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TITLE: Genetics of autistic traits in the general population reveals potential role for immune-related genes in autism spectrum disorder.

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ABSTRACT:

Background: Autism spectrum disorders (ASDs), common complex and highly heritable neurodevelopmental disorders (Tick et al., 2016), represent the extreme manifestation of autistic-like traits (ALTs) measurable in the general population (Robinson et al., 2016). ASDs and ALTs are genetically correlated meaning that common genetic variants for ALTs also play a role in the clinical condition of ASDs (Bralten et al., 2018). In this regard, ALTs may constitute a more accessible and potentially less heterogeneous route to the identification of common risk variants for ASDs.

Method: This study meta-analysed genome-wide association results for four ALTs – ‘attention-to-detail’, ‘imagination’, ‘rigidity’, and ‘social-skills’ – of 4,600 healthy individuals. The existence of a shared genetic aetiology between each ALT and ASDs was tested using summary statistics from the Psychiatric Genomic Consortium of ASDs (n=46,350). Gene-wide and gene-set analyses were used to prioritize genes and investigate the underlying biology of the four ALTs independently. Gene co-expression analyses were performed to highlight enrichment of biological processes across a range of ASD-related brain regions.

Results: We found two novel genome-wide significant loci associated with ‘attention-to-detail’ (*rs6125844*, *rs3731197*). Significant shared genetic aetiology was observed between ASDs and ‘rigidity’. A look-up of the top variants along with gene-wide analyses highlighted immune-related genes in ALTs, namely *RNF114*, *CDKN2A*, *KAZN*, *SPATA2*, and *ZNF816A*. Following gene co-expression network analyses confirmed a role of genes involved in the immune response, together with neuronal and synaptic signalling, differentially expressed ASD-related brain regions for multiple ALTs.

Conclusions: This study offers novel insights into the biology of autistic-like features and

suggests a role of immune regulation in ‘attention-to-detail’ and ‘rigidity’. Also, our results confirm that ASDs and ALTs share genetic loci and processes and thereby encourage the use of population-based quantitative ALTs to address the complex genetics of ASDs.

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