

# 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 (Courvoisier, 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

31 difficult. Further, repetitive behaviors in ASD are sometimes difficult to distinguish from symp-  
32 toms of obsessive compulsive disorder (OCD), which is itself a common co-occurring diagnosis  
33 that shares genetic liability with ASD (Jacob, Landeros-Weisenberger, & Leckman, 2009).  
34 Although OCD symptoms and characteristic repetitive behaviors in ASD are thought to be  
35 phenomenologically distinct (Guo et al., 2017; Jiujiias, Kelley, & Hall, 2017), the boundary  
36 between them is not always clear. Obsessive compulsive symptoms may also be important  
37 in the context of recognizing psychosis. Obsessive compulsive symptoms are present in about  
38 30% of people with SCZ (Swets et al., 2014), and recent evidence has suggested that they may  
39 represent a SCZ risk factor (Barzilay et al., 2018; Meier et al., 2014; Van Dael et al., 2011).

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

## 48 **2 Method**

### 49 **2.1 Study Sample**

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

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

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

## 66 2.2 Assessment Measures

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

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

88 Constantino & Todd, 2005).

89 IQ was measured with the Differential Ability Scales, Second Edition (DAS-II) (Elliot,  
90 2007) and Mullen Scales of Early Learning (MSEL) (Shank, 2011) in children and the Wechsler  
91 Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) in adults. Adaptive skills were  
92 assessed using the Vineland Adaptive Behavior Scales II (Sparrow, Cicchetti, & Balla, 2005).

93 Psychiatric symptoms were assessed using the school-age Child Behavior Checklist (CBCL),  
94 Adult Behavior Checklist (ABCL), Symptom Checklist-90-Revised (SCL-90-R), DISC (Diag-  
95 nostic Interview Schedule for Children), and M-SOPS (Modified Scale of Prodromal Symp-  
96 toms). The CBCL is part of the Achenbach System of Empirically Based Assessment (ASEBA),  
97 and consists of 113 questions about mental health with eight underlying factors (Achenbach  
98 & Rescorla, 2001). It is normed for six to eighteen-year-olds and completed by a parent or  
99 caregiver. The ABCL is an analogous ASEBA scale for adults, normed for ages eighteen to  
100 59 and completed by an adult who knows the participant well (Achenbach & Rescorla, 2003).  
101 The SCL-90-R is a 90-item Likert-type self-report measure of psychiatric symptoms in adults,  
102 with nine underlying factors (Derogatis, 1994). The DISC is a structured diagnostic interview  
103 designed to assess for symptoms of DSM-IV psychiatric disorders in children and adolescents  
104 (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The M-SOPS is a nineteen-item  
105 clinician-rated instrument that measures symptoms of psychosis (McGlashan, Miller, Woods,  
106 Hoffman, & Davidson, 2001).

## 107 **2.3 Analytic Approach**

### 108 **2.3.1 Development of a Psychotic Symptom Index**

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

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

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

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

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

124 **CBCL/ABCL:** The CBCL/ABCL “Thought Problems” factor includes several psychosis-  
125 related items. As item-level CBCL/ABCL data were not available, for version one of the  
126 index we selected a Thought Problems T-score threshold of  $\geq 60$  to identify scores at least  
127 one standard deviation above the mean, and considered these positive. As the CBCL Thought  
128 Problems T-Score can be elevated in nonpsychotic youth with ASD (Biederman et al., 2010;  
129 Duarte, Bordin, de Oliveira, & Bird, 2003; Hoffmann, Weber, König, Becker, & Kamp-Becker,  
130 2016; Mazefsky, Anderson, Conner, & Minshew, 2011; Ooi, Rescorla, Ang, Woo, & Fung,  
131 2011), versions three and four of the index raised the threshold to  $\geq 70$  (i.e., two rather than  
132 one standard deviations above the mean).

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

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

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

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

### 151 **2.3.2 Primary Analysis**

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

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

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

### 167 **2.3.3 Exploratory Regression Analyses**

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

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

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

### 178 **2.3.4 Software and Data**

179 We conducted all analyses in R 3.5.1 (R Core Team, 2018), using functions from dplyr 0.7.8  
180 (Wickham, François, Henry, & Müller, 2018), magrittr 1.5 (Bache & Wickham, 2014), and purrr  
181 0.2.5 (Henry & Wickham, 2019), as well as *chisq.post.hoc* from fifer 1.1 (Fife, 2019), *rescale*  
182 from arm 1.10-1 (Gelman et al., 2018), *geeglm* from geepack 1.2-1 (Hojsgaard, Halekoh, & Yan,  
183 2016), and *tidy* from broom 0.5.0 (Robinson et al., 2018). Analysis scripts are available from  
184 the authors at <https://github.com/amandeepjutla/2019-16p11-psychosis>. The Simons VIP  
185 16p11.2 v10.0 dataset used for this study can be requested through the Simons Foundation  
186 Autism Research Initiative (SFARI, RRID:SC\_004261) online portal, SFARI Base, at <https://base.sfari.org>.  
187

## 188 **3 Results**

### 189 **3.1 Sample Characteristics**

190 The sample represented a broad range of ages ( $M = 23.06, SD = 16.95$  years), with significant  
191 variation among 16p11.2 duplication, 16p11.2 deletion, and noncarriers,  $F(2, 543) = 71.67, p <$   
192  $2.39 \times 10^{-28}$ . Post-hoc comparisons showed significant differences for duplication-deletion,  
193 noncarrier-duplication, and noncarrier-deletion pairwise comparisons. IQ ( $M = 97.69, SD =$   
194  $20.34$ ) also varied significantly among the three groups,  $F(2, 543) = 166.04, p < 4.38 \times 10^{-57}$ ,  
195 with post-hoc comparisons showing that duplication and deletion groups differed from the  
196 noncarrier group, but not from each other.

197 The three groups were not significantly imbalanced in terms of gender composition,  $\chi^2(1) =$   
198  $4.57, p = 0.10$ . They differed in terms of ASD diagnosis,  $\chi^2(1) = 50.49, p = 1.08 \times 10^{-11}$  and  
199 presence of OCD symptoms,  $\chi^2(1) = 24.29, p = 5.31 \times 10^{-6}$ . Post-hoc comparisons for ASD  
200 and OCD showed that, as with IQ, duplication and deletion carriers differed significantly from  
201 noncarriers but not each other.



### 202 **3.1.1 Participants with Psychotic Symptoms**

203 56 of 282 participants screened positive on the CBCL or ABCL (using the  $\geq 70$  T-Score  
204 cutoff), 50 of 271 on SCL-90-R, 23 of 178 on DISC, and 9 of 26 on M-SOPS (**Table 3**).  
205 We observed some degree of overlap for all possible pairwise combinations of these measures  
206 except SCL-90  $\times$  DISC, which was expected because SCL-90 was given only to adults and  
207 DISC only to children. Tests of relationship strength between pairs (**Table 4**) identified a  
208 statistically significant association between CBCL/ABCL  $\times$  DISC (OR 7.71, 95% CI 2.16 -  
209 42.21,  $p = 2.29 \times 10^{-4}$ ).

210 Using the most stringent version of the composite index (version four), nineteen participants  
211 had likely psychotic symptoms. Of these, nine were female and ten were male. Twelve had  
212 16p11.2 duplication, four had 16p11.2 deletion, and three were noncarrier family members.  
213 Seven had a clinical ASD diagnosis, and three had OCD symptoms. Their mean age was 18.03  
214 years ( $SD = 10.93$  years), and mean IQ was 81.95 ( $SD = 19.75$ ).

## 215 **3.2 Predictors of Psychotic Symptoms**

216 The parameters of regression models estimated for the primary analysis are presented in **Table**  
217 **5** (for the entire sample) and **Table 6** (for carrier status-defined subgroups).

### 218 **3.2.1 Hypothesis 1: CNV Carrier Status as Predictor**

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

### 224 **3.2.2 Hypothesis 2: ASD Defined by Clinical Diagnosis as Predictor**

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

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

### 231 **3.2.3 Hypothesis 3: OCD Symptoms as Predictor**

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

### 234 **3.2.4 IQ, Gender and Age as Predictors**

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

### 239 **3.2.5 Exploration of ASD Severity as Predictor**

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

243 Total CSS trended toward significance as a predictor of psychotic symptoms among all  
244 participants who received the ADOS (OR 1.21 for every one point increase in CSS, 95% CI  
245 0.99 - 1.47,  $p = 0.06$ ). We did not find that domain CSS for RRB or SA were significant  
246 predictors.

### 247 **3.2.6 Robustness of Findings**

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

251 Version one, which had a CBCL/ABCL T-Score threshold of  $\geq 60$  and no age cutoff, identi-  
252 fied thirty-five participants as having likely psychotic symptoms. Using this group, duplication  
253 status, ASD diagnosis, and OCD symptoms were significant predictors of psychotic symptoms

254 in the entire sample (duplication: OR 5.13, 95% CI 1.70 - 15.49,  $p < 0.001$ ; ASD diagnosis: OR  
255 2.83, 95% CI 1.08 - 7.40,  $p = 0.03$ ; OCD symptoms: OR 3.32, 95% CI 1.14 - 9.70,  $p = 0.03$ ).  
256 OCD symptoms were also a significant predictor among deletion carriers alone (OR 7.22, 95%  
257 CI 1.30 - 40.09,  $p = 0.02$ ).

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

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

## 268 4 Discussion

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

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

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

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

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

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

304 To our knowledge, this is the first examination of ASD and psychotic symptoms among  
305 16p11.2 CNV carriers. We hope to follow up by more deeply characterizing the 16p11.2 deletion  
306 and duplication phenotypes by conducting in-person interviews, correlating clinical metrics with  
307 neuroimaging findings, and longitudinally following the Simons VIP cohort. Doing so will help  
308 generate hypotheses and insights applicable to psychotic and other symptoms in a general ASD  
309 population.

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## 316 **6 Disclosures**

317 Dr. Veenstra-VanderWeele has consulted or served on an advisory board for Roche Pharma-  
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320 from Springer and Wiley.

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

| Characteristic        | Total<br>n = 546 |           | Duplication<br>n = 109 |           | Deletion<br>n = 131 |           | Noncarrier<br>n = 306 |           | Main effect<br><i>p</i> (ANOVA)   | Post-hoc comparisons<br>Pair<br><i>p</i> (Tukey)   |   |
|-----------------------|------------------|-----------|------------------------|-----------|---------------------|-----------|-----------------------|-----------|-----------------------------------|--|---|
|                       | <i>M</i>         | <i>SD</i> | <i>M</i>               | <i>SD</i> | <i>M</i>            | <i>SD</i> | <i>M</i>              | <i>SD</i> |                                   |  |   |
| Age in years          | 23.06            | 16.95     | 19.84                  | 17.54     | 10.92               | 10.37     | 29.40                 | 15.86     | <b>2.39 × 10<sup>-28***</sup></b> | duplication-deletion<br>noncarrier-deletion<br>noncarrier-duplication<br>duplication-deletion<br>noncarrier-deletion<br>noncarrier-duplication | <0.001***<br><0.001***<br><0.001***<br>0.65<br><0.001***<br><0.001*** |
| IQ                    | 97.69            | 20.34     | 84.59                  | 22.01     | 82.73               | 15.61     | 108.76                | 13.54     | <b>5.38 × 10<sup>-57***</sup></b> |  |   |
|                       | #                | %         | #                      | %         | #                   | %         | #                     | %         | <i>p</i> (χ <sup>2</sup> )        | Pair   | <i>p</i> (Bonferroni-adjusted χ <sup>2</sup> )                        |
| 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      | <b>1.08 × 10<sup>-11***</sup></b> | duplication-deletion<br>noncarrier-deletion<br>noncarrier-duplication  | 1<br><0.001***<br><0.001***   |
| OCD symptoms reported | 35               | 6.41      | 11                     | 10.09     | 18                  | 13.74     | 6                     | 1.96      | <b>5.31 × 10<sup>-6***</sup></b>  | duplication-deletion<br>noncarrier-deletion<br>noncarrier-duplication  | 1<br><0.001***<br>0.002**   |

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

Table 1: Sample characteristics

| Domain               | Measure                    | Age              | Type  | Total<br>n = 546 | Duplication<br>n = 109 | Deletion<br>n = 131 | Noncarrier<br>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<br>n = 546 |            |            | Duplication<br>n = 109 |            |            | Deletion<br>n = 131 |            |            | Noncarrier<br>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         | 24                    | 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 |                     |                     |                  |
|----------------------|------------|-------------------------------------|-------------------------|-----------------------|---------------------|---------------------|------------------|
|                      |            | <i>w/ both measures</i>             | <i>w/ both positive</i> | <i>OR</i>             | <i>95% CI lower</i> | <i>95% CI upper</i> | <i>p</i>         |
| CBCL/ABCL            | × SCL-90-R | 91                                  | 10                      | 2.25                  | 0.74                | 6.77                | 0.12             |
|                      | × DISC     | <b>177</b>                          | <b>20</b>               | <b>7.71</b>           | <b>2.16</b>         | <b>42.21</b>        | <b>0.0002***</b> |
|                      | × 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            | <i>B</i>    | <i>SE</i>   | <i>Wald <math>\chi^2</math></i> | <i>OR</i>   | <i>95% CI lower</i> | <i>95% CI upper</i> | <i>p</i>       |
|----------------------|-------------|-------------|---------------------------------|-------------|---------------------|---------------------|----------------|
| (Intercept)          | -3.98       | 1.45        | 7.57                            | 0.02        | 0.00                | 0.32                | 0.01           |
| <b>Duplication</b>   | <b>2.01</b> | <b>0.73</b> | <b>7.52</b>                     | <b>7.44</b> | <b>1.77</b>         | <b>31.18</b>        | <b>0.006**</b> |
| 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           |
| <b>ASD diagnosis</b> | <b>1.44</b> | <b>0.6</b>  | <b>5.81</b>                     | <b>4.21</b> | <b>1.31</b>         | <b>13.56</b>        | <b>0.02*</b>   |
| 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                        | <i>B</i>   | <i>SE</i>   | Wald $\chi^2$ | <i>OR</i>   | 95% <i>CI</i> lower | 95% <i>CI</i> upper | <i>p</i>    |
|----------------------------------|--|-------------|---------------|-------------|---------------------|---------------------|-------------|
| <i>Duplication carriers only</i> |  |             |               |             |                     |                     |             |
| (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        |
| <i>Deletion carriers only</i>    |  |             |               |             |                     |                     |             |
| (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        |
| <i>Noncarriers only</i>          |  |             |               |             |                     |                     |             |
| (Intercept)                      | -0.71  | 2.91        | 0.06          | 0.49        | 0                   | 146.86              | 0.81        |
| <b>Age in years</b>              | <b>-0.08</b>   | <b>0.03</b> | <b>5.58</b>   | <b>0.93</b> | <b>0.87</b>         | <b>0.99</b>         | <b>0.02</b> |
| 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 | <p><i>Thought Problems T Score <math>\geq 60</math> based on the following:</i></p> <ul style="list-style-type: none"> <li>Hears sound or voices that aren't there</li> <li>Sees things that aren't there</li> <li>Strange behavior</li> <li>Strange ideas</li> <li>Can't get his/her mind off certain thoughts; obsessions</li> <li>Repeats certain acts over and over; compulsions</li> <li>Picks nose, skin, or other parts of body (CBCL) / Picks skin or other parts of body (ABCL)</li> <li>Plays with own sex parts too much</li> <li>Plays with own sex parts in public</li> <li>Stores up too many things he/she doesn't need</li> <li>Deliberately harms self or attempts suicide</li> <li>Nervous movements or twitching</li> <li>Trouble sleeping</li> <li>Talks or walks in sleep</li> <li>Sleeps less than most kids (CBCL) / most people (ABCL)</li> </ul> |
| SCL-90-R  | <p><i>Response of at least "a little bit" to "for the past week, how much were you bothered by . . . ":</i></p> <ul style="list-style-type: none"> <li>The idea that someone else can control your thoughts</li> <li>Hearing voices that other people do not hear</li> <li>Other people being aware of your private thoughts</li> <li>Having thoughts that are not your own</li> </ul>  |
| DISC      | <p><i>At least one DSM-IV schizophrenia symptom within the past year:</i></p> <ul style="list-style-type: none"> <li>Delusions</li> <li>Hallucinations</li> <li>Disorganized speech</li> <li>Grossly disorganized or catatonic behavior</li> <li>Negative symptoms</li> </ul>   |
| M-SOPS    | <p><i>One or more of the following symptoms is present:</i></p> <ul style="list-style-type: none"> <li>Unusual thought content/delusional ideas</li> <li>Suspiciousness/persecutory ideas</li> <li>Grandiosity</li> <li>Perceptual abnormalities/hallucinations</li> </ul>  |

Table S1: Psychotic symptom index measures

| Predictor    | <i>B</i> | SE   | Wald $\chi^2$ | OR   | 95% CI lower | 95% CI upper | <i>p</i> |
|--------------|----------|------|---------------|------|--------------|--------------|----------|
| (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    | <i>B</i> | SE   | Wald $\chi^2$ | OR   | 95% CI lower | 95% CI upper | <i>p</i> |
|--------------|----------|------|---------------|------|--------------|--------------|----------|
| (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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