Genetic Risk for Autism Spectrum Disorders and Neuropsychiatric Variation in the General Population

Topic Autism

Submitter Elise Robinson

SUBMISSION DETAILS

Background Genetic risk factors for autism spectrum disorders (ASDs) exist across the frequency spectrum and can be inherited or de novo. The purpose of this project was to examine the extent to which multiple classes of genetic risk for ASDs are associated with traits and impairments typical of autism in the general population.

Methods Using LD score correlation, a technique that produces genetic correlations using GWAS summary statistics, we first examined the genetic correlation between polygenic, inherited risk for ASDs and traits of social communication disorders in 8 year old children in the general population, measured using the Social and Communication Disorders Checklist in the Avon Longitudinal Study of Parents and Children (ALSPAC, n=5,628).

Secondly, using exome sequencing data from the Simons Simplex Collection (2508 cases, 1911 unaffected siblings), we examined the association between classes of de novo variation associated with ASDs and adaptive functioning in the unaffected siblings of children with ASDs, measured using the Vineland Scales of Adaptive behavior. The de novo variants seen in unaffected individuals are both fewer in count and, on average, less deleterious in content when compared to those seen in ASD cases. To better compare the phenotypic impact of de novo events between cases and controls, we filtered the variants based on their presence/absence in the Exome Aggregation Browser (ExAC) database, a reference panel of over 60,000 individual exomes.

Results Using categorical ASD data from the Psychiatric Genomics Consortium Autism Group (PGC; n=5,305 cases and 5,305 pseudocontrols), ASDs and social communication disorder traits in ALSPAC had a genetic correlation of 0.27 (p= 0.006). We replicated the ALSPAC association using categorical ASD data from the Danish iPSYCH project (n=7,700 cases and 11,127 controls), where the genetic correlation was 0.36 (p=0.0001). The point estimate of genetic correlation between ASDs and general population social communication disorder traits in childhood exceeded each of the genetic correlations estimated between ASDs and other DSM disorders in the PGC (e.g. schizophrenia (r= 0.20), major depressive disorder (r= 0.14), and ADHD (r= -0.03)).

We found evidence of a continuum of functional impairment associated with de novo loss of function and missense mutations. De novo variant burden was associated with degree of functional impairment assessed using the Vineland in both cases (p= 0.0008) and controls (p= 0.005). There was not a statistically significant case-control difference in the strength of the genotype to phenotype association (p=0.06).

Discussion These analyses provide strong evidence that multiple types of genetic risk factors for

ASDs influence social, communication, and developmental variation in the general population. These findings additionally support the notion that diagnostic cutoffs in psychiatry are both phenotypically and genotypically arbitrary, and reinforce arguments that general population variation can be studied to provide insight into severe neuropsychiatric and developmental disorders.

Co-Authors

* Presenting Author

First Name	Last Name	Affiliation	E-mail
Elise *	Robinson *	Massachusetts General Hospital	erobinson@atgu.mgh.harvard.edu
Beate	St Pourcain	University of Bristol	beate.stpourcain@bristol.ac.uk
Verneri	Anttila	Analytical and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA. 2Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. 3Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA.	anttila@broadinstitute.org
Brendan	Bulik-Sullivan	Broad Institute	bulik@broadinstitute.org
Jack	Kosmicki	Harvard University	jkosmicki@fas.harvard.edu
Kaitlin	Samocha	Massachusetts General Hospital	ksamocha@fas.harvard.edu
Julian	Maller	Massachusetts General Hospital	jules@broadinstitute.org

David	Skuse	University College London	dskuse@ich.ucl.ac.uk
Jakob	Grove	Department of Biomedicine, Aarhus University, Aarhus, Denmark	grove@hum-gen.au.dk
Preben Bo	Mortensen	Aarhus University	pbm@ncrr.dk
Anders	Borglum	Aarhus University	anders@biomed.au.dk
Benjamin	Neale	Analytic and Translational Genetics Unit	bneale@broadinstitute.org
Angelica	Ronald	Birkbeck, University of London	a.ronald@bbk.ac.uk
George	Davey Smith	MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK	kz.davey-smith@bristol.ac.uk
Mark	Daly	Massachusetts General Hospital	mjdaly@atgu.mgh.harvard.edu

Hugh Gurling Award No

DISCLOSURE

Financial Relationships I have no real or apparent conflicts of interest to disclose.

Investigational or off-label use of a product NONE

Research Support The UK Medical Research Council and the Wellcome Trust (WT092731/Z/10/Z), and the University of Bristol provided core support for ALSPAC. This work was also supported by the Medical Research Council Integrative Epidemiology Unit (MC_UU_12013/1-9). Funding for the iPSYCH project was provided by the Lundbeck Foundation, Stanley Foundation and the NIMH. Dr. Robinson was supported by National Institutes of Mental Health Grant 1K01MH099286-01A1.

Human or Animal Ethics Board Review Yes

Signature Elise Robinson