Risk Factors and the Evolution of Psychosis in 22q11.2 Deletion Syndrome: A Longitudinal 2-Site Study

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Objective: 22q11.2 Deletion syndrome (22q11.2DS) is associated with high rates of schizophrenia, other neuropsychiatric disorders, and cognitive deficits. The objectives of this 2-center study were to longitudinally assess the trajectories of psychiatric disorders in 22q11.2DS from childhood to adulthood, and to identify risk factors for their emergence. **Method:** A total of 125 children and adults with 22q11.2DS were evaluated at 2 time points, baseline and follow-up (4 years apart), using standardized psychiatric and cognitive measures. **Results:** The rate of mood disorders tended to decrease during childhood and increase during late adolescence. Statistically significant predictors for the presence of a psychotic disorder as well as the severity of positive symptoms at follow-up were identical, and consisted of an anxiety disorder at baseline, lower baseline Full Scale IQ, and a greater decrease in verbal IQ scores between time points. Nine of 10 individuals with an emerging psychotic disorder had an anxiety disorder at baseline. The age of onset for a psychotic disorder was between 14 and 22 years in 82.6% of cases. **Conclusions:** It is important to evaluate the presence of anxiety disorders in children and adolescents with 22q11.2DS, as they are major risk factors for the emergence of psychotic disorders, which usually occur during late adolescence in this at-risk population. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(11):1192–1203. **Key Words:** 22q11.2DS, anxiety, depression, longitudinal, psychosis

22q11.2 Deletion syndrome (22q11.2DS), also known as velocardiofacial syndrome and DiGeorge syndrome, is the most common known microdeletion in human beings, occurring in at least 1 in 4,000 live births.[1,2] The syndrome is associated with high rates of medical comorbidities including cardiovascular and cleft anomalies, hypocalcemia, recurrent infections, and autoimmune diseases due to T-cell deficiency.[2,3] All individuals with 22q11.2DS cope with cognitive deficits. The mean IQ in 22q11.2DS is typically around 75 (within the borderline range of intelligence), but IQ can vary from as low as 40 to greater than 100.[4,5] Cognitive abilities in 22q11.2DS, and verbal IQ and executive functioning in particular, tend to decline with age rather than following a normal developmental trajectory.[4,6,7]

Of all the phenotypes associated with 22q11.2DS, the neuropsychiatric phenotype has been the object of the most research because of very high rates of psychiatric morbidity occurring in approximately 75% of individuals with 22q11.2DS.[8] The common psychiatric comorbidities in 22q11.2DS include attention-deficit/hyperactivity disorder (ADHD; 40%–50% of children), anxiety disorders (occurring in up to 50% of individuals), depressive disorders (reaching 40% during adolescence and young adulthood), and autism spectrum disorders (occurring in 14%–50% of children).[8-12] Many of the common psychiatric disorders in the syndrome are also common in other neurogenetic syndromes and intellectual disabilities.[13,14] However, schizophrenia-like psychotic disorder, occurring in up to

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one-third of individuals with 22q11.2DS,[8,15-19] represents approximately a 10-fold increase in comparison to that in individuals with other developmental disabilities.[20]

To date, there have been only a few publications from longitudinal studies on 22q11.2DS, which are necessary for understanding the developmental trajectories of the neuropsychiatric and neurocognitive phenotypes.[4,17,21] In a study from the Stanford sample, 31 children with 22q11.2DS were evaluated twice at mean ages of 13 and 17 years. At follow-up, one-third of them had developed a psychotic disorder, and the baseline risk factors for psychosis were lower baseline verbal IQ (VIQ), anxiety and depression symptoms, and the catechol-*O*-methyltransferase (*COMT*) Met variant.[17] A main limitation of the study was the small number of participants. Antshel *et al*.[6] evaluated 70 children with 22q11.2DS at 2 time points. The authors found that the rates of major depression, generalized anxiety disorder, and oppositional-defiant disorder increased between the ages of 12 and 15 years. None of the subjects had developed schizophrenia, although several individuals demonstrated prodromal symptoms at their second evaluation. Odd/eccentric symptoms and poor executive functioning predicted the emergence of prodromal symptoms. Another longitudinal study included 69 children with 22q11.2DS who were cognitively evaluated 2 or 3 times.[4] A 10-point decline in Full Scale IQ (FSIQ) scores was found between the baseline evaluation (age 5.5 years) and the endpoint evaluation (age 9.5 years). No association between IQ decline and behavioral measures was observed. These latter 2 longitudinal studies[4,6] consisted of larger samples, as well as remarkably homogeneous age groups. However, the participants were still relatively young and had not yet reached the critical age for developing a psychotic disorder.

The longitudinal work presented here is a continuation of our previous cross-sectional study, for which we pooled psychiatric and cognitive data from the Tel Aviv (TA) and Geneva (GVA) 22q11.2DS samples.[8] This collaboration allows us to combine 2 large cohorts with a broad age range, from childhood to adulthood, thereby covering the critical period for transition to psychosis. All individuals assessed here for the second time were part of the previous study as well.[8]

The study aims were as follows. First, we aimed to longitudinally assess the developmental trajectories of psychiatric disorders in 22q11.2DS in the same 2 samples using standardized diagnostic tools. Based on previous studies,[6,8,17] we hypothesized that the rates of depression and psychotic disorders would increase during adolescence and adulthood, the rate of anxiety disorders would remain stable, and the rate of ADHD would decline with age. Second, we attempted to learn whether psychotic disorders in 22q11.2DS are chronic or whether some individuals recover from psychotic illness. Third, we endeavored to follow the trajectories of cognitive functioning in 22q11.2DS. Based on previous studies,[4,7,8,21] we assumed that there would be a developmental decline in cognitive abilities that would be most pronounced in the verbal domain. Fourth, we wanted to identify predictors for the emergence of psychotic disorders and symptoms in 22q11.2DS. Based on previous findings, we postulated that having the *COMT* Met allele, along with an anxiety disorder at baseline, and a decrease in VIQ between assessments, would predict the presence and severity of psychotic disorders and symptoms at follow-up.[17] Fifth, we wished to perform an exploratory factor analysis on the standard tool used for assessment of psychosis severity, the Positive and Negative Syndrome Scale (PANSS), to identify the factorial structure of psychotic symptoms in individuals with 22q11.2DS. We assumed that, because of their intellectual disability, the items would load differently on the "positive," "negative," and "general" factors of the PANSS for our participants, given that the factors were originally based on studies of non-22q11.2DS patients with schizophrenia.[22]

METHOD

Participants

In a previous publication,[8] we described the recruitment procedure and baseline neuropsychiatric evaluation of 172 individuals with 22q11.2DS who were evaluated at 2 sites, Tel Aviv (TA; n = 86) and Geneva (GVA; n = 86). Of the 172 individuals, 125 (72.7%) returned for follow-up, 64 (31 females and 33 males) from the TA sample and 61 (35 females and 26 males) from the GVA sample. The participants who did not return did not significantly differ from the participants who returned with respect to age (17.2 ± 11.6 versus 15.2 ± 7.7, respectively, t =1.1 p = .26) or psychiatric diagnosis: psychotic disorders (p =.55), anxiety disorders (p =.53), mood disorders (p =.50), and ADHD (p =.51). Our longitudinal participants did, however, have lower baseline FSIQ scores compared to those

who did not return (67.8 ± 14.8 versus 73.6 ± 12.4, respectively, t = 2.4, $p = .03$). The longitudinal sample was composed of 66 female and 59 male participants, with an age range at baseline between 5 and 49 years (mean = 15.1 ± 8.4). The mean interval between the T1 (baseline) and T2 (follow-up) evaluations was 4.3 ± 1.8 years. The presence of a 22q11.2 microdeletion was confirmed in all participants using array comparative genomic hybridization (aCGH) and fluorescent in situ hybridization (FISH) tests.[23] Ten participants (8.0%) were taking antipsychotic medication at baseline, and 19 (15.2%) at follow-up (see Table S1, available online, for the full list of antipsychotic agents).

Participants from the 2 cohorts did not significantly differ in age at T1 (t = 0.03, df = 123, $p = .98$) or sex distribution ($\chi^2 = 1.0$, $p = .32$). Participants differed in terms of the mean time interval between the 2 evaluations (4.9 ± 2.2 [TA] versus 3.6 ± 0.6 years [GVA], df = 123, $p < .001$) and their baseline FSIQ scores (77.1 ± 13.4 [TA] versus 71.9 ± 11.5 [GVA], t = 2.33, df = 123, $p = .02$).

The Institutional Review Board of the Rabin Medical Center and the Department of Psychiatry of the University of Geneva Medical School approved the respective research protocols. Written informed consent was obtained from participants and their parents in both cohorts.

Psychiatric Assessment

A comprehensive clinical assessment was performed in both cohorts at each time point as previously described.[8]

TA Sample. Trained clinicians used the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL) to interview all subjects and their parents.[24] If an affirmative response was given to any symptom category from the screening interview, the related K-SADS module was administered. The adult participants and their parents were interviewed using the Structured Clinical Interview for Axis I *DSM-IV* (SCID).[25] The ADHD items from the K-SADS were added to the SCID to evaluate the presence of ADHD in adults with 22q11.2DS. In the case of discrepant information between sources (e.g., parents and child), diagnosis was decided based on "best clinical judgment" as instructed by the K-SADS guidelines.

GVA Sample. Parents of children and adolescents completed the Diagnostic Interview for Children and Adolescents–Revised (DICA-IV).[26] The SCID was administered to adult participants and their parents. The psychotic disorders supplement of the K-SADS-PL also was administered to all participants.

Diagnostic categories were confirmed during a clinical evaluation of the child and then reviewed by at least 2 child psychiatrists or psychologists at each site. The senior investigators from both sites (D.G. and S.E.) reviewed data from several psychiatric assessments to establish interrater reliability and to verify consistency between diagnostic criteria, although no formal interrater reliability κ values were calculated. The PANSS[22] was administered to all participants at both sites at follow-up (T2) only.

Cognitive Assessment

All participants completed the age-appropriate Wechsler Intelligence Scale to evaluate global intellectual functioning. The Wechsler versions used were the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), the Wechsler Intelligence Scale for Children–Revised (WISC-R, TA cohort), the Wechsler Intelligence Scale for Children–Third Edition (WISC-III, GVA cohort), and the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III).[8] Cognitive testing was performed with all participants at both evaluations, with the exception of a 17-year-old female participant from the TA cohort who was too agitated to be tested at T2.

COMT Genotyping

A blood sample was collected and analyzed from each participant, with the exception of 2 females from TA and 1 male from GVA and the *COMT* Val108/158Met polymorphism (rs4680) was determined.[27] In all, 60 participants were Val carriers and 62 were Met carriers. The Val/Met distribution was similar in both cohorts (Val/Met ratio 29/33 [TA] and 31/29 [GVA], $p = .72$).

Statistical Analyses

The prevalence of psychiatric disorders between the 2 cohorts (TA versus GVA) was compared using χ^2 tests. To examine the longitudinal trajectories of psychiatric disorders, the cohort was divided into 3 age groups: 5 to 10 years, 11 months (children; n = 49, mean age ± SD = 8.4 ± 1.8 years at T1 and 12.4 ± 2.5 years at T2), 11 years to 17 years, 11 months (adolescents; n = 46, 14.0 ± 1.9 years at T1 and 18.3 ± 2.9 years at T2), and more than 18 years (adults; n = 30, 27.6 ± 7.2 years at T1 and 32.3 ± 7.4 years at T2). To assess longitudinal changes in the rates of psychiatric disorders, the McNemar nonparametric test for related samples was used. Longitudinal change in intellectual functioning across the 3 age groups was evaluated using paired t tests. A sex effect on the developmental trajectories of intellectual functioning was evaluated using mixed model regression analyses, which allows for the modeling of the within-subjects factor as a nested variable.[28]

In addition, we conducted a factor analysis of the PANSS items in our sample. The factor analysis was performed using promax rotation, given our assumption that the factors were correlated with each other. Based on the results of the factor analysis, we computed positive, negative, and general symptom scores by summing the corresponding items.

Finally, we performed a logistic and a multiple linear regression to predict the presence of a psychotic

disorder at T2 and the severity of the PANSS positive symptoms at T2. To focus on the emergence of psychotic disorders in our sample, and to minimize the extensive overlap between psychosis, treatment with antipsychotic medication, and comorbid anxiety disorder, we excluded the patients who were diagnosed with a psychotic disorder at T1 as well as those who were older than 30 years at T1 (the typical upper limit in most cases for the evolution of psychosis in 22q11.2DS) from the regression analyses (n = 107 participants included). The inclusion of variables in the regression models was hypothesis driven. Specifically, the following variables were entered: age at T1, COMT Val108/158Met genotype, FSIQ at T1, ΔVIQ, and presence of an anxiety disorder at T1.

RESULTS

Comparison of Rates of Psychiatric Disorder Between Sites

There were few overall differences in the rates of psychiatric disorders between the TA and GVA cohorts at baseline and follow-up. At baseline, there were higher rates of obsessive-compulsive disorder (OCD, 23.4% versus 6.8%; $\chi^2 = 6.5$, $p = .01$) and ADHD (56.3% versus 31.3%; $\chi^2 = 6.9$, $p = .009$) in the TA cohort, and of agoraphobia (1.6% versus 18.2%; $\chi^2 = 6.8$, $p = .009$) in the GVA cohort. At follow-up, the only difference between the cohorts was higher rates of ADHD in the TA cohort (50% versus 27.8%; $\chi^2 = 4.7$, $p = .03$).

Longitudinal Change in Neuropsychiatric Morbidity

The frequencies of each psychiatric disorder in the total sample and in each age group (children: ages 5–10 years; adolescents: ages 11–17; and adults: 18 years and older) at baseline and follow-up are displayed in Table 1. Comorbid anxiety disorders are presented in Table S2, available online. At baseline, 19 of the 66 participants (28.8%) with anxiety disorders had 2 comorbid anxiety disorders, and 5 participants (7.6%) had 3 comorbid anxiety disorders. Similarly, at follow-up, 14 participants (29.8%) with 22q11.2DS had 2 comorbid anxiety disorders, and 4 participants (8.5%) had 3 anxiety disorders. Specific phobia was the most common comorbid anxiety disorder. At baseline, 18 of the 24 participants with comorbid anxiety disorders (75%) had specific phobia. At follow-up, 13 of the 17 participants with comorbid anxiety disorders (76.5%) had specific phobia. Analysis of longitudinal change in psychiatric disorders is displayed in Figure 1. There was a significant increase in the rates of psychotic disorders in the adolescent group ($p = .02$). In the adolescent group, only 1 subject (2.2%) had a psychotic disorder at baseline, whereas 8 subjects (17.4%) presented with a psychotic disorder at follow-up assessment. Mood disorders decreased in children, from 8 (17.4%) to 2 individuals (4.4%) ($p = .07$); and increased in the group of adolescents ($p = .04$), from 4 (9.5%) to 11 (26.2%).

Age of Onset of Psychosis and Frequency of Psychotic Disorders

Of the 23 subjects (13 males and 10 females) with a psychotic disorder (18.4% of the total cohort), 14 had schizophrenia, 3 had schizoaffective disorder, 2 had brief psychotic disorder, 3 had psychotic disorder not otherwise specified (NOS), and 1 had schizophreniform disorder (see Table S3, available online). The age of onset of each psychotic disorder was defined as the age when the patient's condition was first diagnosed by a psychiatrist (Figure 2). The mean age of onset of any psychotic disorder was 17.7 ± 4.2 years (range 11–30 years), and 18.4 ± 4.9 (range 11–30 years) for schizophrenia. Three subjects with a psychotic disorder at baseline (patients 2, 15, and 16, Table S3, available online) did not meet criteria for any psychotic disorder at follow-up. All 3 had typical psychotic symptoms at baseline, including delusions of reference and persecution, auditory hallucinations, and disorganized behavior and speech. In 1 case (patient 16), a clear psychosocial trigger (separation from a girlfriend) preceded his psychotic crisis. The psychotic episode subsequently resolved itself without antipsychotic treatment or psychotherapy. The other 2 patients with transient psychosis were prescribed antipsychotic agents and were no longer taking them at follow-up, suggesting recovery. One patient (patient 15) recovered from his schizophreniform disorder. The other (patient 2) was beginning high school when she recovered from schizophrenia. It is possible that her recovery was facilitated by the stress relief of changing from a regular middle school to a special-needs high school that was better adapted to her individually.

Longitudinal Change in Cognitive Abilities

The longitudinal changes in IQ scores are presented in Table 2. There was a significant decline in FSIQ, VIQ, and performance IQ (PIQ) scores in children and adolescents, and in VIQ only in

TABLE 1 Prevalence of Psychiatric Disorders at Baseline and at Follow-up

Baseline	Children (n = 49)	Adolescents (n = 46)	Adults (n = 30)	Total (n = 125)	*p*
Age, y, m ± SD	8.4 ± 1.8	14.0 ± 1.9	27.6 ± 7.2	15.1 ± 8.4	
Males/females, n	26/23	22/24	11/19	59/66	
Any anxiety disorder, n (%)	23 (46.9)	27 (58.7)	16 (53.3)	66 (52.8)	NS
Separation anxiety disorder[a]	2 (4.1)	3 (6.5)	0 (0)	5 (5.3)	
Specific phobia	14 (28.6)	20 (43.5)	10 (35.7)	44 (35.2)	
Social phobia	5 (10.2)	3 (6.5)	3 (10.7)	11 (8.8)	
Panic disorder	0 (0)	1 (2.2)	0 (0)	1 (0.8)	
Agoraphobia[b]	0 (0)	1 (6.3)	2 (7.1)	3 (4)	
PTSD	0 (0)	0 (0)	0 (0)	0 (0)	
OCD	7 (14.3)	8 (17.4)	4 (14.3)	19 (15.2)	
GAD	5 (10.2)	4 (8.7)	2 (7.1)	11 (8.8)	
Any mood disorder, n (%)	8 (16.3)	5 (10.9)	8 (28.6)	21 (16.8)	NS
Major depressive disorder	5 (10.2)	1 (2.2)	5 (17.9)	11 (8.8)	
Dysthymia	3 (6.1)	5 (10.9)	5 (17.9)	13 (10.4)	
Bipolar disorder I or II	1 (5.6)	0 (0)	0 (0)	1 (0.8)	
Any disruptive disorder, n (%)	31 (63.3)	17 (37)	6 (35.3)	54 (48.2)	*
ADHD[c]	31 (63.3)	14 (30.4)	6 (35.3)	51 (45.5)	
ODD[a]	9 (18.4)	10 (21.7)	1 (5.9)	19 (20)	
Conduct disorder[c]	0 (0)	0 (0)	0 (0)	0 (0)	
Any psychotic disorder, n (%)	2 (4.1)	1 (2.2)	10 (33.3)	13 (10.4)	***
Schizophrenia	1 (2)	1 (2.2)	5 (16.7)	7 (5.6)	
Schizoaffective disorder	0 (0)	0 (0)	2 (6.7)	2 (1.6)	
Schizophreniform disorder	0 (0)	0 (0)	2 (6.7%)	2 (1.6)	
Brief psychotic disorder	0 (0)	0 (0)	1 (3.3)	1 (0.8)	
Psychotic disorder NOS	1 (2)	0 (0)	0 (0)	1 (0.8)	
Other, n (%)					
Substance abuse[b]	0 (0)	0 (0)	3 (10)	3 (4)	
Eating disorder	2 (4.1)	0 (0)	0 (0)	2 (1.6)	
Follow-up	**Children (n = 49)**	**Adolescents (n = 46)**	**Adults (n = 30)**	**Total (n = 125)**	***p***
Age, m ± SD	12.4 ± 2.5	18.3 ± 2.9	32.3 ± 7.4	19.4 ± 8.8	
Males/females, n	26/23	22/24	11/19	59/66	
Any anxiety disorder, n (%)	18 (36.7)	18 (39.1)	11 (36.7)	47 (37.6)	NS
Separation anxiety disorder[a]	1 (2)	0 (0)	0 (0)	1 (1)	
Specific phobia	10 (20.4)	13 (28.9)	8 (26.7)	31 (25)	
Social phobia	8 (16.3)	0 (0)	1 (3.3)	9 (7.3)	
Panic disorder	0 (0)	3 (6.7)	0 (0)	3 (2.4)	
Agoraphobia[b]	0 (0)	0 (0)	0 (0)	0 (0)	
PTSD	0 (0)	0 (0)	2 (6.7)	2 (1.6)	
OCD	2 (4.1)	3 (6.7)	3 (10)	8 (6.5)	
GAD	7 (14.3)	6 (13.3)	3 (10)	16 (12.9)	
Any mood disorder, n (%)	2 (4.1)	11 (24.4)	5 (16.7)	18 (14.5)	*
Major depressive disorder	2 (4.1)	6 (13.3)	2 (6.7)	10 (8.1)	
Dysthymia	0 (0)	6 (13.3)	2 (6.7)	8 (6.5)	
Bipolar disorder I or II	0 (0)	0 (0)	2 (6.7)	2 (2.2)	
Any disruptive disorder, n (%)	29 (59.2)	15 (44.1)	2 (11.8)	46 (46)	**
ADHD[c]	28 (57.1)	12 (35.3)	2 (11.8)	42 (42)	
ODD[a]	9 (18.4)	2 (5.9)	0 (0)	11 (11)	
Conduct disorder[c]	0 (0)	1 (2.9)	0 (0)	1 (1)	
Any psychotic disorder, n (%)	4 (8.2)	8 (17.4)	8 (26.7)	20 (16)	NS
Schizophrenia	2 (4.1)	5 (10.9)	5 (16.7)	12 (9.6)	
Schizoaffective disorder	0 (0)	0 (0)	3 (10)	3 (2.4)	
Schizophreniform disorder	0 (0)	1 (2.2)	0 (0)	1 (0.8)	
Brief psychotic disorder	1 (2)	1 (2.2)	0 (0)	2 (1.6)	
Psychotic disorder NOS	1 (2)	1 (2.2)	0 (0)	2 (1.6)	

TABLE 1 Continued

Follow-up	Children (n = 49)	Adolescents (n = 46)	Adults (n = 30)	Total (n = 125)	*p*
Other					
Substance abuse[b]	0 (0)	0 (0)	2 (6.7)	2 (2.2)	
Eating disorder	0 (0)	0 (0)	0 (0)	0 (0)	

Note: Prevalence rates are shown separately in children, adolescents, and adults, as well as in the total sample. ADHD = attention-deficit/hyperactivity disorder; GAD = generalized anxiety disorder; NOS = not otherwise specified; NS = not significant; OCD = obsessive-compulsive disorder; ODD = oppositional-defiant disorder; PTSD = posttraumatic stress disorder; y = years.

[a]Geneva (GVA) and Tel Aviv (TA) cohorts: evaluated only in participants <18 years.

[b]Geneva cohort: evaluated only in participants ≥18 years.

[c]Geneva cohort: evaluated only in participants <18 years.

**p ≤ .05; **p ≤ .01; ***p ≤ .001.*

adults. The most robust declines ($p = .001$) were in the PIQ scores of children and in the VIQ scores of adolescents. As for sex, the VIQ trajectories were significantly different between male and female subjects: the 2 trajectories were parallel and linearly decreasing over time, with a significant intercept difference in favor of males ($p = .04$).

Comparative studies have suggested that WAIS scores are inherently higher than WISC scores (reviewed in Supplement 1 and Table S4, available online).[29-31] We did not find significant differences between 22q11.2DS subjects who had the same Wechsler version at both time points and those who aged up between evaluations from a WISC-III or WISC-R to the WAIS-III. However, the largest decline in FSIQ scores (a mean decline of 6.2 points) was in the group that changed Wechsler version (see Supplement 1 and Table S4, available online).

Exploratory Factor Analysis on the PANSS

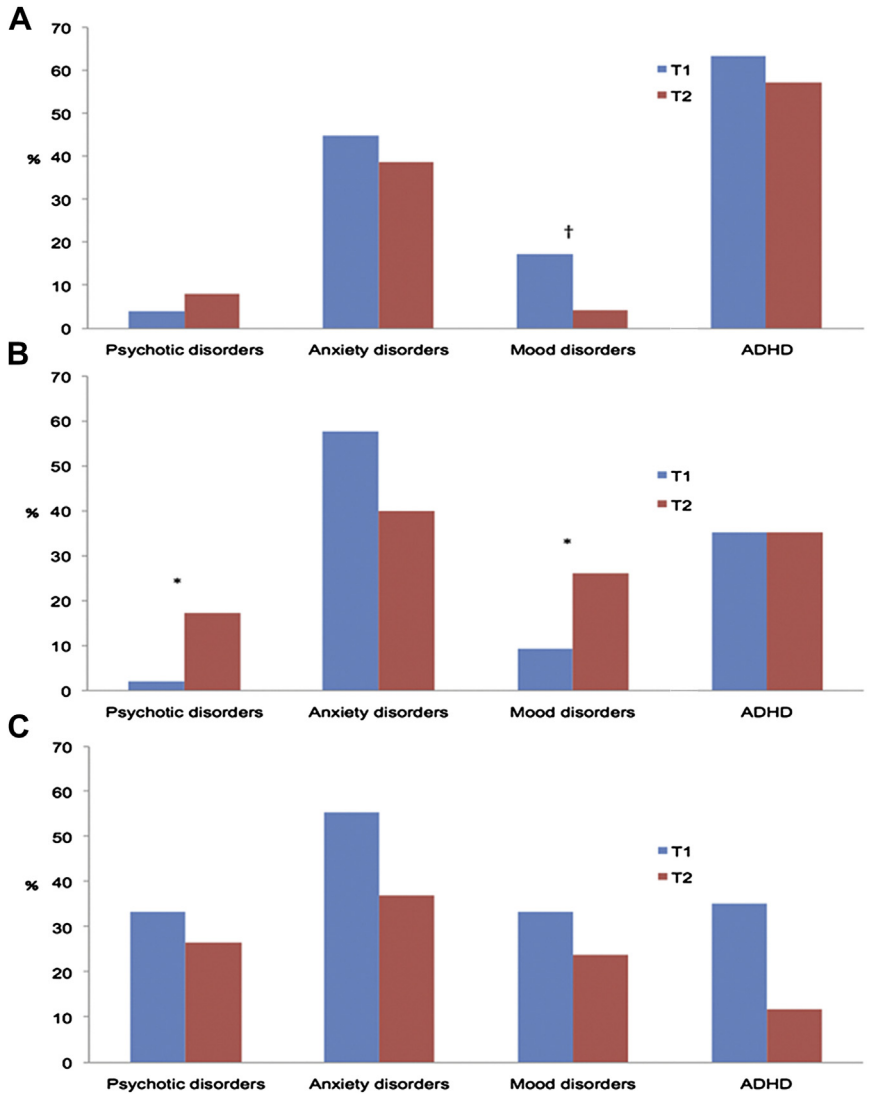
We performed exploratory factor analysis on the PANSS to identify the factorial structure of psychotic symptoms in 22q11.2DS. The analysis indicated 6 factors with an eigenvalue greater than 1; however, the scree plot illustrated a clear 3-factor solution. For this reason, we performed a new factor analysis with 3 factors using promax rotation. The analysis explained 59% of the total variance. The eigenvalues are given in Table 3. Groupings were made using a 0.40 threshold. Based on the results of the factor analysis, we computed a positive symptom factor score (sum of P1, P3, P6, G9, G3, G1, and P2), a negative symptom factor score (sum of N6, N4, N2, N3, N1, G16, N5, N7, and G7), and a general symptom factor score (sum of P4, P7, G2, G4, G5, G8, G11, G12, G13, G14, and G15) for each participant. The 2 cohorts did not differ in terms of severity of positive symptoms ($F_{1,123} = 1.8$, $p = .19$). However, the GVA cohort had significantly higher scores on the negative dimension ($F_{1,123} = 2.5$, $p = .02$), and the TA cohort had higher scores on the general dimension ($F_{1,123} = 16.3$, $p < .001$).

Longitudinal Prediction of Psychotic Disorders and Severity of Psychotic Symptoms

Finally, we used regression models to identify the putative predictors for the emergence of a psychotic disorder at T2 and the severity of PANSS-positive symptoms at T2. The results of a logistic regression revealed that 3 variables were associated with emergence of a psychotic disorder at T2: FSIQ at T1 ($B = -0.07$, $SE = 0.04$, $p = .05$), ΔVIQ ($B = -0.15$, $SE = 0.06$, $p = .01$), and presence of an anxiety disorder at T1 ($B = 2.83$, $SE = 1.23$, $p = .02$). *COMT* Val108/158Met genotype and age at T1 were not statistically significant. Of particular interest, 9 of the 10 individuals with a psychotic disorder that emerged between T1 and T2 were diagnosed with an anxiety disorder at baseline.

The multiple regression revealed that 3 variables were significantly associated with the severity of PANSS-positive symptoms at T2 and explained 22% of the variance: FSIQ at T1 ($B = -0.09$, $SE = 0.04$, $t = -2.42$, $p = .02$), Δ VIQ ($B = -0.18$, $SE = 0.05$, $t = -4.03$, $p < .001$), and the presence of an anxiety disorder at T1 ($B = -2.29$, $SE = 0.78$, $t = -2.92$, $p < .005$). Again, *COMT* genotype and age at T1 were not statistically significant. Indicators of multicollinearity were good (tolerance >0.70 and variance inflation factor <1.5).

FIGURE 1 Longitudinal change in the rates of psychiatric disorders. Note: Longitudinal change in the rates of psychiatric disorders (5–11 years of age at baseline, panel A), adolescents (12–17 years of age at baseline, panel B), and adults (age 18 years and older at baseline, panel C). †$p = .07$, *$p < .05$.

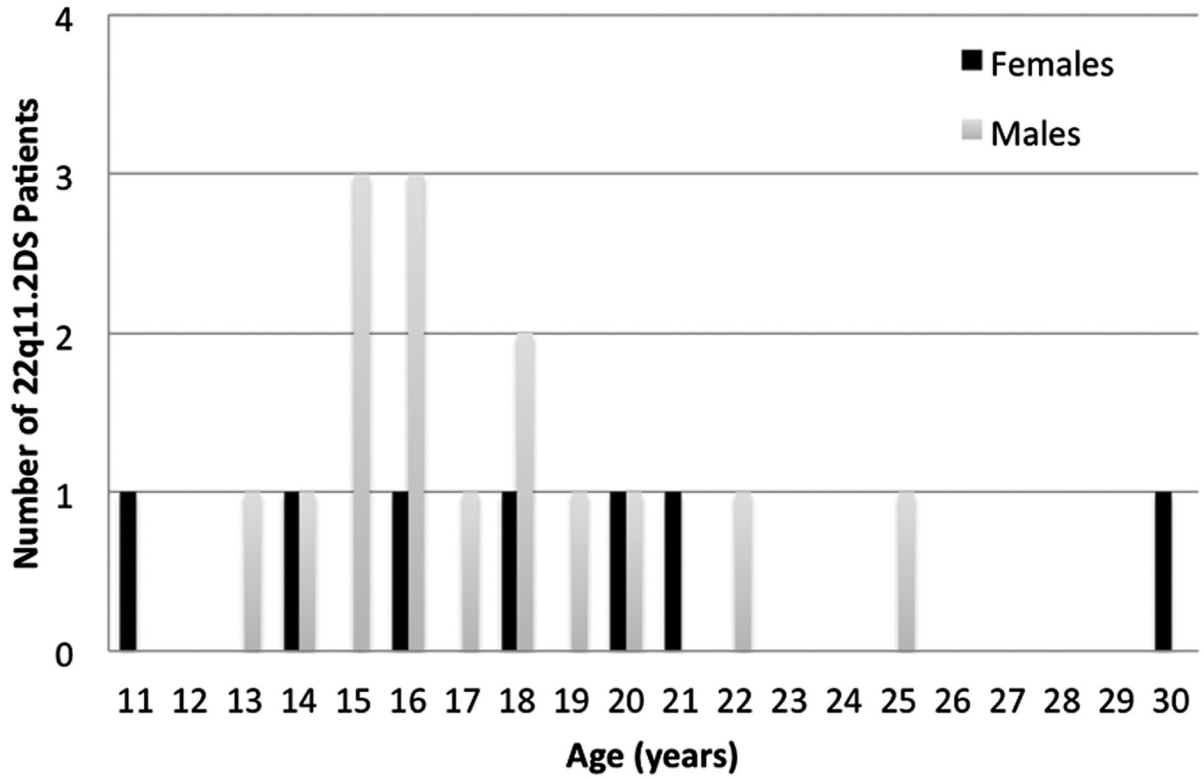


DISCUSSION

In this longitudinal study, we pooled neuropsychiatric data from 2 large cohorts of individuals, ranging in age from children to adults, with 22q11.2DS. The most robust change that we observed between baseline and follow-up was the emergence of a psychotic disorder during late adolescence/early adulthood. These psychotic disorders were chronic in most cases. We also observed a decrease in mood disorders during childhood and an increase in mood disorders from early adolescence to late adolescence/early adulthood. There was a significant decline in 22q11.2DS IQ scores, which was more robust in the group of children and adolescents than in adults. Predictors for the emergence of a psychotic disorder and for the severity of positive symptoms at follow-up were identical, and included the presence of an anxiety disorder at baseline, lower baseline FSIQ, and a large decrease in VIQ between baseline and follow-up.

To our knowledge, this is the largest longitudinal analysis of neuropsychiatric morbidity in 22q11.2DS. Given that our sample included adults, we had a relatively large number (n = 23) of participants with a psychotic disorder. An important dilemma for clinicians and researchers is how to identify the highest risk period for the

FIGURE 2 Distributions of sex and age of psychosis onset (n = 22) in the study cohort.



emergence of psychosis in 22q11.2DS. Although age of onset of a psychotic disorder ranged from 11 to 30 years in our sample, it was between 14 and 22 years for 19 of the 23 participants (83%) with a psychotic disorder (Table S3, available online). The mean age of onset was 17.7 years, earlier than in 2 previous cross-sectional studies of adults with 22q11.2DS.[15,18] In the study by Murphy *et al.*,[18] the mean age of onset of schizophrenia was 26 years (age range 15–46 years), and Bassett *et al.* [15] found age of onset to be 21 years (age range 15–30 years). Later ages of onset in Murphy and Bassett's studies were probably due to the inclusion of adult patients only and the use of cross-sectional designs, which are less accurate for identifying age of onset than are longitudinal designs. In 17 of 23 cases (74%), the psychotic disorder was chronic, that is, schizophrenia or schizoaffective disorder; however, in 6 cases (26%), the psychotic disorders were nonschizophrenic or transient, including psychotic disorder NOS, brief psychotic disorder, and schizophreniform disorder. The fact that psychotic disorders are possibly transient in some cases of individuals with 22q11.2DS is a new idea, and one that is important for clinicians and families treating individuals with 22q11.2DS. This also goes against an earlier conception that psychotic disorders are always chronic and debilitating in 22q11.2DS.[19,32] Our transient psychotic cases suggest that both psychosocial factors and antipsychotic medications probably play an important role in the recovery from psychosis in 22q11.2DS.

In our previous cross-sectional study using the same cohorts, we found an increased rate of mood disorders (primarily depressive disorders) in young adults with 22q11.2DS.[8] Here we observed a more complex developmental trajectory for mood disorders. Mood disorders decreased at follow-up in children and increased in adolescents. It is our clinical observation that many children with 22q11.2DS have trouble adjusting to the academic and social challenges encountered during the transition to elementary school. Some of them may present with depressive symptoms in response to this change, which, as our data suggest, appear to subside in subsequent years, as demonstrated by the decrease in rates of depression in childhood. Although we

TABLE 2 Longitudinal Change in Full Scale IQ (FIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) Scores

IQ Score, M ± SD	Baseline	Follow-up	Change
Children			
FSIQ	77.5 ± 12.6	72.4 ± 11.5	−5.08***
VIQ	81.0 ± 12.0	77.4 ± 12.7	−3.58*
PIQ	77.4 ± 13.1	72.3 ± 11.9	−5.04***
Adolescents			
FSIQ	74.6 ± 12.7	70.3 ± 10.8	−4.23**
VIQ	78.9 ± 14.1	73.8 ± 13.0	−5.04***
PIQ	75.0 ± 13.5	70.8 ± 10.3	−4.14*
Adults			
FSIQ	69.5 ± 11.9	67.5 ± 11.8	−2.00*
VIQ	73.0 ± 13.1	70.3 ± 13.4	−2.70**
PIQ	69.5 ± 10.9	68.7 ± 12.0	−0.77

Note: $p \leq .05$; **$p \leq .01$; ***$p \leq .001$.

have not assessed depression rates in a 22q11.2DS preschool sample, it would be interesting to look at the entire developmental trajectory together to test this theory. A similar difficulty facing the challenges of transition to adulthood may explain the peak in depression that we observe during the transition to adulthood.

We found a longitudinal decline in IQ scores that was similarly significant for both VIQ and PIQ scores in children and adolescents, and less robust for VIQ only in adults. A decline in standardized IQ scores in young individuals who are still developing probably indicates slower cognitive development compared to that in typically developing children, rather than deterioration in cognitive functioning. Only an actual decrease in Wechsler raw scores, which were not analyzed in our study, would indicate cognitive decline.

Longitudinal studies have shown a decrease in IQ scores in children, adolescents, and young adults with 22q11.2DS[4,17,21]; however, the decline was typically more robust for VIQ than for PIQ. A recent study with large, non-22q11.2DS population-based cohorts showed that relative decline in verbal abilities during adolescence was a strong predictor for the later development of psychosis.[33] Here, a more robust decline in VIQ than in PIQ scores occurred only in the adult subgroup, not in children or adolescents. The fact that developmental trajectories of cognitive abilities are more aberrant during early versus late development supports the assumption that, similar to schizophrenia in non-22q11.2DS,[33,34] cognitive deficits are early developmental precursors to the later development of psychosis in 22q11.2DS. Commensurate with previous studies, we found that the decline in VIQ scores in 22q11.2DS is more prominent in females than in males.[4,6]

We conducted a factor analysis for the PANSS scale scores of our 22q11.2DS cohort because we assumed that, because of these individuals' learning disabilities, the factorial structure of the items might differ from the PANSS 3-factor structure.[22] Most factor analyses in non-22q11.2DS schizophrenia patients have yielded a 5-factor solution (positive, negative, disorganized, excited, and depressed factors),[35] casting doubt on the original 3-factor structure. In contrast to these studies, our results pointed to a 3-factor solution with some differences compared to the original PANSS structure.

We found that several items listed on the positive factor (i.e., excitement, grandiosity, and hostility) did not load on the positive factor. Similarly, items listed on the "general" factor (e.g., somatic concerns) loaded on the "positive" factor. In our opinion, there are 2 likely explanations for these differences. First, as far as we know, this is the first PANSS factor analysis performed in patients with intellectual disability, which may very well influence their profile on the PANSS. Second, most patients from the present sample were not diagnosed with a psychotic disorder.

The validity of the "PANSS-positive" factor is supported by the fact that there was no significant difference between the TA and GVA cohorts for the severity of positive symptoms. Furthermore, the fact that the longitudinal predictors of positive psychotic symptoms were identical to the predictors for the emergence of

TABLE 3 Loading of Positive and Negative Syndrome Scale (PANSS) Items in the 22q11.2 Deletion Syndrome Cohort

	General Factor	Negative Factor	Positive Factor
PANSS P1: Delusions			0.941
PANSS P3: Hallucinatory behavior			0.800
PANSS P6: Suspiciousness/persecution			0.789
PANSS G9: Unusual thought content			0.627
PANSS G3: Guilt feelings			0.563
PANSS G1: Somatic concerns			0.435
PANSS P2: Conceptual disorganization			0.429
PANSS N6: Lack of spontaneity and flow of conversation		0.984	
PANSS N4: Passive/apathetic social withdrawal		0.946	
PANSS N2: Emotional withdrawal		0.939	
PANSS N3: Poor rapport		0.916	
PANSS N1: Blunted affect		0.829	
PANSS G16: Active social avoidance		0.713	
PANSS N5: Difficulty in abstract thinking		0.616	
PANSS N7: Stereotyped thinking		0.530	
PANSS G7: Motor retardation		0.478	0.389
PANSS P4: Excitement	1.024		
PANSS G4: Tension	1.007		
PANSS G8: Uncooperativeness	0.832		
PANSS G14: Poor impulse control	0.760		
PANSS P7: Hostility	0.660		
PANSS G11: Poor attention	0.649		
PANSS G2: Anxiety	0.595		
PANSS G15: Preoccupation	0.570		
PANSS G13: Disturbance of volition	0.564		
PANSS G12: Lack of judgment and insight	0.481		
PANSS G5: Mannerisms and posturing	0.442		
PANSS G10: Disorientation	0.394		
PANSS P5: Grandiosity			
PANSS G6: Depression			

Note: Loadings <0.35 are not listed.

psychotic disorders also supports the validity of this factor. By contrast, the differences found between the 2 centers on the negative and general factors may underscore a difficulty and heterogeneity inherent in assessing these symptoms in individuals with developmental disabilities.

We identified several significant predictors for the emergence of a psychotic disorder and for the severity of PANSS-positive symptoms at follow-up, including the presence of an anxiety disorder, low FSIQ at baseline evaluation, and a decrease in VIQ scores between baseline and follow-up evaluations. Some of these predictors were already identified in a previous longitudinal study of the Stanford cohort.[17] The predictive value of having an anxiety disorder at baseline for later development of psychosis was quite robust, as 9 of 10 patients with emerging psychotic disorder in our sample were diagnosed with an anxiety disorder at baseline. A related study with 22q11.2DS children found that anxiety symptoms, and not IQ, strongly and negatively correlated with adaptive functioning.[36] The authors suggested that chronic anxiety and stress via prolonged activation and release of adrenal glucocorticoids may have deleterious effects on the prefrontal cortex and limbic regions, which could contribute to cognitive impairments and the evolution of psychosis in 22q11.2DS.[36]

The *COMT* Met allele, which predicted the onset of psychotic disorders in the Stanford longitudinal study,[7] was not found to be a significant predictor in our cohorts. The inability to replicate the *COMT* result highlights the need for large-scale, multicenter, whole-genome sequencing and whole-genome association studies that will identify the genetic pathways leading to psychosis in 22q11.2DS.

The current study has several limitations that should be noted. The psychiatric measures used did not include an evaluation of autism spectrum disorders, symptoms of which have been frequently reported in 22q11.2DS.[12] The use of raw scores, in addition to age-normed scores, would be useful for assessing cognitive change over time. The longitudinal changes in IQ scores detected in our study were rather small and within the standard error of the mean for nearly all data points. If, as suggested,[29-31] WAIS-III scores are inflated compared to WISC-III scores, then the actual mean decline in FSIQ for the group of adolescents evaluated using a WISC test at baseline and a WAIS-III test at follow-up may be larger and of more robust clinical significance. Furthermore, the fact that there are relatively few statistically significant longitudinal changes in *DSM-IV* disorders (especially in the adults) is most likely the result of reduced statistical power. Finally, we did not include dimensional psychiatric tools, which are highlighted in the recent *DSM-5* and should be included in future longitudinal studies.

In conclusion, we present here the largest longitudinal study to date of individuals with 22q11.2DS. Our psychiatric findings have potentially important implications for prevention and treatment. We ascertained that the age of onset of psychotic disorders usually occurs between the ages of 14 and 22, that depression peaks in the transition to elementary school and during late adolescence/early adulthood, and that anxiety disorders are a robust risk factor for the evolution of psychotic disorders. This suggests that parents and clinicians treating children with 22q11.2DS should be aware of and screen for symptoms of anxiety and depression in children with 22q11.2DS from a young age. Unfortunately there is a paucity of empirical data about the treatment of anxiety, depression, and psychosis in 22q11.2DS. Such studies should be the focus of future research. In the meantime, when depression or anxiety disorders are detected, treatment options known to be effective in typically developing children, such as cognitive behavioral therapy and use of selective serotonin reuptake inhibitors, can be implemented. &

CG Clinical Guidance

- In individuals with 22q11.2DS, psychotic disorders typically emerge between the ages of 14 and 22 years.
- Psychotic disorders in individuals with 22q11.2DS are chronic in most cases, but they can also be transient.
- The prevalence of mood disorders in 22q11.2DS increases during late adolescence and early adulthood.
- Anxiety disorders occur in approximately one-half of individuals with 22q11.2DS and represent a major risk factor for psychosis in this population.
- In general, a greater than average decrease in verbal IQ (VIQ) scores may accompany the emergence of psychosis.
- Given that individuals with 22q11.2DS are at increased risk for psychosis, we recommend screening them at least once a year, during adolescence and up to age 30, for the presence of psychiatric disorders including psychosis, anxiety disorders, and depression.

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SUPPLEMENT 1

Comparative studies suggest that Wechsler Adult Intelligence Scale (WAIS) scores are inherently higher than Wechsler Intelligence Scale for Children (WISC) scores.[1-3] For example, a comparison of Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) to Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) test scores in adolescents at age 16 years showed that their WAIS-III scores were 2 to 5 points higher than their WISC-IV scores when these individuals were assessed using both versions.[1] Furthermore, other comparative studies demonstrate that the discrepancy between Wechsler Adult Intelligence Scale–Revised (WAIS-R)/Wechsler Intelligence Scale for Children–Revised (WISC-R) and WISC-IV/WAIS-III scores (WAIS scores consistently higher than WISC scores) is greater in individuals with intellectual disabilities than in those with normal IQ.[2,3]

To verify the effect of this inequality on our results, we divided our sample into 3 groups: those individuals who were tested with a WISC at both time points; those who were tested with a WISC at T1 and with a WAIS-III at T2; and those who were tested with a WAIS-III at both time points. Repeated-measures analysis of variance did not support significant differences among the 3 subgroups ($F_{2,112} = 1.72$, $p = .18$). As can be seen in Table S4, available online, a decrease in Full Scale IQ (FSIQ) scores was greatest (−6.2 [8.4] points) for the second group, subjects who underwent a WISC test at T1 and a WAIS-III test at T2.

TABLE S1 Antipsychotic Treatment of Study Participants at Baseline and Follow-up

Antipsychotic Medication	Baseline	Follow-up
Participants on antipsychotics, n (%)	10 (8.0)	19 (15.2)
Olanzapine, n	3	4
Risperidone, n	2	3
Clotiapine, n	1	2
Clozapine, n	1	2
Fluphenazine, n	1	1
Amisulpiride, n		2
Aripiprazole, n		1
Cyamemazine, n		1
Amisulpiride + metyrosine, n	1	
Risperidone + fluphenazine, n	1	
Risperidone + amisulpiride, n		1
Aripiprazole + cyamemazine, n		1
Risperidone + fluphephenazine + clotiapine, n		1

TABLE S2 Prevalence Rates of Comorbid Anxiety Disorders for the Total Sample at Baseline and Follow-up

Baseline	Subjects With 2 Comorbid Disorders, n	Subjects With 3 Comorbid Disorders (Third Disorder), n
Specific phobia and separation anxiety disorders	1	1 (Social phobia)
Specific phobia and OCD	8	
Specific phobia and GAD	4	2 (Social phobia)
Social phobia and agoraphobia	1	2 (Specific phobia)
Separation anxiety disorder and OCD	1	
Separation anxiety disorder and GAD	2	
OCD and GAD	2	
Follow-up	**Subjects With 2 Comorbid Disorders, n**	**Subjects With 3 Comorbid Disorders (Third Disorder), n**
Specific phobia and social phobia	3	
Specific phobia and agoraphobia	1	
Specific phobia and OCD	2	
Specific phobia and GAD	4	1 (Social phobia)
Specific phobia and PTSD	1	1 (GAD)
Social phobia and OCD	1	
Social phobia and GAD	1	
OCD and PTSD		
OCD and GAD	1	1 (Separation anxiety disorder), 1 (Agoraphobia)

Note: GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder.

TABLE S3 Age of Onset and Exact Diagnosis of Psychotic Disorder in Individuals With 22q11.2DS and Comorbid Psychotic Disorder at Baseline (T1) and Follow-up (T2)

Patient	Sex	Age of Onset, y	Psychotic Disorder at T1	Psychotic Disorder at T2
1	Female	14	Psychotic disorder NOS	Schizophrenia
2	Female	11	Schizophrenia	—
3	Male	13	—	Schizophrenia
4	Male	15	—	Psychotic disorder NOS
5	Female	16	—	Brief psychotic disorder
6	Male	15	—	Schizophrenia
7	Male	14	—	Schizophreniform disorder
8	Male	16	—	Schizophrenia
9	Female	18	—	Brief psychotic disorder
10	Female	16	Schizophrenia	Schizophrenia
11	Male	22	—	Schizophrenia
12	Male	19	—	Psychotic disorder NOS
13	Male	20	—	Schizophrenia
14	Male	18	Schizophreniform disorder	Schizophrenia
15	Male	17	Schizophreniform disorder	—
16	Male	15	Brief psychotic disorder	—
17	Female	16	Schizophrenia	Schizophrenia
18	Male	25	Schizophrenia	Schizophrenia
19	Female	21	Schizophrenia	Schizoaffective disorder
20	Female	20	Schizoaffective disorder	Schizophrenia
21	Male	18	Schizophrenia	Schizophrenia
22	Female	unknown (adolescence)	Schizophrenia	Schizoaffective disorder
23	Female	30	Schizoaffective disorder	Schizoaffective disorder

Note: NOS = not otherwise specified; y = years.

TABLE S4 Comparison of Full Scale IQ (FSIQ) Scores Based on the Wechsler Scale Version

IQ Test at T1	IQ Test at T2	FSIQ at T1, Mean ± SD	FSIQ at T2, Mean ± SD	Δ FSIQ
WISC-R or WISC-III	WISC-R or WISC-III	75.1 ± 11.2	71.4 ± 11.6	−3.7 (8.9)
WISC-R or WISC-III	WAIS-III	75.2 ± 13.0	69.04 ± 7.9	−6.2 (8.4)
WAIS-III	WAIS-III	70.2 ± 12.8	67.92 ± 11.9	−2.3 (5.7)

Note: WAIS-III = Wechsler Adult Intelligence Scale—Third Edition; WISC-III = Wechsler Intelligence Scale for Children—Third Edition; WISC-R = Wechsler Intelligence Scale for Children—Revised.

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