in our large cohort. **Methods:** We performed a retrospective chart review on records of 1,629 patients with 22q11.2DS evaluated from 1992-2024 under an IRB approved protocol. **Results:** Twenty-three patients were reported as having SN (1.4%, 14 per 1,000 births). 87% were male, 65% white, and 90% had a standard LCR22A-LCR22D deletion. One patient with a SN had a LCR22B-LCR22D deletion. We also noted a patient with SN and a distal LCR22E-LCR22F deletion. **Conclusions:** The prevalence of SN appears to be no higher within our 22q11.2DS cohort compared with the general population. Family history and urinary tract anomalies will be discussed.

153: Telangiectasia in the Distribution of the Superior Vena Cava – a Novel Phenotype in 22q11.2 Deletion Syndrome: A Case Report

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[1]Children's Health Ireland at Crumlin

A 13-year-old male was referred to our dermatology outpatient department with asymptomatic matted telangiectasia affecting the upper chest, upper back, shoulder, neck and mandible in a symmetrical pattern. There was no involvement of the mucosal surfaces, no history of epistaxis and no family history of telangiectasia. These lesions had first appeared at 8-years of age and increased in size and number during puberty. He underwent extensive workup including skin biopsy and genetics for hereditary haemorrhagic telangiectasia (HHT) and HHT-like syndromes. No underlying cause was identified and treatment with pulsed dye laser was unsuccessful. In 2022, genetic testing with trio whole exome sequencing was undertaken which demonstrated a 22q11.2 deletion with a 1.3Mb deletion. Parental genetic testing confirmed that neither parent had this deletion. His background history is significant for attention deficit hyperactivity disorder, anxiety and obsessive traits. He also has a prior history of gastrointestinal symptoms including intermittent vomiting, loose stool and hyperphagia. Following his diagnosis he was noted to have subtle physical characteristics consistent with his underlying genetic diagnosis of 22q11.2 deletion syndrome. The 22q11.2 deletion syndrome has a wide clinical spectrum, affecting multiple organ systems. Common features include congenital anomalies, cardiac and palatal abnormalities; autoimmune diseases; endocrine, immune, renal and gastrointestinal complications; speech and language delays; and variable cognitive deficits and neuropsychiatric conditions. Associated dermatological presentations have rarely been reported in the literature. We present a case of 22q11.2 deletion syndrome presenting with telangiectasia in the distribution of the superior vena cava, investigation of which led to his diagnosis. This is the second case of telangiectasia in this exact distribution to present to our department in a patient with 22q11 deletion syndrome. This suggests that this may be a previously under-recognized manifestation of 22Q11.2 deletion syndrome. To our knowledge, there a no previous cases reported in the literature.

154: Development, Evaluation and Implementation of a Psychoeducation Program for Families Affected by 22q11DS*

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Background: A novel diagnosis of 22q11.2 deletion syndrome (22q11DS) leaves many parents in search of reliable information about the impact of the condition on their child, and of access to adequate (health care) services and support. This often solitary search occurs amidst an emotionally turbulent phase, where parents are also looking to move towards acceptance of the presence of 22q11DS in their family. There is a pressing need for professional support, guidance and information to caregivers at this stage. As of yet, evidence-based programs offering such psychoeducation to families affected by 22q11DS are largely lacking. Methods: In close collaboration with the Dutch patient support association Stichting Steun 22Q11 we are setting up a project to develop, evaluate, and implement an evidence-based psychoeducation program for parents whose child has recently (in the last two years) been diagnosed with 22q11DS. Results: At the current stage, we are defining the building-blocks of this group-program. To this end, next to available literature on comparable programs largely in other populations, we use input from qualitative interviews with parents (current n=44) of children with 22q11DS. Emerging themes include 'acceptance and disclosure of the condition'; 'understanding and coping with associated risks'; 'developmental perspective on required medical monitoring and care'; 'psychosocial and cognitive development'; and 'managing future expectations'. Conclusions: We are preparing a pilot of the psychoeducational program, including six (pairs of) parents/caregivers and comprising five sessions addressing the identified themes, led by professionals with expertise on that particular topic. Evaluation will include quantitative and qualitative assessment of several domains for parents (and where applicable children), including perceived agency and competency, quality of life and stress, and overall well-being. Results will inform optimizing both content and practicalities concerning the program, which then will be implemented in the context of an outpatient 22q11DS clinic within an academic children's hospital.

155: The Sleep Detectives: Co-designing a Protocol for Longitudinal Tracking of Sleep Health and Cognition in Children and Young People Living with Copy Number Variants

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Many young people living with copy number variants (CNV) present with insomnia and fragmented sleep. In 22q11.2DS, sleep disruption is associated with symptoms of ADHD and anxiety and has major impacts on children, their families and carers. Multimodal phenotyping of sleep behavior and neurophysiology should therefore be prioritized, and affords opportunities for early detection and intervention, stratification of mental health trajectories, and mechanistic insights into neurobiological mechanisms of psychiatric risk.

Building on our previous cross-sectional studies [1,2], we are now working with stakeholders to co-design a framework for longitudinal measurement of sleep behaviours, sleep EEG, inflammatory biomarkers and cognition in children and young people living with 22q11.2DS, 1q21.1 deletions or 16p11.2 duplications. We are currently:

- Collaborating with a stakeholder group of "Sleep Detectives" to set our priorities, co-design methods, and pilot protocols.
- Developing a pipeline to stratify sleep and circadian parameters in children and young people carrying CNV, using nearable, wearable (wrist-worn actigraphy and EEG headbands) and high-density EEG technologies.
- Optimising low-burden, repeatable measures of sleep-sensitive cognition, including processing speed and working memory.
- Using (i) statistical models and machine learning to develop a predictive framework mapping between sleep, cognition and psychiatric symptoms and (ii) biophysical models and blood biomarkers to infer potential synaptic, circuit and inflammatory mechanisms driving or mediating sleep and cognitive phenotypes.

Here, we report on our development of customized cognitive tests and sleep wearables for use with 6–15-year-old children, highlighting specific considerations important to People with Lived Expertise. Using these approaches has allowed detection of potential biomarkers of thalamocortical network dysfunction based on our analysis and Dynamic Causal Modelling of sleep-dependent oscillations in 22q11.2DS.

[1] Moulding H.J. et al. (2020) *Psychological Medicine* 30:1-12 PMID: 31144615

[2] Donnelly N.A., Bartsch U. et al. (2022) *eLife* 75482 PMID: 36039635

156: Anxiety and Adaptive Function in Teens with Chromosome 22q11.2 Deletion Syndrome

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Background: Individuals with chromosome 22q11.2 deletion (22q; Velocardiofacial or DiGeorge) syndrome are at increased risk for anxiety. In children ages 7-14 years, higher anxiety scores are related to lower adaptive functioning (AF; real-world living skills that support independence). However, this has yet to be explored in adolescence. We examine the relation between anxiety and AF in teens ages 12-18 years with 22q compared to typically developing (TD) peers. **Methods**: Participants were part of a larger study of psychosis proneness in 22q and included 107 (57 with 22q; 50 TD) adolescents of which 52 were female, 55 were male. Mean age was 14.8 +/- 2.1 years. Study procedures of interest were parent-completed questionnaires including the Spence Children's Anxiety Scale and the Adaptive Behavior Assessment System for Children, 2nd Edition (ABAS-II). Spence Total Anxiety Score and ABAS-II GAC (Global Adaptive Composite) scores were compared using t-tests (for means) and chi-square test. Pearson correlation coefficients were used to determine the associations between variables. **Results**: 41% of 22q participants had elevated (t>60) anxiety scores compared to only 4% of TD participants ($x^2(1) = 16.9$, $p<0.01$). Mean anxiety scores were significantly higher in the 22q group (22q: 58.4 $\pm$13.8 vs. TD: 44.1 $\pm$ 6.6; t(df)=tstat, $p< 0.01$), and AF was significantly lower among teens with 22q compared to TD teens (22q: 73.9 $\pm$ 15.3 vs. TD: 112 $\pm$ 10.1; t(df)=tstat, $p< 0.04$). Anxiety and AF were negatively correlated in 22q teens ($r= -0.29$, $p = 0.04$). **Conclusion**: Based on our sample, elevated anxiety is quite common among adolescents with 22q relative to their typically developing peers. Additionally, these elevated rates of anxiety are negatively associated with AF. This data suggests that anxiety's impact on everyday functioning remains relevant for individuals with 22q as they continue into adolescence.

157: Talking to the Teacher: the Value of Behavioral Observations of Children with 22q11DS in the Classroom

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Background: Children with 22q11.2 deletion syndrome (22q11DS) are at an elevated risk of atypical neurodevelopmental trajectories, including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). The Developmental Assessment of Genetically Susceptible Youth (DAGSY) clinic in Toronto, Canada provides interdisciplinary assessments for children with 22q11DS or with other genetic variants associated with psychiatric risk. Assessment includes a detailed diagnostic interview, psychometric testing, parent questionnaires, and a teacher interview. We examined the added value of teacher interviews on the diagnostic process. **Methods:** Parents completed questionnaires assessing ASD and ADHD (Social Responsiveness Scale, SRS, and the Swanson, Nolan and Pelham questionnaire, SNAP-IV, respectively). Teachers completed a semi-structured phone interview, and the presence of relevant social and attention concerns were documented as binary (yes/no) variables. Concordance between teacher and parent reports was quantified and impact of teacher interviews on clinical practice was examined. **Results:** Parent and teacher reports relevant to ASD were available for 31 children with 22q11.2 deletion (17/31 (55%) female, mean age 10.4 years (range 6-17 years); 5/31 (16%) received a DSM 5 diagnosis of ASD). Reports relevant to ADHD were available for 22 children (12/22 (55%) female, mean age 9.7 years (range 6-15 years), 7/22 (32%) diagnosed with ADHD). Parent and teacher reports relevant to ASD were concordant in 25/31 (81%) cases. Data from teachers altered the diagnosis in 2/31 (6%) cases. Reports relevant to ADHD were concordant in 14/22 (64%) cases; teacher-reported information altered the diagnosis in 6/22 (27%) cases. **Conclusions:** Information from teacher interviews may alter diagnostic conclusions in school-aged children with 22q11DS. Teachers provide clinically relevant information about the child's behavior and a better understanding of resources available in the school context. As part of a comprehensive assessment, teacher interviews may promote confidence in diagnostic conclusions and facilitate tailored recommendations towards promoting the child's development.

158: Leveraging Early Genetic Diagnoses: The Exemplary Case of 22q11.2 Deletion Syndrome in Addressing Caregiver Needs in Neurodevelopmental Disorders

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This lecture delves into the increasing trend of early diagnosis of pathogenic genetic variants associated with neurodevelopmental and psychiatric disorders (NPDs). Focused on the vital aspect of psychological support post-genetic diagnosis, we present findings from a comprehensive literature review. Key areas explored include how caregivers receive information about NPD vulnerabilities linked to genetic variants, the challenges they face, and the provision of psychological support. Drawing from two decades of in-depth study on the 22q11.2 deletion syndrome, we shed light on the complex needs of caregivers. The discussion encompasses topics such as effective communication of the diagnosis, early identification of NPD signs, and coping with stigma and a lack of medical expertise outside specialized genetics clinics. Notably, the absence of psychotherapeutic support for parents is highlighted, emphasizing the struggle caregivers face with unmet needs regarding the longer-term NPD implications of a genetic diagnosis such as 22q11.2 deletion syndrome. In conclusion, we advocate for the evolution of the field beyond the explanation of genetic diagnoses, urging the development of comprehensive approaches to support caregivers in effectively communicating and managing NPD implications throughout a child's lifespan.

159: Development and Delivery of Psychoeducational and Parenting Programmes for 22q11.2DS Families in Ireland

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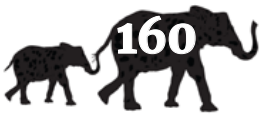
Background: Higher incidence of psychiatric conditions among individuals with 22q11.2DS is well established. Information about future mental health difficulties is often omitted or poorly delivered at time of diagnosis leading to increased stress and anxiety for parents and caregivers. Psychoeducational programmes increase knowledge, understanding, and could alleviate parental fears. As part of the integrated care provided to children with 22q11.2DS, a number of initiatives for parents were piloted and evaluated over a period of six years. The aim is to present a summary of our experience of delivering psychoeducation and parenting support for parents and caregivers of children with 22q11.2DS. **Methods:** A qualitative study to assess parental knowledge and need for psychoeducational programme was conducted in 2017. Based on the results a programme of four sessions was designed, covering key developmental stages (2018-2019). Anonymous feedback was obtained to guide future development. A suit of video psychoeducational materials was developed (2022) to increase accessibility and a parenting programme was piloted (2023). **Results:** Our qualitative study demonstrated the need for a psychoeducational programme and guided the development of topics. Two cycles of psychoeducational sessions were offered between 2018-2019 attended by 25 adults. Feedback was obtained from attendees using Likert scale questions (range 1 to 5) and free text. The sessions met the expectations of 89% of the participants (Mean 4.3). Content and structure were rated highly, 94% of the attendees (Mean 4.5). Evidence-based parenting programme was run in a small feasibility group. Parents moved significantly towards achieving individual and child-oriented goals. A common positive theme was the value of being part of a support group and sharing experiences with other parents. **Conclusion:** Our studies demonstrated feasibility and benefits for parents. The small sample sizes are limiting factor. The practical difficulties for parents attending and the lack of dedicated clinical time is an ongoing challenge.



160: Semi-structured Interviews with Parents/Caregivers of Children with 22q11.2 Deletion Syndrome Highlight Areas Where Support is Needed

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Background: Caregivers of children with 22q11.2 Deletion Syndrome (22qDS) manage complex medical, neurodevelopmental, and psychological concerns. Finding resources and support is daunting, as parents must understand a myriad of topics. We conducted semi-structured qualitative interviews with parents of children with 22qDS to guide the development of parent support groups. **Methods**: Parents of children with 22qDS were contacted after expressing interest in supporting 22q program development and were invited to participate in one of two 90-minute focus groups. The focus groups were held via Zoom and were facilitated by 2 psychologists. Discussions followed a semi-structured interview guide developed by a multidisciplinary team of clinicians in the 22q Program. Interviews were audio-recorded and transcribed. Three independent coders used a rapid qualitative analysis approach to generate themes. **Results**: Of 15 families contacted, 11 parents consented and 9 participated in an interview. Focus groups were conducted between March and April 2022. Interviews were conducted in English (the primary language of all participants). Parents represented 2 male and 6 female children who ranged in age from 11 months to 12 years at the time of the interview (average 6.81 years). Interview topics included Medical (general pediatrics, cardiology), Nutrition and Growth, Immunology, Speech and Language, Early Literacy and Educational Services, Social Support, and Psychology/Psychiatry. Across domains, common themes included a need for anticipatory guidance. Participants also expressed a need for education and assistance with complex medical decision-making. **Conclusions**: Given the broad 22qDS phenotype, it is unsurprising that parents expressed a need for greater anticipatory guidance and assistance with medical decision-making. Topics for anticipatory guidance included expectations for developmental milestones and school transitions. Specific medical decision-making issues included speech surgery and transitions from gastrostomy tube to oral feedings. We are using these data to guide the development of parent support groups and informative materials.

161: Evaluating the Relationship Between Parent Mental Health, Parenting Skills, and Child Behavioural Issues in Families Affected by 22q11.2 Deletion Syndrome *

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Background: 22q11 Deletion Syndrome (22q11DS) is the most common microdeletion syndrome with broad phenotypic variability. Many children with 22q11DS have disorders such as autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), and intellectual disability (ID), which can come with varied challenges. A few studies have shown a significant relationship between parenting styles and behavioural issues in children with 22q11DS. Additionally, the health problems associated with 22q11DS can impact the mental health of patients as well as their families. Like parents of children with other chronic diseases, parents of children with 22q11DS may be at an increased risk of poor psychological well-being. In this study, we aim to examine the relationship between parent mental health, parenting skills, and behavioural issues in children with 22q11DS. **Method:** 81 caregivers of children with 22q11DS completed an online survey with well-established questionnaires regarding parenting styles (coercive parenting, positive encouragement, parental consistency, and parent-child relationship), child behaviour (internalizing and externalizing behavioural issues), symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD). Correlation analyses and linear regression models were run to examine the relationship between parenting style, child behaviour, and mental health. **Results:** Symptoms of depression, anxiety and PTSD in parents predicted internalizing behavioural issues in their children with 22q11DS. Depression and anxiety predicted externalizing behavioural issues. We found no mediation effect between study variables, meaning that parenting skills and parental mental health independently influence child behaviour. Additionally, parent mental health was a stronger predictor of behavioural issues in the child with 22q11 compares to parenting styles. **Conclusions:** Caregivers of children with 22q11 express a high need for mental health support and help in acquiring better skills to manage the children's behaviour. This would likely increase the wellbeing of parents as well as their child with 22q11DS.

162: Co-Production: a Transition Clinic for Young People with 22q11.2 Deletion Syndrome.

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Background: A key outcome from developing a rare disease model of care has been the novel establishment of a transition clinic in St James Hospital for young adults living with the genetic disorder 22q11.2ds. An example of Co-Production in practice, The clinic is an innovative multi-site initiative between CHI at Crumlin, St James Hospital, HSE Disability and the patient organisation 22q Ireland. The clinic was established to improve long-term outcomes and optimise referrals to speciality colleagues using care co-ordination; reduce patient and family stress, improve patient experience and improve patient outcomes; and to demonstrate an example of a co-produced transferable model of care for rare diseases. **Methods**: Informed by qualitative research (literature review 2020, This pilot Transition Clinic was developed through multi-stakeholder collaboration involving the patient organisation 22q Ireland, both the paediatric and adult leads in Ireland, the 22q Care Coordinator, and was informed by the 22q Ireland Young Experts by Experience Panel (YEEP). Key phases of the Transition Clinic include communication with and assessment of young people in preparation for transition by the care coordinator; clinical appointments in both paediatric and adult hospital settings during the years of transition aged 16 to 21 with the adult and paediatric leads; and individual patient needs tailored during the transition process, including best practise guidelines to ensure best clinical outcomes. **Results:** Reported patient benefits recorded include an improved service user experience including reduced patient and parental stress and anxiety; reduced health service waiting times; improved health literacy, increased patient and parental satisfaction with the transition process; improved quality of care; and improved patient outcomes. **Conclusion:** The co-production methodology has resulted in improved understanding of the complex rare disease 22q11.2ds; increased opportunities for interdisciplinary, cross-hospital site collaboration; and increased referral rates for multi-disciplinary care.

163: BE-WEHL Wellness Education for Families of Children with Behavioral Health Challenges

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Introduction: Anxiety disorders have been reported in 60% of individuals with 22q11.2 deletion syndrome (22q11.2DS). Integrative Health (IH) modalities like mindfulness, yoga, and general wellness education have shown to be effective in improving mental health for children and adolescents, as well as easing stress among parents of children with complex needs. A recent survey of 77 caregivers of children with 22q11.2DS, followed at the Children's Hospital of Philadelphia (CHOP), found IH therapies helpful (94%) and sought IH therapies for stress and relaxation. BE-WEHL, a family-based wellness education curriculum for families of children with behavioral health challenges, was designed at CHOP as a virtual intervention. Feasibility and acceptability of BE-WEHL for families diagnosed with/at risk for mild-moderate behavioral health disorders, including anxiety and depression, was explored - with the goal of implementing for families whose children have 22q11.2DS. **Methods:** From 2020 to 2022, 52 families from underserved urban communities, identified through Behavioral Health clinicians, participated. The demographic was primarily Black (62%), with a significant portion of female patients (69%) and an average age of 13 years. The program, delivered by a Community Wellness Educator, spanned five weeks covering topics including yoga, mindfulness, and nutrition, supported by a wellness kit. Feedback was gathered to assess program delivery effectiveness. **Results:** A high completion rate (79%) and engagement were observed, with three family members attending each session on average. Caregiver feedback (n=16) was overwhelmingly positive as 100% indicated the classes were helpful. Highlighted benefits included improved family health and the intention to continue with acquired skills, specifically yoga (93%) and nutrition (88%). **Conclusions:** BE-WEHL's pilot demonstrated strong acceptability and positive feedback, making it a promising family-based intervention which we plan to implement in the coming months for families of children with 22q11.2DS, offering a novel, financially accessible, and evidence-informed approach to family-centered wellness education.

164: Characteristics of Motor Patterns in Infants with 22q11.2DS: Bayley Trends and Early Signs of Neuromotor Impairment

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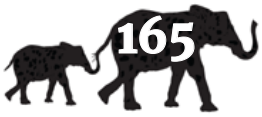
Background: Neurodevelopmental delays are a common clinical feature of 22q11.2DS. Several potential factors impacting early neurodevelopment including hypotonia, visual-vestibular disturbances, and sensory-motor challenges are described in existing literature. Developmental motor delays are documented in the literature; however, few studies describe neuromotor trends in infants. The goal of this study is to describe early data trends from Bayley Scales of Infant Development-4 (BSID 4) scores and clinical observations of motor patterns with infants receiving care at Seattle Children's Hospital (SCH) 22q clinic. **Methods:** We completed a retrospective review of electronic medical records for patients with 22q11.2DS who were seen in the SCH 22q Infant Neurodevelopmental Clinic between Jan 2022-Jan 2024. Patients received a developmental evaluation completed by the SCH 22q Clinical Psychologist and Occupational Therapist using the BSID 4. Areas evaluated included Cognitive, Fine Motor and Gross Motor domains, as well as clinical observations of movement patterns. Demographic data included age, gender, race/ethnicity. Descriptive data collected across groups included age of diagnosis and comorbidities. **Results:** Between Jan 2022- Jan 2024, 13 patients with 22q11.2DS received a multidisciplinary developmental evaluation. The cohort included: M_{age} *= 11 months, range 7-15 months*; 7 males, 6 females; diverse racial backgrounds and comorbidities. Preliminary data on BSID 4 scores shows relatively commensurate cognitive and fine motor scores with lower trending gross motor scores. Further clinical observations identified atypical motor differences including; delays in weight bearing in 10 patients, hand preference in 4 patients and tonal asymmetries in 2 patients. **Conclusions:** Patients with 22q11.2DS often present with multifactorial neurodevelopmental challenges necessitating school age support. We found that identifying characteristics of early sensory-motor disturbances in infancy allowed for timely caregiver education, specialized referrals and targeted patient interventions. This study is our first step in characterizing developmental trends for infants with 22q11.2DS. Further study is imperative in understanding the unique developmental needs of this special population to modify testing protocols and provide optimal early intervention.



165: Investigating Convergence of Neurodevelopmental Mechanisms Between 16p11.2 CNV and Cullin3 (*Cul3*) using Brain Cortical Organoids

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Background: The 16p11.2 CNV and Cullin3 ubiquitin ligase (Cul3) are both confidently implicated in Neurodevelopmental Disorders (NDDs) with genome-wide significance (FDR < 0.001). Furthermore, one of the genes within 16p11.2 CNV codes for an adaptor protein for Cul3, and this protein complex regulates the levels of a small GTPase RhoA. Previously, we have demonstrated that RhoA is upregulated in 16p11.2 organoids and in the brain of Cul3 mouse. Here, we are investigating additional points of convergence between these mutations in the human-derived models. **Methods**: To investigate the convergent molecular and cellular mechanisms behind these mutations, we engineered iPSCs with Cul3 haploinsufficiency ($Cul3^{+/-}$) using CRISPR-Cas9 technology. One of these mutations (E246X stop gain) replicated the mutation observed in the patient with autism. We then generated brain cortical organoids from several different haploinsufficient $Cul3^{+/-}$ clones, and the organoids were used to investigate size, neuron migration, network dynamics, proteomic and transcriptomic signatures at the single cell level. **Results**: Our initial characterization revealed that both 16p11.2 and $Cul3^{+/-}$ organoids exhibit severely impaired neuronal migration, marked by a lower number of neurons migrating out of mutant organoids and a shorter migration distance compared to controls. Furthermore, we found RhoA upregulation in both organoid models, consistent with the results from the mouse. Some of the axonal cytoskeletal proteins were differentially expressed in Cul3 organoids. We are carrying out single cell transcriptomic profiling to evaluate defects in specific cell type populations. **Conclusion**: The study demonstrates the utility of human brain organoid models for investigating the convergent mechanisms of ASD-related mutations. The 16p11.2 and $Cul3^{+/-}$ organoids exhibit impaired neuronal migration, possibly reflecting defects seen in the fetal brain. Finally, the RhoA upregulation provides a potential molecular mechanism for the observed migration defects, given its role in cytoskeletal dynamics, neurite outgrowth and cell migration.

166: Changes in Brain Structure and Associated Functions in children with 22q11.2 deletion syndrome versus Controls: A six-year Longitudinal Study

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[1]University of North Carolina-Chapel Hill; [2]Duke University Medical Center; [3]Harvard Medical School

Background: Children with 22q11.2 Deletion Syndrome (22q11DS) are at-risk for altered neurocognitive and neuropsychiatric dysfunction, with a variety of brain structures/functions being associated with these difficulties (Ge et al., 2024). *The purpose of this study is to examine key brain structures in children with 22q11DS and track their trajectories and associated changes in function over time.* **Methods:** Participants included 77 children with 22q11DS and 81 age- and sex-matched controls. The 22q11DS group was 10.5 years of age and 53.4% male, while the control group was 10.9 years and 53.1% male. Socioeconomic status was similar in both groups. Brain imaging utilized a GE MRI Tesla 1.5 or 3.0, with images collected at study entry and every 3 years. Targeted brain structures included corpus callosum (CC), lobules, cerebellum, cingulate, gray (GM) and white matter (WM) volumes, caudate, nucleus accumbens, and hippocampus. Positive and negative symptoms were detailed using the SIPS/SOPS. Analyses employed MANCOVA with age, sex, and total intracranial volume as covariates. **Results:** After adjustment, results revealed medium to large effect sizes for the group-by-time interactions for reductions in the right parietal and occipital lobes in 22q11DS. A significant group effect was seen for a decrease in right cerebellar WM volumes and for an increase in CC volumes in the 22q11DS group. The main effect of group on the GM volumes was significant, but there were no significant group-by-time interactions in GM volumes from T1 to T3 in the four lobules or cerebellar regions. *Figure 3* illustrates a decline in GM of the superior temporal region from T1-T3 in 22q11DS, with increasing positive prodromal symptoms being manifested. **Conclusions:** These findings support studies noting the differential longitudinal trajectories of brain structures in 22q11DS when compared to controls, inviting further longitudinal examination of the neurobiological mechanisms underlying neurodevelopmental manifestations in this pediatric population.

167: Neurodevelopmental Disorders and Executive Function in a Clinical Sample of Children and Adolescents with 22q11.2

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Background: Individuals with 22q11.2 deletion syndrome are at an increased risk for neurodevelopmental disorders, functional impairment and executive dysfunction. With respect to the former, less is known about individuals with 22q11.2 duplication syndrome. Early identification is required to prevent poor outcome. Follow-up of individuals with 22q11.2 in Norway is currently mainly limited to regular scheduled assessment of physical variables. The aim of the current study is to assess adaptive and executive functioning in individuals with 22q11.2 and to screen for neurodevelopmental disorders. **Methods:** Consecutive recruited participants with 22q11.2 deletion or duplication syndrome between the ages of 3-18 years are screened for neurodevelopmental disorders and executive dysfunction. The screening package for neurodevelopmental disorders consists of Social Communication Questionnaire (SCQ) and ADHD Rating Scale-IV (ADHD RS). Adaptive function is assessed with Vineland Adaptive Behavior Scales–third edition. The parent version of Behavioral Rating Inventory of Executive function (BRIEF-P-2) is used to assess executive function. Descriptive statistical analysis is performed. **Results:** This is an ongoing study. We expect to present preliminary results for approximately 30 participants. Currently around 15 participants are recruited. The presentation will include the analysis of demographic and diagnostic variables with a special focus on the reported prevalence of autism and ADHD compared to results from the current screening process. Adaptive and executive functioning of included participants will be explored. In addition, potential syndrome-specific manifestations of neurodevelopmental disorders will be reported on. **Conclusions:** Preliminary results from an ongoing study assessing adaptive and executive functioning and screening for neurodevelopmental disorders in a clinical sample of children and adolescents with Copy Number Variations in region 22q11.2 will be discussed.

168: Threat Sensitivity and Neuropsychiatric Disorders in Individuals with 22q11.2 Deletion Syndrome

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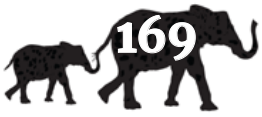
Background: Individuals with chromosome 22q11.2 Deletion Syndrome (22q11.2DS) are at high risk for developing neuropsychiatric disorders across the lifespan. Despite this risk, little is known about longitudinal markers shaping risk pathways. Heightened threat sensitivity, a dysregulated set of responses to real or potential cues of threat in the environment, is a plausible neurocognitive factor that could place individuals with 22q11.2DS at increased risk for neuropsychiatric disorders. In non-affected individuals, the link between increased threat sensitivity and internalizing disorders is well documented. However, there remains a gap in our understanding of threat sensitivity in individuals with 22q11.2DS and how emotion processing patterns are associated with their increased risk of neuropsychiatric disorders. The current study examines behavioral indices of threat processing in children and adults with 22q11.2DS across the lifespan. **Methods:** Under an IRB approved study, 306 individuals with 22q11.2DS (Females=148; Mean Age=19.2, SD=9.65) completed two emotion tasks (i.e., the Penn Emotion Recognition Task and Penn Emotion Differentiation Task) from the Penn Computerized Neurocognitive Battery. Analysis is ongoing including examining differences in accuracy and reaction time parameters to threat conditions (angry and fear emotion trials) compared to neutral and non-threat (e.g., happy emotion trials) conditions; results of the semi-structured clinical assessment specifically examining clinical symptoms and neuropsychiatric disorders; and creating a threat sensitivity factor using data reduction techniques (confirmatory factor analyses) on behavioral data. Logistic regressions will explore relations between threat sensitivity and neuropsychiatry disorders. Interactions with sex, age, comorbidities such as absence or presence of congenital heart disease and deletion size, will be tested. **Results:** Data collection is complete and full data analyses will be discussed at the meeting. **Conclusions:** Understanding patterns of threat sensitivity in individuals with 22q11.2DS is important, especially given the high rates of psychopathology in this condition. We will discuss our findings compared with unaffected individuals.



169: 22q Microdeletion Predisposes iPSC derived Microglial like Cells to Increased Activity *

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As the brain's resident macrophage, microglia contribute to a myriad of developmental, homeostatic, and pathological mechanisms. One key aspect which allows for microglia's dynamism is their metabolic flexibility. Given that nine of the canonical thirty genes deleted in 22q.11.2 have links to mitochondrial or metabolic function, diminished metabolic capacity may contribute to microglial dysfunction and contribute to the development of 22q.11.2 Deletion Syndrome's association with neuropsychiatric symptoms. Our study sought to investigate how the microdeletion altered microglial function using an hESC based CRISPR-CAS9 edited isogenic cell model. We utilized our previously published protocol for differentiation into microglial like cells (iMG) and characterized transcriptomic and functional aspects of microglial function. We found, *in-vitro,* that the transcriptomes of microglia harboring the deletion expressed genes relevant to immune responses, inflammatory response, and positive regulation of cell activation at higher levels compared to their isogenic counterparts. Similarly, after stimulation with a low dose (2 ng/ml) of interferon gamma, differentially expressed genes upregulated in deleted iMG were enriched in chemokine receptor activity, as well as in phagocytic pathways. We further saw these trends towards increased activation in deleted after xenotransplantation of iMG, with GO terms for upregulated genes including metabolic processes, nitrogen compound metabolic process and cell cycle. Future work will characterize synaptic uptake of these cells both *in-vitro,* and *in-vivo.*

170: Convergent Biology among Copy Number Variants Associated with Schizophrenia

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In this exciting new project, we will compare the molecular and cellular consequences of CNV with high risk for schizophrenia, including deletions at chromosomal locations 2p16 (localized to the NRXN1 gene), 3q29, 15q13.3, 22q11.2, and duplication at 16p11. A consistent but surprising observation about these SZ-associated rare variants is their similarity in both effect size and phenotypic characteristics. We hypothesize that the high penetrance of these rare SZ mutations derive from large effects at the molecular and cellular levels. We further hypothesize that the downstream consequences of these variants converge on shared molecular targets and/or cellular pathways. To test these hypotheses, we will leverage the Genomic Psychiatry Cohort (GPC), a diverse cohort with significant representation of African ancestry. We will generate iPSC lines from individuals with SZ who carry one of these five defined variants (n=20 of each genotype, 100 iPSC lines total), prioritizing underrepresented minorities. Controls (n=40) will be matched by genomic background to the SZ cases, increasing the rigor of our study. We will test the hypothesis that SZ-associated rare mutations cause molecular perturbations in neurons at the level of chromatin accessibility and gene expression and that genes or pathways impacted by two or more of these SZ-associated variants converge, with more overlap than expected by chance. We will validate molecular pathways using multimodal cellular phenotypic levels of analysis. Identifying the specific biological processes that are disrupted by SZ-associated loci will open a window into the complex molecular biology of this disorder. The substrate for our mechanistic studies will include subjects with diverse genetic backgrounds that have been historically underrepresented in genetic studies, ensuring that our results are generalizable to these communities, who suffer disproportionately from adverse mental health outcomes. At the meeting, our most recent results will be presented.

171: Analyzing Mitochondrial Deficits in 22q11.2 Deletion in Developing Neural Models *

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Background: 22q11.2 deletion (22qDel) is a 3Mb deletion that causes the hemizygosity of dozens of genes, including nine nuclear-encoded mitochondrial genes. However, little is known regarding the mechanisms of 22qDel mitochondrial phenotypes and their contribution to human cortical development. We hypothesize that reduced expression of mitochondrial proteins encoded by the 22q11.2 locus impacts mitochondria, thereby affecting neuronal development. **Methods:** Induced pluripotent stem cells (iPSCs) from neurotypical study subjects were genetically engineered to isogenic 22qDel iPSCs using CRISPR/Cas9. Cortical organoids derived from the isogenic 22qDel iPSCs and their clonal controls were differentiated and grown to d50, d100, and d150 in vitro (DIV) (N=5/genotype/time-point). Tandem mass tagging (TMT) was conducted to multiplex protein quantification across each organoid DIV. Western blotting was performed to quantify the expression of various mitochondrial proteins in neural progenitor cells (NPCs) and organoids. **Results:** Proteomic analysis of 22qDel organoids across early developmental time points indicated broad dysregulated expression of mitochondrial proteins, beyond those directly affected by 22qDel, including decreased expression of complexes in the electron transport chain (ETC). Complex reduction was verified in organoids using an oxidative phosphorylation (OXPHOS) antibody mix that reports the expression of assembled complexes. **Conclusions:** Proteomic and bioinformatic analysis from isogenic 22qDel organoids suggests that mitochondrial vulnerabilities emerge in 22qDel throughout cortical development and may lead to dysregulated mitochondrial translation and complex expression of the ETC. Future directions of this project will utilize study participant 22qDel iPSC lines to investigate mechanisms of mitochondrial phenotypes.

172: The Role of screening Tools in the Psychiatric Evaluation of Children with 22q11.2 DS

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Background: Children with 22q11.2 Deletion Syndrome (22q11.2DS) are more likely to present with neurodevelopmental conditions and develop psychiatric problems throughout their life span than peers not affected by the deletion. Currently in Ireland there is one specialised interdisciplinary 22q clinic led by a general paediatrician and a clinic coordinator. Psychiatry assessments are provided upon request by members of the hospital liaison psychiatry team. The aim of this report is to summarise the clinical profile of our cohort of patients with 22q11.2DS referred to psychiatry. **Methods:** Descriptive study of the findings following a psychiatric review and exploration of the Child Behavioral Checklist 6-18y (CBCL) and Teacher Report Form (TRF) profiles based on the Internalizing/ Externalizing/ Total Problems Scores and the DSM-oriented scales. **Results:** A total of 117 referrals, of children age 5-19, were sent to psychiatry. 90 assessments were conducted including re-referrals. 63 (70%) young people met the diagnostic criteria for at least one psychiatric condition, anxiety disorder being the most prevalent diagnosis, followed by ADHD. CBCL questionnaire scores were available for 54 (46%) of the cases. The average score for Internalizing Problems in our cohort was within the clinical range (64, SD 11.74), Externalizing problems – normal range (54, SD 10.18), Total Problems – borderline range (63, SD 9.00). TRF scores were recorded for 50 (42%) cases. Similar profile was reported by teachers. On the CBCL DSM oriented scales the average score for depressive and anxiety problems were within the borderline range (65, SD 8.59 and 65, SD 12.18 respectively). **Conclusion:** Our data reaffirm the importance of early psychiatric screening in the young 22q population and the benefit of using formal measuring tools in conjunction with clinical assessment to identify areas of concerns in and support clinical formulation.

173: Psychophysiological Deficits in 22q11DS *

David Parker[2,3], Sid Imes[2,3], Gabrielle Ruban[2,3], Brett Henshey[1,2], Nicholas Massa[2,3], Grace Lee[1], Bruce Cuthbert[2,4], Opal Ousley[4], Elaine Walker[5], Erica Duncan[2,4] , Joseph Cubells[3,4]
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Background: The 22q11.2 deletion syndrome (22q11DS) is one of the most robust genetic predictors of the development of psychosis and other psychiatric illnesses. In this study, we examined performance on multiple putative psychophysiological biomarkers of psychosis risk in 22q11DS subjects and healthy comparison subjects (HC), and examined the associations of these markers with cognitive and clinical symptoms. **Methods:** 22q11.2DS (n=37) and HC subjects (n=32) completed a sensorimotor reactivity measure (finger-tapping task (FT)) and four psychophysiological measures (acoustic startle response (ASR), auditory mismatch negativity (MMN), auditory steady-state response, and resting state EEG)) as part of the Emory 22q11DS project. Magnitude and latency of the ASR, mismatch negativity event related potentials (ERPs), and EEG neural oscillations were quantified. Cognition was measured with the MATRICS and Wisconsin Card Sorting Test. Group-by-Sex ANOVAs were completed with age as a covariate. Significant psychophysiological variables were compared to clinical and cognitive measures. **Results:** Compared to HC subjects, 22q11.2DS subjects had: slower FT performance ($p<.001$), significantly fewer startlers in the ASR paradigm ($p<.001$), lower startle magnitude ($p<.002$) and slower ASR onset latency ($p= .019$), a smaller (in absolute magnitude) MMN ERP response to double-deviant stimuli ($p=.041$), reduced 40 Hz Steady-State evoked ($p= .029$) and single-trial power ($p=.005$), and high intrinsic neural activity in the delta/theta ($p<.002$) and gamma frequency ranges ($p=.006$). Slower FT speed was associated with higher SIPS positive symptoms, and all psychophysiological measures were strongly associated with cognitive measures. **Conclusions:** We examined a number of putative biomarkers of psychosis risk in 22q11DS subjects compared to HCs. Significant differences were observed across psychophysiological measures and these were strongly associated with cognitive performance. Future work will use multivariate methods to clarify the relationship between psychophysiological measures and clinical and cognitive outcomes in 22q11DS.

174: Environmental Influence on the Patients with 22q11.2 and 16p11.2 Deletions and Duplications *

Yelyzaveta Snihirova[1], Therese van Amelsvoort[1], Claudia Vingerhoets[1], Mieke van Haelst[2], David E.J. Linden[1] & Dennis van der Meer[1,3]

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22q11.2 and 16p11.2 are two genomic regions that are frequently involved in copy number variations (CNVs), either deletions or duplications of DNA segments. These CNVs are associated with various neurodevelopmental disorders, including schizophrenia, autism, and intellectual disability. However, the influence of environmental factors such as socioeconomic status, lifestyle and stress on phenotypic variability and well-being of carriers has not been studied yet. In this study, we aimed to compare the environmental profiles of individuals with 22q11.2CNVs and 16p11.2CNVs. We compared various environmental measures in 22q11.2 deletion (n=107) and duplication carriers (n=20), and 16p11.2 deletion (n=35) and duplication carriers (n=5) from an ongoing study cohort on CNVs and deep phenotyping. Using standardised questionnaires and structured interviews, we assessed various environmental measures, such as substance use, birth complications, socioeconomic status, sleep quality, family environment, and adverse life events. We performed chi-square and Kruskal-Wallis tests to compare the groups on these measures. We found no significant difference in number of life adverse events, substance use and birth complications between the groups. However, we found significant differences in socioeconomic status (mother's education (Chi-squared= 42.94, p=0.02) and occupation type (Chi-squared=113.47, p<0.001), sleep quality (narcolepsy (Chi-squared=23.99, p<0.001) and night terrors (Chi-squared=14.66, p=0.002)). We also found a significant difference in the medians of negative family environment (Kruskal-Wallis test, Chi-squared=7.80, p=0.05), with 16p11.2 duplication individuals having a significantly higher median (more negative family environment) than 16p11.2 deletion carriers and 22q11.2 duplication carriers ($p < 0.05$). Our results suggest that individuals with 22q11.2 and 16p11.2 CNVs have distinct environmental profiles, which may contribute to their phenotypic variability and clinical outcomes. These findings highlight the importance of considering environmental factors in diagnosing and treating patients with these CNVs, and the need for further research to make a more personalized approach. Funding acknowledgement NIH_5U01 MH119740 to TvA

175: Working Group of European 22q11 Expertise Centers: Organizational Differences, Similarities and Opportunities

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Background: Children with 22q11.2 deletion (DS) and duplication (DUPL) syndrome and their families may display different medical and psychosocial needs. During and after transition into adulthood new questions on occupational, relational and/or residential issues, and coping strategies may arise, next to medical challenges in adulthood. These needs can often (partially) be met by well-organized local, regional and / or national clinics. Differences in level of organization, specialty involvement, and shared care solutions between centers may have historical or pragmatic origins, as well as distinct implications for patients. In this study we explore the design features of 22q11 outpatient clinics in different European expertise centers. **Methods:** Within the recently started working group on 22q11 within the European Refence Network (ERN) for rare and/or complex craniofacial anomalies and ear, nose and throat (ENT) disorders (CRANIO), we carried out a survey on design features of regional and national 22q11 reference centers. **Results:** Of the 10 centers involved, responses from 7 centers (3 national, 4 regional function) were received. Adherence populations ranged from 800.000 to 17.000.000 inhabitants; cohort sizes ranged from 30 to 600 patients. Centers that were also involved in 22q11DUPL care, reported that these patients formed 10% of their cohort. Fractions of pediatric vs adult patients varied largely, from 100 vs 0% to 12 vs 88%. The most prevalent specialties involved were ENT-surgery and speech pathology; besides, there were large differences over specialty types involved: medical or surgical, and childhood or adult care. **Conclusions:** A European working group of 22q11 expertise centers has been founded. Large differences in geographic function, cohort size, focus on childhood or adult care and on 22q11DS solely or also on 22q11DUPL exist. The working group may provide an effective platform to raise trans-national standards of care, to exchange experiences, and to boost research opportunities and knowledge transfer.

176: Phenotypical Characteristics of Children with 22q11 Duplication Syndrome: A Clinical Chart Review Analysis

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Introduction: 22q11.2 deletion syndrome (22q11DS) and 22q11.21 duplication syndrome (22q11DupS) are genomic disorders that result from unequal crossover during meiosis. Therefore, the incidence is expected to be equal. Nevertheless, in literature a higher prevalence of 22q11DS is found in clinical cohorts. This study aims to complement our current knowledge about the phenotypical presentation of 22q11DupS, thereby helping clinical recognition. In this study we analyze the clinical phenotype of 22q11DupS in a large Dutch series of patients and in relation to existing literature. This study also describes the prevalence of scoliosis and impeded speech intelligibility, areas often not reported in literature.
Methods: A retrospective chart review was carried out, including 38 children (median age 8.5, range 1-18 years) with 22q11DupS. Moreover, we also conducted a literature review to integrate our findings within the larger cohort. **Results**: The median age at diagnosis postnatally was 4 years. Parental inheritance was present in 68.4% of the families. Congenital heart defects were present in 7/27 (26%) patients, T cell lymphocytopenia in 2/21 (9.5%), scoliosis in 4/20 (20%), feeding problems in 10/20 (50%) and eye/vision anomalies in 19/23 (82.6%) and congenital urogenital anomalies 2/21 (9.5%). Cleft palate was present in 2/32 (6.3%), velopharyngeal insufficiency in 4/21 (19%) and hypernasal speech in 5/23 (21.7%), speech intelligibility was determined as insufficient in 10/22 (45%). Thyroid and parathyroid dysfunction were absent in all patients. Developmental delay and psychiatric problems were present in 50% of the patients. **Conclusion**: Children with 22q11DupS show a wide variation congenital and clinical problems. Our data confirms results found in previous literature. The prevalence of various problems is different compared to the 22q11.2 DS and warrants adapted screening and follow-up guidelines for children with 22q11DupS, opposed to those for 22q11.2DS. More and larger (multicenter) cohorts are needed to minimize the risk of bias.

177: Maternal 22q11.2 Triplication (LCR22A-LCR22D) Resulting in a 22q11.2 Duplication (LCR22A-LCR22D) in Two Siblings*

Kelly Regan-Fendt[1,2,3], Bekah Wang[1,2], Daniel E. McGinn[1,2], Audrey Green[1,2], Victoria Giunta[1,2], Lydia Rockart[1,2], Emma Schiavone[1,2], Conner Weinberg[1,2], Oanh Tran[1,2], T. Blaine Crowley[1,2], Beverly S. Emanuel[1,2,3], Elaine H. Zackai[1,2,3], and Donna M. McDonald-McGinn[1,2,3,4]

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Background: 22q11.2 duplication syndrome (22q11.2DupS) is expected to be as common as 22q11.2 deletion syndrome (22q11.2DS), resulting from meiotic NAHR in patients with *de novo* CNVs, previously reported in 1 in 850 and 1 in 992 pregnancies respectively. Despite this prevalence, few 22q Centers report experience with 22q11.2DupS while families continue seeking guidance. In our 22q11.2DupS cohort (n=275), features overlap with 22q11.2DS including structural anomalies/medical problems, neurocognitive/behavioral differences - but the overall frequency is reduced. Familial cases (72%-78%) are more common than 22q11.2DS (~10%) leading to identification of undiagnosed relatives with significant genetic counseling implications. Here we report an atypical family where the proband presented with a standard LCR22A-LCR22D duplication due to a maternal 22q11.2 triplication (LCR22A-LCR22D). **Methods:** The 12-year-old male presented at 7 years-of-age with FTT, asthma, allergies, epistaxis, cerumen impaction, constipation, sacral dimple, macrocephaly, ADHD, dyslexia, sleep difficulties, language disorder, poor impulse control, developmental delay and autism. **Results:** Familial studies identified a standard 22q11.2 duplication (LCR22A-LCR22D) in the 8-year-old brother with severe eczema, food allergies, asthma, s/p T&A, hydrocele, constipation, macrocephaly, learning differences, language disorder, ADHD, and autism; and a maternal 22q11.2 triplication (22q11.21(18,916,843_21,465,659)x4. Mother has a right aortic arch, mixed hearing loss, astigmatism, recurrent otitis media, chronic rhinosinusitis, hypodontia following multiple extractions, dysphagia, GERD, constipation, sacral dimple, osteoarthritis, urinary incontinence, migraines, learning differences, mood dysregulation, and ADHD. Paternal 22q11.2DupS studies were negative. Maternal grandparents were unavailable for testing. **Conclusion:** 22q11.2 triplication has previously been reported four times in the literature, all had cognitive deficiencies, 3/4 had cardiac anomalies, and 2/4 had hearing impairment. Given both children are affected herein, we can assume the mother has a double duplication in trans resulting in a 100% recurrence risk. Thus, this family highlights the frequency of the condition and the importance of parental studies to provide accurate genetic counseling.

*Indicates Junior Investigator

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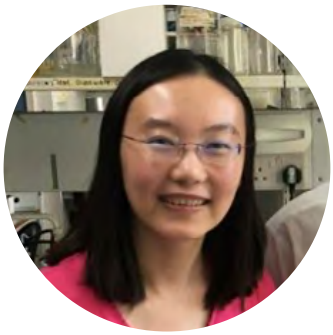

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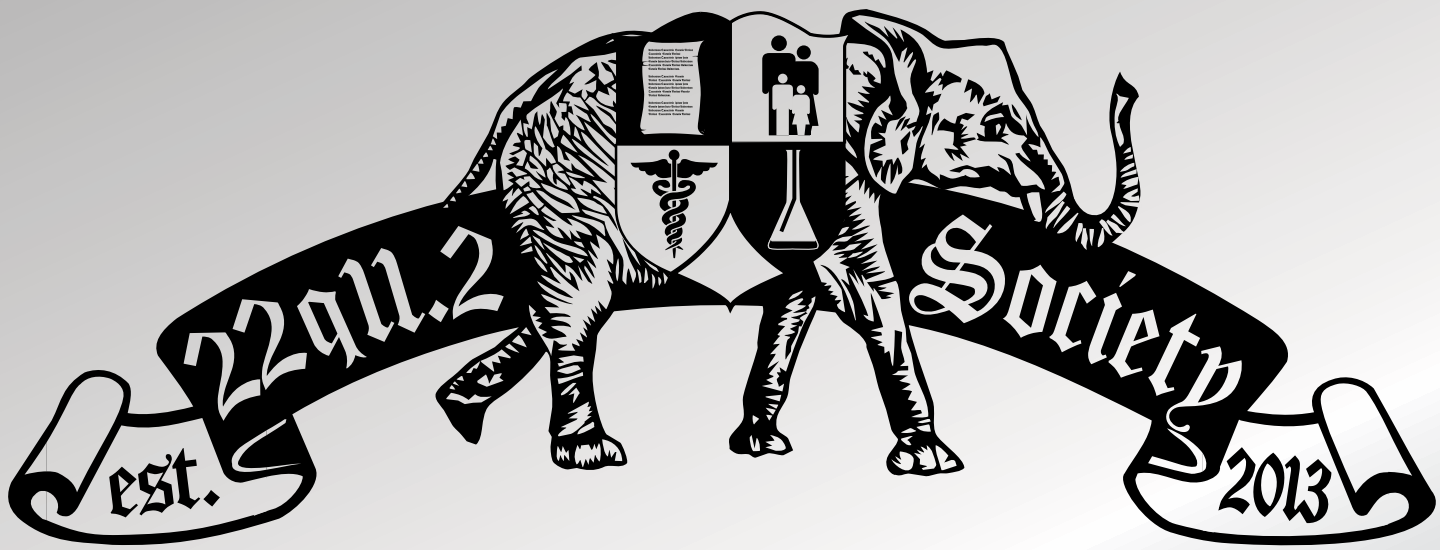

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