# 16p11.2 duplication as a model of psychosis in autism spectrum disorder

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## Background and Significance

- People with **autism spectrum disorder** (ASD) are over three times more likely to develop schizophrenia (SCZ) than the general population,[1] but identifying ASD youth with emerging **psychosis** who may be at risk of SCZ is difficult.[2]

- Augmenting the traditional identification of categorical symptoms with multimodal phenotypic data could improve risk assessment. Structured interviews can detect subtle psychotic experiences. Neuroimaging can also play a role; in ASD, functional connectivity tends to be decreased between the anterior insula (AI) and posterior cingulate cortex (PCC)but increased between the AI and dorsal anterior cingulate cortex (dACC)[3,4], with the reverse pattern present in SCZ.[5,6]

- Robust phenotypic signatures of psychosis risk in the ASD population remain elusive, however, in large part due to disease heterogeneity.

- A deliberate, narrow focus on characterizing the psychotic phenotype in **16p11.2 duplication** carriers makes this problem more tractable. 16p11.2 copy number variation (CNV; either duplication or deletion) is among the strongest genetic risk factors for ASD,[7,8] and 16p11.2 duplication (but *not* deletion) is *also* a strong genetic risk factor for SCZ.[9]

## Specific Aims

- Aim 1: Conduct detailed structured interviews with 16p11.2 CNV carriers to establish the **clinical profile** of psychosis in 16p11.2 duplication.
  - H1a: Psychosis will be more common in dup than del.
  - H1b: ASD diagnosis will be a stronger predictor of psychosis in dup than del.
  - H1c: ASD severity will predict psychosis in dup.

- Aim 2: Analyze functional connectivity in 16p11.2 duplication carriers and noncarriers to establish **neural correlates** of psychosis in 16p11.2 duplication
  - H2a: dup+psychosis will show ↑AI-PCC and ↓AI-dACC compared to noncarriers.
  - H2b: dup+psychosis will show ↑ AI-PCC and ↓ AI-dACC compared to dup-psychosis
  - H2c: Among dup:
    - AI-PCC connectivity strength will predict severity of psychosis
    - AI-dACC connectivity strength will predict ASD severity.

## Participants

- Study participants will be those recruited for the Simons Foundation Autism Research Initiative (SFARI) Variation in Individuals Project (VIP) cohort of 16p11.2 CNV carriers and their noncarrier relatives.[10] Between 2011 and 2014, all participants underwent cognitive and behavioral phenotyping at one of three sites, and a subset underwent neuroimaging at one of two sites. 546 participants total were evaluated (109 16p11.2 duplication, 131 16p11.2 deletion, 306 noncarrier relatives).

## Measures

- IQ: obtained in all participants using the Wechsler Abbreviated Scale of Intelligence (WASI).[11]

- ASD: categorical diagnosis was ascertained in all participants based on clinical judgment and informed by multiple measures; all CNV carriers underwent the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2),[12] which can produce a dimensional measure of ASD severity.[13]

- PSYCHOSIS: Most participants were not specifically assessed for psychosis. In previous work, I derived an indicator of likely psychotic symptoms using existing measures.[14] I will conduct the Structured Interview for Prodromal Symptoms (SIPS)[15] with all CNV carriers who either have an ASD diagnosis or screened positive by the indicator (a total of 36 participants: 18 duplication carriers and 18 deletion carriers). I will conduct as many assessments as possible at the 2019 VIP cohort annual family meeting and arranging to evaluate the rest at one of the three phenotyping sites where they were initially assessed, or, as a fallback, via videotelephony. For each case, I and another rater will review a videorecording of the SIPS evaluation independently and determine if clinical psychosis is present. If there is disagreement, we will discuss the case until agreement is reached.

- NEUROIMAGING: 222 participants underwent a standardized neuroimaging protocol using one of two identically-configured scanners at separate sites. The protocol included acquisition of resting-state fMRI data (TR = 3000ms, TE = 30ms, FA = 90°, matrix = 72mm × 72mm, FOV = 216 mm$^2$, slice thickness = 3.0mm, 124 repetitions, 6m12s scan time).

## Analytic Plan

- Aim 1: Compare frequency of psychosis between CNV groups using $\chi^2$ (H1a); estimate logistic regression models to test whether categorical ASD diagnosis (H1b) or ADOS-2 calibrated severity score (H1c) predicts psychosis.

- Aim 2: Compare group-level correlation strength between regions of interest in the AI and PCC and in the AI and dACC (H2a, H2b); estimate linear regression models to test whether *z*-transformed AI-PCC and AI-dACC connectivity predict severity of psychosis and ASD symptom severity respectively.

## Future Directions

- Following this work, I will investigate the extent to which findings apply beyond 16p11.2 duplication carriers. I will assess patients in the prodromal psychosis clinic at Columbia University to determine the generalizablity of Aim 1's findings, and I will examine neural correlates of ASD and psychotic symptoms in the large Adolescent Brain Cognitive Development (ABCD) cohort to determine whether any neural signatures identified in Aim 2 are reproducible.

- I will also prospectively follow 16p11.2 CNV carriers to evaluate how psychotic symptoms evolve over time.

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