Psychotic symptoms in 16p11.2 copy number variant carriers

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Abstract: 16p11.2 copy number variation (CNV) is implicated in neurodevelopmental disorders, with the duplication and deletion associated with autism spectrum disorder (ASD) and the duplication associated with schizophrenia (SCZ). The 16p11.2 CNV may therefore provide insight into the relationship between ASD and SCZ, distinct disorders that co-occur at an elevated rate and are difficult to distinguish from each other and from common co-occurring diagnoses such as obsessive compulsive disorder (OCD), itself a potential risk factor for SCZ. As psychotic symptoms are core to SCZ but distinct from ASD, we sought to examine their predictors in a population (n = 546) of 16p11.2 CNV carriers and their noncarrier siblings recruited by the Simons Variation in Individuals Project. We hypothesized that psychotic symptoms would be most common in duplication carriers followed by deletion carriers and noncarriers, that an ASD diagnosis would predict psychotic symptoms among CNV carriers, and that OCD symptoms would predict psychotic symptoms among all participants. Using data collected across multiple measures, we identified 19 participants with psychotic symptoms. Logistic regression models adjusting for gender, age, and IQ found that 16p11.2 duplication and ASD diagnosis predicted psychotic symptom presence. Our findings suggest that the association between 16p11.2 duplication and psychotic symptoms is independent of ASD diagnosis and that ASD diagnosis and psychotic symptoms may be associated in 16p11.2 CNV carriers.

Lay Summary: Either deletion or duplication at chromosome 16p11.2 raises the risk of autism spectrum disorder, and duplication, but not deletion, has been reported in schizophrenia. In a sample of 16p11.2 deletion and duplication carriers, we found that having the duplication or having an autism diagnosis may increase the risk of psychosis, a key feature of schizophrenia.

Keywords: Chromosomes, Human, Pair 16; Chromosome Deletion; Chromosome Duplication; Autism Spectrum Disorder; Schizophrenia Spectrum and Other Psychotic Disorders; Obsessive-Compulsive Disorder; Phenotype.

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1 Introduction

The BP4-BP5 16p11.2 copy number variant (CNV) involves approximately 600 kilobases and 29 genes (Simons VIP Consortium, 2012). Though rare in the general population, the CNV is enriched in individuals with developmental delay or psychiatric illness. Both the 16p11.2 deletion and duplication are associated with autism spectrum disorder (ASD) (Weiss et al., 2008), and 16p11.2 duplication is associated with schizophrenia (SCZ) (McCarthy et al., 2009). The 16p11.2 CNV may provide insight into the complex relationship between symptoms of ASD and symptoms of SCZ, which, while considered distinct psychiatric disorders, converge at the levels of diagnosis, neurodevelopment and epidemiology.

At a diagnostic level, ASD and SCZ share features. In ASD, impaired social-emotional reciprocity is a requirement for the diagnosis (Lord, Elsabbagh, Baird, & Veenstra-VanderWeele, 2018). In SCZ, psychotic symptoms, sometimes called "positive symptoms," are often the disorder's most prominent manifestation, and can be defined as symptoms demonstrating gross impairment in the ability to distinguish between inner experience and the external environment (Lieberman & First, 2018). Psychotic symptoms include delusional beliefs and perceptual disturbances, and are quite distinct from ASD. However, another core SCZ feature, the so-called "negative symptoms," include diminished emotional expression and asociality, and share many features with ASD's social impairment (Hommer & Swedo, 2015).

The nosology of ASD and SCZ in fact has a long and complicated history (Kolvin, 1971; J. Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009; Wolff, 2004). It has long been recognized that subtle symptoms, such as delay and abnormality in language, often precede the emergence of frank psychotic behavior (Courvoisie, Labellarte, & Riddle, 2001; Millan et al., 2016), and SCZ increasingly has been placed in a neurodevelopmental context (Insel, 2010; Owen, O'Donovan, Thapar, & Craddock, 2011; J. L. Rapoport, Giedd, & Gogtay, 2012). A recent meta-analysis showed that ASD and SCZ co-occur more frequently than chance would suggest, with SCZ over three times as common in individuals with ASD as in controls (Zheng, Zheng, & Zou, 2018).

These areas of convergence highlight the importance of recognizing psychotic symptoms in ASD. Yet the communication impairment and repetitive speech or behavior associated with ASD can make assessment and differentiation of delusional beliefs and perceptual disturbances

difficult. Further, repetitive behaviors in ASD are sometimes difficult to distinguish from symptoms of obsessive compulsive disorder (OCD), which is itself a common co-occurring diagnosis that shares genetic liability with ASD (Jacob, Landeros-Weisenberger, & Leckman, 2009). Although OCD symptoms and characteristic repetitive behaviors in ASD are thought to be phenomenologically distinct (Guo et al., 2017; Jiujias, Kelley, & Hall, 2017), the boundary between them is not always clear. Obsessive compulsive symptoms may also be important in the context of recognizing psychosis. Obsessive compulsive symptoms are present in about 30% of people with SCZ (Swets et al., 2014), and recent evidence has suggested that they may represent a SCZ risk factor (Barzilay et al., 2018; Meier et al., 2014; Van Dael et al., 2011).

We sought to examine predictors of psychotic symptoms in 16p11.2 CNV carriers. By doing so, we hoped to yield insights relevant to psychosis in the broader ASD population, improving the understanding of ASD, SCZ, and the relationship these disorders have with each other and with OCD. We hypothesized that: 1) psychotic symptoms are most common in 16p11.2 duplication carriers followed by 16p11.2 deletion carriers and noncarriers, 2) the presence of an ASD diagnosis predicts an increased risk of having psychotic symptoms among CNV carriers, and 3) OCD symptoms will predict psychotic symptoms among both CNV carriers and noncarriers.

2 Method

2.1 Study Sample

Probands all have the same 600kb BP4-BP5 16p11.2 CNV mediated by segmental duplications (chromosome 16 position 29,652,999-30,199,351 in hg19). Probands were identified by routine clinical testing and were recruited by the Simons Variation in Individuals Project (VIP) (Simons VIP Consortium, 2012), a large study of specific recurrent genetic variants that contribute to the risk of ASD and other neurodevelopmental disorders. Their biological relatives had cascade genetic testing to identify additional carriers. Any carriers with known pathogenic mutations affecting the brain in addition to the 16p11.2 CNV were excluded. This method produced the complete Simons VIP cohort of 658 participants: 127 16p11.2 duplication, 137 16p11.2 deletion, and 394 noncarrier relatives. Our study included all cohort members who were evaluated for

ASD and completed an IQ assessment. 546 participants met these criteria: 109 with 16p11.2 duplication, 131 with 16p11.2 deletion, and 306 noncarriers.

Within the study sample, we compared several baseline characteristics of 16p11.2 duplication, 16p11.2 deletion, and noncarrier participants. Mean age and IQ were compared using analysis of variance (ANOVA), with Tukey's procedure used for post-hoc pairwise comparisons. Gender, ASD diagnosis, and OCD symptoms were compared using χ^2, with Bonferroni-adjusted χ^2 for post-hoc comparisons (**Table 1**).

2.2 Assessment Measures

Participants underwent a standardized assessment performed by trained clinicians that encompassed self-report, parent-report, interview, and observation measures, with the measures a particular participant received varying based on age and carrier status (**Table 2**).

ASD diagnoses were made based on clinical judgment informed by the results of clinician-administered and self- or caregiver-report measures. The Autism Diagnostic Observation Scale, Second Edition (ADOS-2) (Lord et al., 2012), a clinician-administered observational measure, was administered to all participants except noncarrier parents of carrier children or participants in whom the measure's use was not feasible due to limitations of cognition or mobility. An ADOS-2 assessment involves the administration of one of four modules designed for different levels of verbal ability and, in the case of Module 4, age. Raw scores are produced for core domains of social affect (SA) and restricted/repetitive behaviors (RRB), as well as a combined "total" raw score for overall ASD symptomatology. These raw scores can be converted into scaled "Calibrated Severity Scores" (CSS) that range from 1 to 10 and represent a standardized quantification of ASD symptom severity (Gotham, Pickles, & Lord, 2009; Hus, Gotham, & Lord, 2014; Hus & Lord, 2014). The Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur, & Lord, 2003), an interview with the participant's parent or caregiver, was administered to all participants in whom ASD was suspected. Self- or caregiver-report measures were also used to inform the clinical ASD diagnosis, including the Broad Autism Phenotype Questionnaire (BAPQ) (Hurley, Losh, Parlier, Reznick, & Piven, 2007), Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) and Social Responsiveness Scale (SRS)/Social Responsiveness Scale-Adult Research Version (SRS-ARV) (Constantino, 2005;

Constantino & Todd, 2005).

IQ was measured with the Differential Ability Scales, Second Edition (DAS-II) (Elliot, 2007) and Mullen Scales of Early Learning (MSEL) (Shank, 2011) in children and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) in adults. Adaptive skills were assessed using the Vineland Adaptive Behavior Scales II (Sparrow, Cicchetti, & Balla, 2005).

Psychiatric symptoms were assessed using the school-age Child Behavior Checklist (CBCL), Adult Behavior Checklist (ABCL), Symptom Checklist-90-Revised (SCL-90-R), DISC (Diagnostic Interview Schedule for Children), and M-SOPS (Modified Scale of Prodromal Symptoms). The CBCL is part of the Achenbach System of Empirically Based Assessment (ASEBA), and consists of 113 questions about mental health with eight underlying factors (Achenbach & Rescorla, 2001). It is normed for six to eighteen-year-olds and completed by a parent or caregiver. The ABCL is an analogous ASEBA scale for adults, normed for ages eighteen to 59 and completed by an adult who knows the participant well (Achenbach & Rescorla, 2003). The SCL-90-R is a 90-item Likert-type self-report measure of psychiatric symptoms in adults, with nine underlying factors (Derogatis, 1994). The DISC is a structured diagnostic interview designed to assess for symptoms of DSM-IV psychiatric disorders in children and adolescents (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The M-SOPS is a nineteen-item clinician-rated instrument that measures symptoms of psychosis (McGlashan, Miller, Woods, Hoffman, & Davidson, 2001).

2.3 Analytic Approach

2.3.1 Development of a Psychotic Symptom Index

A psychosis-specific measure, the M-SOPS, was only administered to 26 participants. We therefore derived a composite index of psychotic symptoms by combining M-SOPS responses with data collected from the CBCL/ABCL, SCL-90-R, and DISC, which all include questions assessing for psychotic symptoms **(Table S1)**. 463 (84.80%) participants received at least one of these four measures, and 276 (50.55%) received two or more.

For each measure, we derived a binary variable indicating a screen-positive or negative for presence/absence of psychotic symptoms based on predefined criteria. Then, for each pairwise combination of measures, we examined the extent to which positive screens co-occurred and

performed Fisher's exact test to assess the strength of their relationship.

If a subject screened positive by at least two different measures, we considered the composite index to be positive, reflecting the likely presence of psychotic symptoms. To interrogate the robustness of this indicator, we created and compared four versions of the composite index. Version one, which we created first, was the least stringent. Version two used an age cutoff, version three used a stricter CBCL/ABCL threshold, and version four incorporated both.

Positive screens by each measure comprising the index were operationalized as follows:

CBCL/ABCL: The CBCL/ABCL "Thought Problems" factor includes several psychosis-related items. As item-level CBCL/ABCL data were not available, for version one of the index we selected a Thought Problems T-score threshold of ≥ 60 to identify scores at least one standard deviation above the mean, and considered these positive. As the CBCL Thought Problems T-Score can be elevated in nonpsychotic youth with ASD (Biederman et al., 2010; Duarte, Bordin, de Oliveira, & Bird, 2003; Hoffmann, Weber, König, Becker, & Kamp-Becker, 2016; Mazefsky, Anderson, Conner, & Minshew, 2011; Ooi, Rescorla, Ang, Woo, & Fung, 2011), versions three and four of the index raised the threshold to ≥ 70 (i.e., two rather than one standard deviations above the mean).

SCL-90-R: We selected four items reflecting specific psychotic symptoms distinct from ASD from the SCL-90-R "psychoticism" factor: "the idea that someone else can control your thoughts," "hearing voices that other people do not hear," "other people being aware of your private thoughts," and "having thoughts that are not your own." We considered a response of at least "a little bit" to any of these items to be a positive screen.

DISC: For each DSM-IV diagnosis assessed by the DISC interview, data were available regarding the number of symptoms endorsed but not which were endorsed specifically. We considered endorsement of at least one schizophrenia symptom within the past year to represent a positive screen.

M-SOPS: Five M-SOPS items assess symptoms of psychosis: "unusual thought content or delusional ideas," "suspiciousness or persecutory ideas," "grandiosity," "perceptual abnormalities or hallucinations," and "disorganized communication." The presence of at least one of these symptoms (with the exception of "disorganized communication," which we did not consider given its non-specificity) represented a positive screen.

Versions one and three of the index did not incorporate an age cutoff. However, since true psychosis in young children is rare, with childhood-onset schizophrenia typically not presenting before age seven (Baribeau & Anagnostou, 2013), versions two and four required that a participant be at least seven years old to be positively identified with psychotic symptoms.

2.3.2 Primary Analysis

As index version four was the most stringent, incorporating both the raised CBCL threshold and the age cutoff, we used it to identify participants likely to have psychotic symptoms. We then examined predictors of the presence of psychotic symptoms by conducting a series of logistic regressions. All models used generalized estimating equations (GEEs) to control for intra-family correlations (Hanley, Negassa, deB Edwardes, & Forrester, 2003).

Our predictor variables of interest, which we selected *a priori*, were CNV carrier status, age, IQ, clinical ASD diagnosis, OCD symptoms (as measured by endorsement of at least one OCD symptom in the past year during the DISC interview) and gender. Prior to conducting any analyses, we ruled out multicollinearity by inspecting the correlation matrix between scaled versions of all variables.

Our primary analysis included four regression models. The first was estimated for the entire sample, and included all predictors of interest. The second, third and fourth models were estimated for subgroups of the sample defined by carrier status (i.e., 16p11.2 deletion carriers, 16p11.2 duplication carriers, and noncarriers), and each included all predictors of interest except carrier status. All analyses used unscaled variables for ease of interpretability.

2.3.3 Exploratory Regression Analyses

To determine whether ASD severity could predict the presence of psychotic symptoms, we estimated exploratory regression models that substituted the categorical ASD diagnosis predictor with continuous ADOS CSS values.

Total CSS values for participants who received ADOS Modules 1, 2 or 3 were available to us as part of the Simons VIP dataset. For those who received ADOS Module 4, we derived total CSS values from item-level data (Hus & Lord, 2014). For all ADOS modules, we derived SA and RRB domain CSS values from item-level data where available (Hus et al., 2014). 210

participants who did not receive the ADOS were excluded from exploratory models in which total CSS was a predictor. An additional 59 participants who lacked item-level data were excluded from models in which domain CSS values were predictors.

2.3.4 Software and Data

We conducted all analyses in R 3.5.1 (R Core Team, 2018), using functions from dplyr 0.7.8 (Wickham, François, Henry, & Müller, 2018), magrittr 1.5 (Bache & Wickham, 2014), and purrr 0.2.5 (Henry & Wickham, 2019), as well as *chisq.post.hoc* from fifer 1.1 (Fife, 2019), *rescale* from arm 1.10-1 (Gelman et al., 2018), *geeglm* from geepack 1.2-1 (Hojsgaard, Halekoh, & Yan, 2016), and *tidy* from broom 0.5.0 (Robinson et al., 2018). Analysis scripts are available from the authors at https://github.com/amandeepjutla/2019-16p11-psychosis. The Simons VIP 16p11.2 v10.0 dataset used for this study can be requested through the Simons Foundation Autism Research Initiative (SFARI, RRID:SC_004261) online portal, SFARI Base, at https://base.sfari.org.

3 Results

3.1 Sample Characteristics

The sample represented a broad range of ages ($M = 23.06, SD = 16.95$ years), with significant variation among 16p11.2 duplication, 16p11.2 deletion, and noncarriers, $F(2, 543) = 71.67, p < 2.39 \times 10^{-28}$. Post-hoc comparisons showed significant differences for duplication-deletion, noncarrier-duplication, and noncarrier-deletion pairwise comparisons. IQ ($M = 97.69, SD = 20.34$) also varied significantly among the three groups, $F(2, 543) = 166.04, p < 4.38 \times 10^{-57}$, with post-hoc comparisons showing that duplication and deletion groups differed from the noncarrier group, but not from each other.

The three groups were not significantly imbalanced in terms of gender composition, $\chi^2(1) = 4.57, p = 0.10$. They differed in terms of ASD diagnosis, $\chi^2(1) = 50.49, p = 1.08 \times 10^{-11}$ and presence of OCD symptoms, $\chi^2(1) = 24.29, p = 5.31 \times 10^{-6}$. Post-hoc comparisons for ASD and OCD showed that, as with IQ, duplication and deletion carriers differed significantly from noncarriers but not each other.

3.1.1 Participants with Psychotic Symptoms

56 of 282 participants screened positive on the CBCL or ABCL (using the $\geq$ 70 T-Score cutoff), 50 of 271 on SCL-90-R, 23 of 178 on DISC, and 9 of 26 on M-SOPS **(Table 3)**. We observed some degree of overlap for all possible pairwise combinations of these measures except SCL-90 $\times$ DISC, which was expected because SCL-90 was given only to adults and DISC only to children. Tests of relationship strength between pairs (**Table 4**) identified a statistically significant association between CBCL/ABCL $\times$ DISC (OR 7.71, 95% CI 2.16 - 42.21, $p = 2.29 \times 10^{-4}$).

Using the most stringent version of the composite index (version four), nineteen participants had likely psychotic symptoms. Of these, nine were female and ten were male. Twelve had 16p11.2 duplication, four had 16p11.2 deletion, and three were noncarrier family members. Seven had a clinical ASD diagnosis, and three had OCD symptoms. Their mean age was 18.03 years ($SD = 10.93$ years), and mean IQ was 81.95 ($SD = 19.75$).

3.2 Predictors of Psychotic Symptoms

The parameters of regression models estimated for the primary analysis are presented in **Table 5** (for the entire sample) and **Table 6** (for carrier status-defined subgroups).

3.2.1 Hypothesis 1: CNV Carrier Status as Predictor

Hypothesis 1, that psychotic symptoms would be most common in 16p11.2 duplication carriers followed by 16p11.2 deletion carriers and noncarriers was partially supported by our finding that, in the model estimated for the entire sample, 16p11.2 duplication carrier status predicted psychotic symptom presence (OR 7.44, 95% CI 1.77 - 31.18, $p = 0.006$). Neither deletion carrier status nor noncarrier status was a significant predictor.

3.2.2 Hypothesis 2: ASD Defined by Clinical Diagnosis as Predictor

Hypothesis 2, that ASD diagnosis would predict presence of psychotic symptoms among 16p11.2 CNV carriers, was partially supported by our finding that categorical ASD diagnosis predicted psychotic symptom presence in the entire sample (OR 4.21, 95% CI 1.31 - 13.56, $p = 0.02$).

An insufficient number of noncarriers had an ASD diagnosis, or co-occurring psychotic symptoms, to interpret findings against other subgroups. ASD diagnosis did not reach statistical significance as a predictor among either CNV carrier-defined subgroup alone.

3.2.3 Hypothesis 3: OCD Symptoms as Predictor

Hypothesis 3, that OCD symptoms would predict the presence of psychotic symptoms among both carriers and noncarriers, was not significantly supported by our findings.

3.2.4 IQ, Gender and Age as Predictors

IQ and gender were not significant predictors of the presence of psychotic symptoms in the entire sample or any of its subgroups. Age reached statistical significance as a negative predictor among noncarriers (OR 0.93 for every year increase in age, 95% CI 0.87 - 0.99, $p = 0.02$), but as only three noncarriers had psychotic symptoms, this finding is likely to be artifactual.

3.2.5 Exploration of ASD Severity as Predictor

The parameters of exploratory models that substituted categorical ASD diagnosis with continuous ADOS Calibrated Severity Scores (CSS) are presented in **Table S2** (for total CSS) and **Table S3** (for domain CSS).

Total CSS trended toward significance as a predictor of psychotic symptoms among all participants who received the ADOS (OR 1.21 for every one point increase in CSS, 95% CI 0.99 - 1.47, $p = 0.06$). We did not find that domain CSS for RRB or SA were significant predictors.

3.2.6 Robustness of Findings

Less stringently-defined versions of the composite psychotic symptom index produced results similar to the version four results reported above. Duplication status and ASD diagnosis consistently predicted psychotic symptoms.

Version one, which had a CBCL/ABCL T-Score threshold of ≥ 60 and no age cutoff, identified thirty-five participants as having likely psychotic symptoms. Using this group, duplication status, ASD diagnosis, and OCD symptoms were significant predictors of psychotic symptoms

in the entire sample (duplication: OR 5.13, 95% CI 1.70 - 15.49, $p < 0.001$; ASD diagnosis: OR 2.83, 95% CI 1.08 - 7.40, $p = 0.03$; OCD symptoms: OR 3.32, 95% CI 1.14 - 9.70, $p = 0.03$). OCD symptoms were also a significant predictor among deletion carriers alone (OR 7.22, 95% CI 1.30 - 40.09, $p = 0.02$).

Version two, which added the requirement that a participant to be at least seven years old to be identified with psychotic symptoms, reduced the number identified from thirty-five to thirty. Here, duplication status and ASD diagnosis, but not OCD, were significant predictors of psychotic symptoms in the entire sample (duplication: OR 6.29, 95% CI 1.86 - 21.25, $p < 0.01$, ASD: OR 2.80, 95% CI 1.02 - 7.70, $p = 0.046$).

Version three, which had no age cutoff but raised the CBCL/ABCL threshold, reduced participants identified as likely having psychotic symptoms from thirty-five to twenty-one. Duplication status and ASD continued to predict psychotic symptoms in the entire sample (duplication: OR 6.64, 95% CI 1.81 - 24.39, $p < 0.01$; ASD: OR 4.13, 95% CI 1.27 - 13.37, $p = 0.02$). OCD was not statistically significant.

4 Discussion

Our findings indicate an association between 16p11.2 duplication status and psychotic symptoms. This aligns with previous studies that reported the 16p11.2 duplication in schizophrenia genetic samples (Giaroli, Bass, Strydom, Rantell, & McQuillin, 2014; McCarthy et al., 2009; Rees et al., 2014; Steinberg et al., 2014). The deletion was not significantly associated with psychotic symptoms, suggesting that, unlike ASD risk, which is seen with both the duplication and the deletion, psychosis risk may be specific to the duplication. Independent of the type of CNV, ASD was also a significant predictor of psychosis risk among 16p11.2 CNV carriers.

Though we did not find an association between psychotic symptoms and OCD, we did find that OCD symptoms were more common in 16p11.2 CNV carriers than noncarriers. This suggests that 16p11.2 may warrant future exploration in genetic studies of OCD, which currently are limited (Fernandez, Leckman, & Pittenger, 2018). As of now, 16p11.2 duplication has been described in, but not specifically associated with, OCD (McGrath et al., 2014).

This study has important strengths, primarily pertaining to the unique Simons VIP sample.

The specific focus on a rare genetic variant allowed us to minimize underlying genetic heterogeneity in exploring the relationship between ASD and risk of psychotic symptoms. Further, we tested convergent validity across multiple measures within our psychotic symptom index. We also were able to verify the stability of our results using alternate versions of the composite psychotic symptom index with different levels of stringency.

This study also has important limitations. Our focus on a rare CNV, despite its advantages, necessarily restricted our sample size, which in turn restricted the statistical power we could achieve. The ratio between the number of participants with psychotic symptoms and the number of predictors in our regression models, while in an acceptable range (van Smeden et al., 2016; Vittinghoff & McCulloch, 2007), could have introduced a potential for overfitting, particularly in subgroup analyses, though our sensitivity analyses were partially able to address this.

Finally, our psychotic symptom index, though carefully developed, used a combination of self- and parent-report measures with varying levels of specificity for psychosis. The CBCL/ABCL Thought Problems factor includes behavioral symptoms other than psychosis, and DISC incorporates DSM-IV "negative" schizophrenia symptoms that overlap with ASD. However, with the SCL-90-R and M-SOPS, we were able to use individual items with high specificity, and M-SOPS in particular was designed specifically for the detection of psychosis. Still, it is conceivable that at least some participants identified as having symptoms by the index may not have "true" clinical psychosis. The relationship between psychotic symptoms as identified by all versions of our measure and 16p11.2 duplication status is, however, consistent with existing literature, lending support to our method's validity.

To our knowledge, this is the first examination of ASD and psychotic symptoms among 16p11.2 CNV carriers. We hope to follow up by more deeply characterizing the 16p11.2 deletion and duplication phenotypes by conducting in-person interviews, correlating clinical metrics with neuroimaging findings, and longitudinally following the Simons VIP cohort. Doing so will help generate hypotheses and insights applicable to psychotic and other symptoms in a general ASD population.

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6 Disclosures

Dr. Veenstra-VanderWeele has consulted or served on an advisory board for Roche Pharmaceuticals, Novartis, and SynapDx, has received research funding from Roche Pharmaceuticals, Novartis, SynapDx, Seaside Therapeutics, and Forest, and has received an editorial stipend from Springer and Wiley.

Drs. Jutla, Turner, Snyder, and Chung report no biomedical financial interests or potential conflicts of interest.

Characteristic	**Total** n = 546		**Duplication** n = 109		**Deletion** n = 131		**Noncarrier** n = 306		**Main effect**	**Post-hoc comparisons**	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p* (ANOVA)	Pair	*p* (Tukey)
Age in years	23.06	16.95	19.84	17.54	10.92	10.37	29.40	15.86	$\mathbf{2.39 \times 10^{-28}}$***	**duplication-deletion**	**<0.001*** **
										noncarrier-deletion	**<0.001*** **
										noncarrier-duplication	**<0.001*** **
IQ	97.69	20.34	84.59	22.01	82.73	15.61	108.76	13.54	$\mathbf{5.38 \times 10^{-57}}$***	duplication-deletion	0.65
										noncarrier-deletion	**<0.001*** **
										noncarrier-duplication	**<0.001*** **
	#	%	#	%	#	%	#	%	*p* (χ^2)	Pair	*p* (Bonferroni-adjusted χ^2)
Female gender	292	53.48	53	48.62	63	48.09	176	57.52	0.10	N/A: no significant main effect	
ASD diagnosis	48	8.79	17	15.60	27	20.61	4	1.31	$\mathbf{1.08 \times 10^{-11}}$***	duplication-deletion	1
										noncarrier-deletion	**<0.001*** **
										noncarrier-duplication	**<0.001*** **
OCD symptoms reported	35	6.41	11	10.09	18	13.74	6	1.96	$\mathbf{5.31 \times 10^{-6}}$***	duplication-deletion	1
										noncarrier-deletion	**<0.001*** **
										noncarrier-duplication	**0.002****

***: $p < 0.001$
**: $p < 0.01$
*: $p < 0.05$

Table 1: Sample characteristics

Domain	**Measure**	**Age**	**Type**	**Total** n = 546	**Duplication** n = 109	**Deletion** n = 131	**Noncarrier** n = 306
ASD	ADOS	Youth and Adults	Clinician assessment of participant	315	97	121	97
	ADI-R	Youth and Adults	Interview with parent	116	33	74	9
	BAPQ	Adults	Questionnaire (participant)	252	36	13	203
	SCQ	Youth	Questionnaire (parent)	237	60	102	75
	SRS	Youth	Questionnaire (parent)	237	60	101	76
	SRS-ARV	Adults	Questionnaire (individual who knows participant well)	253	39	12	202
IQ	Mullen	Youth	Clinician assessment of participant	63	22	30	11
	DAS-II Early Years (Lower)	Youth	Clinician assessment of participant	28	8	12	8
	DAS-II Early Years (Upper)	Youth	Clinician assessment of participant	60	13	24	23
	DAS-II School Age	Youth	Clinician assessment of participant	151	35	65	51
	WASI	Adults	Clinician assessment of participant	271	42	14	215
Psychiatric symptoms	CBCL	Youth	Questionnaire (parent)	194	47	85	62
	ABCL	Adults	Questionnaire (individual who knows participant well)	88	37	12	39
	SCL-90-R	Adults	Questionnaire (participant)	271	43	14	214
	DISC	Youth	Interview with parent	178	42	81	55
	M-SOPS	Youth and Adults	Clinician assessment of subject	26	15	8	3

Table 2: Phenotypic assessment measures

Measure	**Total** n = 546			**Duplication** n = 109			**Deletion** n = 131			**Noncarrier** n = 306		
	# Received	*# Positive*	*% Positive*	*# Received*	*# Positive*	*% Positive*	*# Received*	*# Positive*	*% Positive*	*# Received*	*# Positive*	*% Positive*
CBCL/ABCL	282	56	19.86	84	27	32.14	97	21	21.65	101	8	7.92
SCL-90-R	271	50	18.45	43	19	44.19	14	7	50	214	24	11.21
DISC	178	23	12.92	42	7	16.67	81	8	9.88	55	8	14.55
SOPS	26	9	5.06	15	5	11.9	8	3	3.7	3	1	1.82

Table 3: Index measures by carrier status

Pairwise combination			Number of participants		Relationship strength			
			w/ both measures	*w/ both positive*	*OR*	*95% CI lower*	*95% CI upper*	*p*
CBCL/ABCL	×	SCL-90-R	91	10	2.25	0.74	6.77	0.12
	×	**DISC**	**177**	**20**	**7.71**	**2.16**	**42.21**	**0.0002*** **
	×	M-SOPS	25	5	1.83	0.25	15.77	0.67
SCL-90-R	×	M-SOPS	17	3	5.96	0.35	391.49	0.25
	×	DISC	N/A: no co-occurrence between items					
DISC	×	M-SOPS	9	1	4.58	0.04	543.93	0.42

***: p <0.001
**: p <0.01
*: p <0.05

Table 4: Pairwise combinations between index measures

Predictor	***B***	**SE**	**Wald χ^2**	**OR**	**95% CI lower**	**95% CI upper**	**p**
(Intercept)	-3.98	1.45	7.57	0.02	0.00	0.32	0.01
Duplication	**2.01**	**0.73**	**7.52**	**7.44**	**1.77**	**31.18**	**0.006****
Deletion	0.51	0.89	0.32	1.66	0.29	9.55	0.57
Age in years	0.01	0.01	0.37	1.01	0.98	1.03	0.55
IQ	-0.01	0.01	0.53	0.99	0.97	1.02	0.47
ASD diagnosis	**1.44**	**0.6**	**5.81**	**4.21**	**1.31**	**13.56**	**0.02***
OCD symptoms	0.73	0.74	0.97	2.08	0.49	8.91	0.33
Gender	0.01	0.47	0.00	1.01	0.40	2.53	0.98

***: p <0.001
**: p <0.01
*: p <0.05

Table 5: Predictors of psychotic symptoms in entire sample

Predictor	***B***	**SE**	**Wald χ^2**	**OR**	**95% CI lower**	**95% CI upper**	***p***
			Duplication carriers only				
(Intercept)	-1.79	1.52	1.39	0.17	0.01	3.26	0.24
Age in years	0.02	0.02	1.29	1.02	0.99	1.05	0.26
IQ	-0.01	0.02	0.41	0.99	0.96	1.02	0.52
ASD diagnosis	1.49	0.81	3.4	4.46	0.91	21.81	0.07
OCD symptoms	N/A : no duplication carriers positive for psychotic symptoms had OCD symptoms						
Gender	-0.29	0.68	0.18	0.75	0.2	2.85	0.67
			Deletion carriers only				
(Intercept)	-6.52	3.62	3.25	0.00	0.00	1.76	0.07
Age in years	0.00	0.03	0.02	1.00	0.95	1.06	0.90
IQ	0.02	0.03	0.46	1.02	0.96	1.08	0.50
ASD diagnosis	1.41	1.17	1.45	4.10	0.41	40.63	0.23
OCD symptoms	1.94	1.17	2.76	6.99	0.70	69.31	0.10
Gender	0.47	1.24	0.14	1.60	0.14	18.05	0.70
			Noncarriers only				
(Intercept)	-0.71	2.91	0.06	0.49	0	146.86	0.81
Age in years	**-0.08**	**0.03**	**5.58**	**0.93**	**0.87**	**0.99**	**0.02**
IQ	-0.03	0.03	0.85	0.97	0.91	1.03	0.36
ASD diagnosis	N/A: no noncarriers positive for psychotic symptoms had ASD						
OCD symptoms	2.09	1.46	2.05	8.12	0.46	142.96	0.15
Gender	0.56	1.69	0.11	1.75	0.06	47.71	0.74

***: p <0.001
**: p <0.01
*: p <0.05

Table 6: Predictors of psychotic symptoms within carrier status-defined subsets

Measure	**Item(s)**
CBCL/ABCL	*Thought Problems T Score $\geq$ 60 based on the following:*
	Hears sound or voices that aren't there
	Sees things that aren't there
	Strange behavior
	Strange ideas
	Can't get his/her mind off certain thoughts; obsessions
	Repeats certain acts over and over; compulsions
	Picks nose, skin, or other parts of body (CBCL) / Picks skin or other parts of body (ABCL)
	Plays with own sex parts too much
	Plays with own sex parts in public
	Stores up too many things he/she doesn't need
	Deliberately harms self or attempts suicide
	Nervous movements or twitching
	Trouble sleeping
	Talks or walks in sleep
	Sleeps less than most kids (CBCL) / most people (ABCL)
SCL-90-R	*Response of at least "a little bit" to "for the past week, how much were you bothered by . . . ":*
	The idea that someone else can control your thoughts
	Hearing voices that other people do not hear
	Other people being aware of your private thoughts
	Having thoughts that are not your own
DISC	*At least one DSM-IV schizophrenia symptom within the past year:*
	Delusions
	Hallucinations
	Disorganized speech
	Grossly disorganized or catatonic behavior
	Negative symptoms
M-SOPS	*One or more of the following symptoms is present:*
	Unusual thought content/delusional ideas
	Suspiciousness/persecutory ideas
	Grandiosity
	Perceptual abnormalities/hallucinations

Table S1: Psychotic symptom index measures

Predictor	***B***	**SE**	**Wald χ^2**	**OR**	**95% CI lower**	**95% CI upper**	***p***
(Intercept)	-2.3	1.59	2.08	0.10	0.00	2.29	0.15
Duplication	0.60	0.66	0.82	1.82	0.50	6.70	0.37
Deletion	-0.86	0.85	1.02	0.42	0.08	2.25	0.31
Age in years	0.02	0.01	2.25	1.02	0.99	1.05	0.13
IQ	-0.02	0.01	1.68	0.98	0.96	1.01	0.19
Total CSS	0.19	0.10	3.56	1.21	0.99	1.47	0.06
OCD symptoms	-0.05	0.87	0.00	0.95	0.17	5.22	0.95
Gender	-0.13	0.52	0.06	0.88	0.32	2.42	0.80

***: p <0.001
**: p <0.01
*: p <0.05

Table S2: ADOS Total Calibrated Severity Score as predictor of psychotic symptoms

Predictor	***B***	**SE**	**Wald χ^2**	**OR**	**95% CI lower**	**95% CI upper**	***p***
(Intercept)	-1.79	1.87	0.92	0.17	0.00	6.47	0.34
Duplication	0.81	0.88	0.84	2.24	0.40	12.53	0.36
Deletion	-0.27	0.98	0.07	0.77	0.11	5.23	0.79
Age	0.03	0.02	3.47	1.03	1.00	1.06	0.06
IQ	-0.03	0.01	5.64	0.97	0.94	0.99	0.02
RRB CSS	0.10	0.14	0.52	1.11	0.84	1.47	0.47
SA CSS	0.13	0.13	1.08	1.14	0.89	1.46	0.30
OCD symptoms	0.33	0.79	0.17	1.39	0.30	6.54	0.68
Gender	0.65	0.62	1.10	1.91	0.57	6.42	0.29

***: p <0.001
**: p <0.01
*: p <0.05

Table S3: ADOS domain calibrated severity scores as predictors of psychosis

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