NAME OF PRESENTING AUTHOR: Varun Warrier

EMAIL ADDRESS OF PRESENTING AUTHOR: vw260@medschl.cam.ac.uk

Genetic correlates and consequences of phenotypic heterogeneity in autism

Varun Warrier[1], Yira Zhang[1], Freddy Cliquet[2], Jakob Grove[3], Hilary Martin[4], Thomas Rolland[2], Celia van der Merwe[5], Claire Leblond-Manry[2], Anders Borglum[3], Elise Robinson[5], Thomas Bourgeron[2], Simon Baron-Cohen[1]

[1] Department of Psychiatry, University of Cambridge, Cambridge, UK

[2.] Institut Pasteur, Paris, France

[3.] Department of Biomedicine, Aarhus University, Aarhus, Denmark

[4.] Wellcome Trust Sanger Institute, Hinxton, UK

[5.] Harvard T.H. Chan School of Public Health, Harvard, Boston, Massachusetts, USA

KEYWORDS: Autism, heterogeneity, sex differences

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.

GRANT SUPPORT: Wellcome Trust