Predictors of psychotic symptoms among 16p11.2 copy number variant carriers

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Conflict of Interest
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Introduction

- 16p11.2 copy number variation (CNV) is rare in the general population but enriched in individuals with developmental delay or psychiatric illness, with 16p11.2 duplication and deletion associated with autism spectrum disorder (ASD)[1] and 16p11.2 duplication associated with schizophrenia (SCZ).[2]
- The 16p11.2 CNV may therefore provide insight into the relationship between symptoms of ASD and symptoms of SCZ, which, though distinct disorders, co-occur at an elevated rate and share clinical features, such that they can be difficult to distinguish from each other.[3] Further, some features of ASD are difficult tot distinguish from symptoms of obsessive-compulsive disorder (OCD)[4], which itself may represent a SCZ risk factor.[5] As psychotic symptoms are core to SCZ but distinct from ASD, we sought to examine their predictors in a population of 16p11.2 CNV carriers and their noncarrier siblings.
- We hypothesized that psychotic symptoms are most common in duplication carriers followed by deletion carriers and noncarriers; that an ASD diagnosis predicts psychotic symptoms among CNV carriers; and that OCD symptoms predict psychotic symptoms among both carriers and noncarriers.

Method

- The study sample included 109 16p11.2 duplication carriers, 131 16p11.2 deletion carriers, and 306 non-carriers recruited by the Simons Variation in Individuals Project[6], a large study of specific recurrent genetic variants that contribute to the risk of ASD and other neurodevelopmental disorders.
- For all participants, ASD diagnoses were made based on clinical judgment informed by the results of clinician-administered and self- or caregiver-report measures, including the Autism Diagnostic Observation Scale, Second Edition (ADOS-2). IQ was measured with the Differential Ability Scales, Second Edition (DAS-II) in children and the Wechsler Abbreviated Scale of Intelligence (WASI) in adults.
- As a psychosis-specific measure, the M-SOPS (Modified Scale of Prodromal Symptoms) was only administered to a minority of participants, we derived a composite index of likely psychotic symptom presence by combining M-SOPS responses with data collected across other measures: the Child Behavior Checklist (CBCL) / Adult Behavior Checklist (ABCL), the Symptom Checklist-90-Revised (SCL-90-R) and the Diagnostic Interview Schedule for Children (DISC).
- For each measure, we developed a threshold by which a participant would be considered to have "screened positive" for psychotic symptoms, and we considered psychotic symptoms to overall be present if a participant 1) screened positive by at least two separate measures and 2) was at least seven years old.
- We estimated logistic regression models to examine predictors of the presence of psychotic symptoms. Models used generalized estimating equations to adjust for intra-family correlations. Our predictor variables of interest, which we selected *a priori*, were CNV carrier status, age, IQ, clinical ASD diagnosis, presence of OCD symptoms, and gender. To explore the relationship between ASD severity and presence of psychotic symptoms, exploratory models substituted the categorical ASD diagnosis predictor with continuous ADOS Calibrated Severity Score (CSS) values.

Table 1: Baseline characteristics of 16p11.2 CNV carriers and their non-carrier siblings.

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*
Age	23.06	16.95	19.84	17.54	10.92	10.37	29.40	15.86	**2.39×10^{-28}**	**dup-del**	**< 0.001**
										noncarrier-del	**< 0.001**
										noncarrier-dup	**< 0.001**
IQ	97.69	20.34	84.59	22.01	82.73	15.61	108.76	13.54	**5.38×10^{-57}**	dup-del	0.6
										noncarrier-del	**< 0.001**
										noncarrier-dup	**< 0.001**
	#	*%*	*#*	*%*	*#*	*%*	*#*	*%*	*p* (χ^2)	Pair	*p*
Female gender	292	53.48	53	48.62	63	48.09	176	57.52	0.10	N/A	
ASD dx	48	8.79	17	15.60	27	20.61	4	1.31	**1.08×10^{-11}**	dup-del	1
										noncarrier-del	**< 0.001**
										noncarrier-dup	**< 0.001**
OCD sx	35	6.41	11	10.09	18	13.74	6	1.96	**5.31×10^{-6}**	dup-del	1
										noncarrier-del	**< 0.001**
										noncarrier-dup	**0.002**

Table 2: Psychotic symptom index measures

Measure	Total n = 546			Duplication n = 109			Deletion n = 131			Noncarrier n = 306		
	# Rec.	*# Pos.*	*%*	*# Rec.*	*# Pos.*	*%*	*# Rec.*	*# Pos.*	*%*	*# Rec.*	*# Pos.*	*%*
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	11.90	8	3	3.70	3	1	1.82

Table 3: Predictors of psychotic symptoms

Predictor	*B*	SE	Wald χ^2	OR	95% CI	*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	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 dx	**1.44**	**0.60**	**5.81**	**4.21**	**1.31 - 13.56**	**0.02**
OCD sx	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

Results

- Both 16p11.2 CNV carrier groups differed from the non-carrier group in terms of IQ, ASD diagnosis, and presence of OCD symptoms, and there was significant variation among the three groups in terms of age **(Table 1)**.
- More than half of the sample received at least one of the measures comprising the psychotic symptom index **(Table 2)**. Nineteen participants screened positive on at least two measures and were at least seven years old.
- Duplication carrier status and categorical ASD diagnosis predicted psychotic symptoms **(Table 3)**. ASD severity as measured by CSS did not significantly predict psychotic symptoms in exploratory analyses. Contrary to our hypotheses, we did not find that deletion carriers were more likely to have psychotic symptoms than noncarriers, nor did we find that OCD symptoms were a psychotic symptom predictor.

Discussion

- The association identified between 16p11.2 duplication status and psychotic symptoms aligns with previous studies that reported the 16p11.2 duplication in schizophrenia genetic samples.[7,8] 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 CNV type, ASD was 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.

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