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The Psychosis Spectrum in 22q11.2 Deletion Syndrome Is Comparable to That of Nondeleted Youths

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ABSTRACT

BACKGROUND: Chromosome 22q11.2 deletion syndrome (22q11DS) is a promising model for studying psychosis risk. Direct comparisons of psychosis features between 22q11DS and nondeleted (ND) individuals are limited by inconsistency and small samples. In the largest study to date, we compare 22q11DS to ND in comorbidities, functioning, cognition, and psychosis features across the full range of overall severity.

METHODS: ND youths ($n = 150$) ages 9 to 24 years were matched to 22q11DS individuals ($n = 150$) on age and sex, stratifying for presence of psychosis spectrum disorder. Individuals were evaluated for psychosis using the Structured Interview for Prodromal Syndromes, and for attention-deficit/hyperactivity, substance-related, and mood disorders. Differential item functioning analysis addressed whether 22q11DS differs from ND in the probability of clinically significant ratings while holding constant the overall level of psychosis.

RESULTS: Onset of psychosis proneness was similar among 22q11DS (mean: 11.0 years) and ND (mean: 12.1 years) individuals. Accounting for higher overall psychosis symptoms, 22q11DS participants were still more likely to manifest impaired stress tolerance, avolition, and ideational richness; ND individuals were more likely to exhibit unusual thoughts, persecutory ideas, and bizarre thinking. Cognition was impaired in 22q11DS, but it did not correlate with symptoms except ideational richness. Comorbid anxiety disorders were more likely in psychosis spectrum 22q11DS; substance-related disorders were more likely in ND. Global assessment of function was similar in 22q11DS and ND individuals, except among those with low total Structured Interview for Prodromal Syndromes scores.

CONCLUSIONS: Individuals with 22q11DS share overarching similarities with ND individuals in psychosis symptoms and age of onset for psychosis proneness; this continues to support the 22q11DS model as a valuable window into mechanisms contributing to psychosis.

Keywords: Clinical high risk, DiGeorge syndrome, Prodromal, Psychosis, 22q11.2 Deletion syndrome, Schizophrenia

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Risk for psychotic illness is markedly elevated in 22q11.2 deletion syndrome (22q11DS), reaching 25% or higher by adulthood (1–4). The syndrome arises from a 1.5 to 3.0 megabase hemizygous deletion on the short arm of chromosome 22 in approximately 1:4000 live births, producing a variable phenotype of neuropsychiatric and physical features including cardiac, palate, endocrine, and immunologic abnormalities (5–7). Psychiatric disorders are prevalent, with increased risk for autism, attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, and psychotic disorders (1,4,8). The risk for psychosis represents a 25-fold increase over the general population and 10-fold over other developmentally delayed populations (9,10). Connections are emerging to putative genetic and cognitive mediators of risk (10–13), and 22q11DS is increasingly recognized as an informative window for understanding genetic and neurobiological substrates of psychosis risk (2,14).

Research in psychotic illness has evolved to examine psychosis as a spectrum, with common risk factors shared across diagnoses such as schizophrenia, schizoaffective disorder, and mood disorders with psychotic features (15–17). Subthreshold symptoms in the psychosis spectrum are investigated in an effort toward early identification of psychosis proneness, with criteria defining an “at-risk mental state” or “prodrome” for individuals with significant symptomatic burden who do not meet criteria for schizophrenia spectrum disorders (17–20). Likewise, psychosis proneness is a focus of research in 22q11DS (8,21–25).

In earlier work comparing 22q11DS with nondeleted (ND) individuals, Bassett *et al*. (26) examined features of schizophrenia in 16 adults with 22q11DS and 46 ND adults with the illness, and they found no difference in age of onset, global functioning, or prevalence and severity of hallucinations, delusions, or negative and disorganized symptoms; however,

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individuals with 22q11DS experienced a lower prevalence of comorbid substance abuse. Another study of adults with schizophrenia comparing 22q11DS (n = 18) and ND (n = 65) also reported no difference in age of onset, positive symptoms, or negative symptoms, but found that lifetime global functioning reached lower levels in ND than in 22q11DS (27). The subthreshold psychosis-prone state was contrasted between 30 adolescents with 22q11DS and 81 ND individuals. Assessment with the Positive and Negative Syndrome Scale demonstrated higher negative symptoms, lower general functioning, and older age of onset for the ultra-high risk state in 22q11DS (25). Another study used the Structured Interview for Prodromal Syndromes to compare 23 adolescents with 22q11DS to matched ND individuals with and without schizotypal personality disorder; of 19 measures reflecting positive, negative, disorganized, and general symptoms, 22q11DS was differentiated from schizotypal personality disorder only by greater deficits in ideational richness and motor disturbance (28). Limited by small sample size, these few direct comparisons were conducted across broad diagnostic categories and did not account for potential differences in symptom burden. Differences in psychosis features may be either obscured or exaggerated by disparities in the overall severity of psychosis.

Here, we aim to evaluate the generalizability of psychosis-related findings in 22q11DS to ND individuals by directly comparing characteristics of psychosis symptoms between 150 youths with 22q11DS and 150 ND individuals representative of their deleted counterparts. To achieve this, we enriched the ND group for psychosis symptoms through a screening process. Control individuals were selected to mirror the 22q11DS sample in the proportion classified as psychosis spectrum; both consist of subjects recruited from community and medical clinic settings. We examine age of onset, psychosis symptomatology, cognition, comorbidities, and general functioning.

METHODS AND MATERIALS

Sample Selection and Matching

Participants with 22q11DS and ND individuals ages 9 to 24 years were drawn from two ongoing studies, prospectively designed to facilitate direct comparisons by implementing the same phenotypic procedures. Both groups were recruited from medical clinics and community sources. Each of the 150 participants with 22q11DS was matched to a ND control (1:1) based on age and sex; matches were made within the same psychosis category (i.e., 22q11DS participants classified as psychosis spectrum were matched to ND individuals also classified as psychosis spectrum, and nonpsychosis spectrum 22q11DS participants were matched to nonpsychosis spectrum ND individuals). The psychosis spectrum classification includes individuals with both threshold and subthreshold levels of psychosis. Matching produced 150 ND individuals with the same proportion of individuals with (n = 94) and without (n = 56) psychosis symptoms. Race was not included as a parameter because the 22q11DS sample was predominantly Caucasian, whereas the ND sample was largely African American. The final matched samples of 22q11DS (n = 150) and ND (n = 150) did not differ by age or sex (Table 1). Race and estimated socioeconomic status were significantly different between the two groups ($p < .001$)—however, we were able to analyze Caucasian subsamples of the two groups with equivalent socioeconomic status, generating results that do not contradict those of the whole study population, though some effects were no longer statistically significant (Supplemental Tables S3 and S4, and Supplemental Figures S2–S4). See Supplement for detailed sample selection and matching procedures.

Instruments and Measures

Both groups were assessed for psychosis and other psychopathology with the complete Structured Interview for Prodromal Syndromes (29,30) and parts of the Kiddie-Schedule for Affective Disorders and Psychosis (31), as well as for medical, social, and treatment histories. Kiddie-Schedule for Affective Disorders and Psychosis sections assessed DSM-IV psychosis-, mood-, and substance-related disorders and ADHD. Family history of psychopathology in first-degree relatives was assessed using an abbreviated version of the Family Interview for Genetics Studies (32).

Reading proficiency was calculated for each participant using the Wide Range Achievement Test 4 reading subtest (33). Other cognitive measures were assessed using the Penn Computerized Neurocognitive Battery, which has been extensively characterized (34–36). Cognition in 22q11DS and ND is compared with 12 neurocognitive tasks assessing four cognitive domains, including executive function, episodic memory, complex cognition, and social cognition (Supplemental Table S1). The Supplement further describe the above-mentioned instruments and measures.

Scoring and Consensus Diagnosis

Elicited clinical symptoms were rated according to the 19 items on the Scale of Prodromal Symptoms (SOPS) with standardized anchors on a 7-point scale: 0 = absent, 1 = questionably present, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe (but not psychotic), 6 = severe and psychotic/extreme (29,30). Only symptoms occurring in the preceding 6 months were considered. Threshold psychotic disorders were determined using DSM-IV-TR criteria (37). We additionally established criteria for “psychosis proneness” to include individuals with one or more clinically significant positive subthreshold symptoms (with or without recent onset or worsening), as well as those with two or more significant negative and disorganized symptoms. All individuals who were psychosis prone or psychotic were considered a part of the psychosis spectrum.

Criteria were tabulated for diagnoses of ADHD, mood disorders, and substance-related disorders based on Kiddie-Schedule for Affective Disorders and Psychosis. Diagnoses were assigned based on DSM-IV-TR criteria (37). Narrative case summaries were composed for each subject and presented at consensus case conferences where SOPS scores and diagnoses were finalized. Global assessment of function (GAF) was also determined by consensus based on overall psychological, social, and occupational functioning according to Structured Interview for Prodromal Syndromes anchors