Genetic correlates and consequences of phenotypic heterogeneity in autism

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ABSTRACT:

The substantial heterogeneity in autism is a challenge for investigating the aetiology of autism and translating research findings to support autistic people. To address this, we first conducted factor analyses of the autistic traits questionnaire 24,000 autistic individuals and identified six correlated factors: 1. Insistence on sameness; 2. Social Interaction; 3. Sensory-motor; 4. Self-harm; 5. Idiosyncratic communication; 6. Conversational skills. Factor analyses improved the interpretability of results and SNP heritability of the autism features compared to summed scores. Using data from 19 different core and associated autism features, we identified significant associations between multiple genetic risk factors and autism features, including with autism PGS. High impact de novo variants and autism PGS were independently associated with autism liability and are associated with different features. For instance, PGS for educational attainment and autism were associated with several of the six factors. In contrast, high impact de novo variants were associated primarily with associated autism features. We investigated differences in PGS based on ID and sex. Notably, we identified a significant over-transmission of autism PGS in females without ID compared to males. This effect increased when restricting to individuals with average or above average IQ. There were modest differences in SNP heritabilities between different definitions of autism. Finally, GWAS of autism features in autistic individuals had modest genetic correlations with autism. Heterogeneity in autism is complex and multifactorial and impacts the interpretability of genetic findings in autism.

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