A Genetics-First Approach to Understanding Variation in Neuropsychiatric Outcomes: The 22q11.2 Deletion Syndrome

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Understanding the Pediatric Psychiatric Phenotype of 22q11.2 Deletion Syndrome

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Abstract

Aim. The purpose of this article is to provide an overview of current insights into the neurodevelopmental and psychiatric manifestations of 22q11.2 deletion syndrome (22q11DS) in children and adolescents.

Recent findings. The pediatric neuropsychiatric expression of 22q11DS is characterized by high variability, both inter-individual and intra-individual (different expressions over the lifespan). Besides varying levels of intellectual disability, the prevalence of autism spectrum disorders, attention deficit disorders, anxiety disorders, and psychotic disorders in young individuals with 22q11DS is significantly higher than in the general population, or in individuals with idiopathic intellectual disability. Possible explanations for this observed phenotypic variability will be discussed, including genetic pleiotropy, gene-environment interactions, the age-dependency of phenotypes, but also the impact of assessment and ascertainment bias as well as the limitations of our current diagnostic classification system.

Implications. The implications inferred by these observations mentioned above bear direct relevance to both scientists and clinicians. Observations regarding the neuropsychiatric manifestations in individuals with 22q11DS exemplify the need for a *dimensional approach* to neuropsychiatric assessment, in addition to our current categorical diagnostic classification system. The potential usefulness of 22q11DS as a *genetic model* to study the early phases of schizophrenia as well as the phenomenon of neuropsychiatric pleiotropy observed in many CNV's will be delineated. From a clinical perspective, the importance of *regular neuropsychiatric evaluations* with attention to *symptoms* not always captured in diagnostic categories and of *maintaining equilibrium* between individual difficulties and competencies and environmental demands will be discussed.

Keywords: 22q11DS, psychiatry, pleiotropy, pediatric psychiatry, clinical implications, schizophrenia.

Autism Spectrum and Psychosis Risk in the 22q11.2 Deletion Syndrome. Findings from a Prospective Longitudinal Study

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Background: Individuals with 22q11.2 deletion syndrome (22q11DS) have a 25% risk for schizophrenia and related psychotic disorders. Some have hypothesized that Autism Spectrum Disorders (ASD) diagnosed in children with 22q11DS may actually represent the social-communicative defects often observed during the early developmental stages of schizophrenia.
Methods: We prospectively studied 89 children with 22q11DS to test this hypothesis. At baseline, the Autism Diagnostic Interview was used to assess ASD, evaluating both current and early childhood behaviors. At follow-up, the Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS) was used to determine development of a psychotic disorder or psychotic symptoms.
Results: The average age (±SD) at first and last assessments was 14.3±1.9 and 19.0±3.0 years, respectively. Nineteen (21.3%) children developed a psychotic disorder. Contrary to our hypothesis, there was no significant difference in the proportion that developed a psychotic disorder, comparing those with (n=9, 17.3%) and those without ASD at baseline (n=10, 27%; OR = 0.500, 95% CI = 0.160 – 1.569, p = 0.235). Similar results were obtained using autistic symptom severity as quantitative predicting variable, psychotic symptoms as the outcome, and when correcting for age, gender and full scale IQ.
Conclusion: Results indicate that in children with 22q11DS, early childhood autistic features are not associated with an increased risk for subsequent development of psychotic disorders or symptoms, replicating previous retrospective findings in adults with 22q11DS. These results indicate that ASD and psychotic disorders can emerge independently, as pleiotropic phenotypes in the context of 22q11DS.

Keywords: Schizophrenia, comorbidity, 22q11DS, velocardiofacial syndrome, high risk, genetic.

Abbreviations: 22q11DS: 22q11.2 deletion syndrome; ASD: autism spectrum disorder; ADI: autism diagnostic interview; FSIQ: full scale intelligence quotient

Abstract

Neurocognition and Adaptive Functioning in a Genetic High Risk Model of Schizophrenia

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Background. Identifying factors that influence functional outcome is an important goal in schizophrenia research. The 22q11.2 deletion syndrome (22q11DS) is a unique genetic model with high risk (20-25%) for schizophrenia. This study aimed to identify potentially targetable domains of neurocognitive functioning associated with functional outcome in adults with 22q11DS.

Methods. We used comprehensive neurocognitive test data available for 99 adults with 22q11DS (n=43 with schizophrenia) and principal component analysis to derive four domains of neurocognition (Verbal Memory, Visual and Logical Memory, Motor Performance, and Executive Performance). We then investigated the association of these neurocognitive domains with adaptive functioning using Vineland Adaptive Behavior Scales (VABS) data and a linear regression model that accounted for the effects of schizophrenia status and overall intellectual level.

Results. The regression model explained 46.8% of the variance in functional outcome ($p < 0.0001$). Executive Performance was significantly associated with functional outcome ($p = 0.048$). Age and schizophrenia were also significant factors. The effects of Executive Performance on functioning did not significantly differ between those with and without psychotic illness.

Conclusion. The findings provide impetus for further studies to examine the potential of directed (early) interventions targeting Executive Performance to improve long-term adaptive functional outcome in individuals with, or at high-risk for, schizophrenia. Moreover, the neurocognitive test profiles may benefit caregivers and clinicians by providing insight into the relative strengths and weaknesses of individuals with 22q11DS, with and without psychotic illness.

Keywords: adaptive functioning, neurocognition, schizophrenia, 22q11DS, high-risk.

Abstract

A Normative Chart for Cognitive Development in a Genetically Selected Population

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Abstract

Certain pathogenic genetic variants impact neurodevelopment and cause deviations from typical cognitive trajectories. Understanding variant-specific cognitive trajectories is clinically important for informed monitoring and identifying patients at risk for comorbid conditions. Here, we demonstrate a variant-specific normative chart for cognitive development for individuals with 22q11.2 deletion syndrome (22q11DS). We used IQ data from 1365 individuals with 22q11DS to construct variant-specific normative charts for cognitive development (Full Scale, Verbal, and Performance IQ). This allowed us to calculate Z-scores for each IQ datapoint. Then, we calculated the change between first and last available IQ assessments (delta Z-IQ-scores) for each individual with longitudinal IQ data (n = 708). We subsequently investigated whether using the variant-specific IQ-Z-scores would decrease required sample size to detect an effect with schizophrenia risk, as compared to standard IQ-scores. The mean Z-IQ-scores for FSIQ, VIQ, and PIQ were close to 0, indicating that participants had IQ-scores as predicted by the normative chart. The mean delta-Z-IQ-scores were equally close to 0, demonstrating a good fit of the normative chart and indicating that, as a group, individuals with 22q11DS show a decline in IQ-scores as they grow into adulthood. Using variant-specific IQ-Z-scores resulted in 30% decrease of required sample size, as compared to the standard IQ-based approach, to detect the association between IQ-decline and schizophrenia ($p<0.01$). Our findings suggest that using variant-specific normative IQ data significantly reduces required sample size in a research context, and may facilitate a more clinically informative interpretation of IQ data. This approach allows identification of individuals that deviate from their expected, variant-specific, trajectory. This group may be at increased risk for comorbid conditions, such as schizophrenia in the case of 22q11DS.

Key words: Cognitive development, IQ, high-risk, pathogenic genetic variant, 22q11DS, schizophrenia, normative chart.

Within-Family Influences on Dimensional Neurobehavioral Traits in a High-Risk Genetic Model

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Background: Genotype-first and within-family studies help to elucidate factors that contribute to psychiatric illness expression. Combining these approaches, we investigated the patterns of influence of parental phenotypes, a high-impact variant, and schizophrenia on dimensional neurobehavioral phenotypes implicated in major psychiatric disorders.

Methods: We quantitatively assessed cognitive (FSIQ, VIQ, PIQ), social, and motor functioning in 82 adult individuals with a *de novo* 22q11.2 deletion (22 with schizophrenia), and 148 of their unaffected parents. We calculated within-family correlations and effect sizes of the 22q11.2 deletion and schizophrenia, and used linear regressions to assess contributions to the neurobehavioral phenotypes.

Results: Proband-parent intra-class correlations (ICC) were significant for cognitive measures (e.g., FSIQ ICC=0.549, $p<0.0001$), but not for social or motor measures. Compared to biparental scores, the 22q11.2 deletion conferred significant impairments for all phenotypes assessed (effect sizes -1.39 to -2.07 SD), strongest for PIQ. There were further decrements in those with schizophrenia. Regression models explained up to 37.7% of variance in IQ, and indicated that for proband IQ, parental functioning had larger effects than schizophrenia expression.

Conclusions: This study, for the first time, disentangles the impact of a high-impact variant from the modifying effects of parental background and schizophrenia on important dimensional neurobehavioral phenotypes. Results suggest that, independent of effects of the 22q11.2 deletion and schizophrenia, there are parental modifying effects on cognitive functioning, in contrast to the pattern for social and motor functioning. The findings set the stage for studies to elucidate the contributing genetic factors, their overlap with schizophrenia risk, and sharing between major risk groups.

Keywords: Genetics, variable expression, quantitative traits, parental phenotypes, 22q11.2 deletion syndrome, schizophrenia.

Abstract

Using Common Genetic Variation to Examine Phenotypic Expression and Risk Prediction in 22q11.2 Deletion Syndrome

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Abstract

The 22q11.2 deletion syndrome (22q11DS) is associated with a 20 – 25% risk for schizophrenia. In a cohort of 962 individuals with 22q11DS we examined the shared genetic basis between schizophrenia and schizophrenia-related early trajectory phenotypes: subthreshold symptoms of psychosis, low baseline intellectual functioning, and cognitive decline. We studied the association of these phenotypes with two polygenic scores, derived for schizophrenia and intelligence, and evaluated their use for individual risk prediction in 22q11DS. Polygenic scores were not only associated with schizophrenia and baseline IQ, respectively, but schizophrenia polygenic score was also significantly associated with cognitive (verbal IQ) decline and nominally associated with subthreshold psychosis. Further, comparing the tail-end deciles of the schizophrenia and IQ polygenic score distributions, 33% versus 9% of 22q11DS subjects had schizophrenia, and 63% versus 24% had intellectual disability. Collectively, these data show both a shared genetic basis for schizophrenia and schizophrenia-related phenotypes, and highlight the future potential of polygenic scores for risk stratification among individuals with highly, but incompletely, penetrant genetic variants.