Bidirectional genetic overlap between autism spectrum disorder and cognitive traits

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Abstract

Objective

Autism Spectrum Disorder (ASD) is a highly heritable condition with a large variation in cognitive function. Here we investigated the shared genetic architecture between cognitive traits (intelligence (INT) and educational attainment (EDU)), and risk loci jointly associated with ASD and the cognitive traits.

Methods

We included data from genome-wide association studies (GWAS) of INT (n = 269,867), EDU (n = 766,345) and ASD (cases n = 18,381, controls n = 27,969). We used the bivariate causal mixture model (MiXeR) to estimate the total number of shared genetic variants, and conditional and conjunctional false discovery rate (cond/conjFDR) to identify specific overlapping loci.

Results

The MiXeR indicated 12.7k genetic variants associated with ASD, with 12.0k shared with EDU and 11.1k shared with INT (Dice: 0.90–0.91), with both positive and negative relationships within overlapping variants. The majority (59%-68%) of estimated shared loci have concordant effect directions, with a positive, albeit modest, genetic correlation between ASD and EDU (r_g=0.21, p = 2e-13) and INT (r_g=0.22, p = 4e-12). We discovered 43 loci jointly associated with ASD and cognitive traits (conjFDR < 0.05), of which 27 were novel for ASD. FUMA analysis revealed significant differential expression of candidate genes in the cerebellum and frontal cortex.

Conclusion

We quantified the genetic architecture shared between ASD and cognitive traits, demonstrated mixed effect directions, and identified the associated genetic loci and molecular pathways. The findings suggest that common genetic risk factors for ASD can underlie both better and worse cognitive functioning across the ASD spectrum, with different underlying biology.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social communication and interaction as well as restrictive, repetitive patterns of behavior, interest or activities [1]. Recent studies have shown that the prevalence of ASD is 1–2% [2] which has increased in the past two decades [3]. There is a large heterogeneity in cognitive functioning in ASD; with severe forms having poor cognitive functioning while others across the spectrum have better and quite extraordinary cognitive skills [4]. These large differences in cognitive ability are important for outcome [5], but the biological underpinnings for this mixed pattern of cognitive performance in ASD is not yet fully understood. Further, there is also a notion that cognitive characteristics of ASD are not necessarily deficits, but could be regarded as normal human variation [6].

The pathogenesis of ASD is considered to originate from complex interactions between environmental [7] and genetic factors, with an estimated heritability of ~ 80% [8]. Previous studies have shown a heterogeneous genetic architecture,

with contributions from both common and rare genetic variants [9, 10]. Several common genetic variants have been discovered for ASD. The largest genome-wide association study (GWAS) of ASD to date included n = 18,381 cases and n = 27,969 controls and identified five genome-wide-significant loci [11]. Leveraging the results from ASD with three other phenotypes (schizophrenia, major depression, and educational attainment (EDU) seven additional loci were identified [11]. However, individually these common variants have small effects, and collectively explain a small portion of the overall liability, leaving a large fraction of the heritability undiscovered [12]. Meanwhile, recent statistical tools have enabled the calculation of an individual's genetic risk for ASD using polygenic risk scores (PGRS), which may have relevance for clinical research [13] and show promise for clinical utility in the future [14].

Intelligence and EDU are highly heritable traits which are major determinants of human health and well-being [15, 16]. Furthermore, there is phenotypic linkage between ASD and IQ/EDU and evidence of potential shared genetics [11]. Common genetic factors underlying variation in INT are also overlapping with those associated with brain volumes [17]. Thus, it is likely that common variants may relate to both the large variation in cognitive function, as well as with the large variation in brain volumes that characterize ASD [18]. Mean brain size is, however often enlarged [19], a trait that associates with high INT [20]. Furthermore, the frontal cortex and cerebellum have both been implicated in ASD pathology [21] with a tendency of large frontal lobes associated with small cerebellar volumes [22].

Recent studies suggest that 35% of ASD patients have an intellectual disability [2]. Among these patients, more than 500 rare pathogenic mutations have been discovered [23]. However, studies on rare variants may have been biased towards inclusion of patients with intellectual disability and not high-functioning ASD, which could explain why they have not offered insights into mechanisms underlying the associations between ASD and high INT [23, 24]. On the other hand, there are indications that high-functioning ASD may have been over-represented in GWAS [24, 25], which have shown a positive genetic correlation (r_g) between ASD and cognitive abilities [11, 26], with r_g = 0.2–0.3 [11, 27]. This is intriguing given that one third of ASD patients have intellectual disability [2]. However, despite the overall positive r_g, there are likely variants with an opposite effect on ASD and INT as well.

We have previously reported large polygenic overlaps despite low genetic correlation in mental disorders such as schizophrenia, ADHD and depression [28–30] by using the new statistical tool bivariate causal mixture model (MiXeR) [31]. This method allows for estimating a total number of shared genetic variants, irrespective of genetic correlations between traits [31]. As such, it allows for the detection of a mixture of effect directions that would otherwise be missed with methods such as Linkage disequilibrium score regression (LDSR) [32]. Furthermore, the MiXeR results can be followed up with analysis to identify the genetic risk variants jointly associated with two traits, using conditional and conjunctional false discovery rate (condFDR/conjFDR) which increases the statistical power [31, 33]. By analyzing the molecular function of overlapping genes [34] it is possible to shed light on mechanisms underlying both high and low cognitive performance in ASD. Furthermore, while INT and EDU traits are both related to cognitive function, they have somewhat different genetic architecture [35], and seem to be associated with different characteristics among patients with ASD [36]. Thus, it is relevant to include both INT and EDU when investigating overlapping genetic architecture between ASD and cognitive traits.

Here, we took advantage of recent large GWAS data to determine the degree of overlapping genetic architecture between ASD and cognitive traits (INT and EDU) by applying MiXeR method. Second, we identified risk loci shared between ASD and the cognitive traits using the cond/conjFDR method. Third, we annotated the identified loci to determine tissue expression and molecular functions of shared risk variants for ASD and cognitive traits [37].

Methods

Study participants

We obtained GWAS results in the form of summary statistics (p values and z-scores) for the relevant phenotypes [11, 38, 39], see Table 1.

Data on Autism Spectrum Disorder (ASD) were acquired from the Psychiatric Genomics Consortium (PGC) [11]. The dataset was a meta-analysis of the population-based iPSYCH project [40] and five family-based trio samples of European ancestry (n=5,305) [41], including a total of 18,381 ASD cases, and 27,969 controls.

General Intelligence was based on data from 269,867 individuals across 14 cohorts, primarily consisting of data from the UK Biobank (n = 195,653) [39]. These studies assessed INT using various cognitive tests and were all operationalized to a *general intelligence* factor (g-factor). *In the majority of cohorts, the g-factor was based on* results on 13 different cognitive tests that required verbal and mathematical reasoning (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20016) [42]. The included GWAS data from UK biobank are mainly from individuals of European descent [43].

Educational Attainment (EDU) is measured as the number of years of completed schooling [44]. The GWAS data for EDU used in our analysis includes public available summary statistic from a meta-analysis of data from the Social Science Genetic Association Consortium (SSGAC), with a sample size of 766,345 individuals after excluding data from 23andMe [16]. The meta-analysis was performed using an inverse-weighted fixed effects model implemented in the METAL software (http://csg.sph.umich.edu/abecasis/metal/), of 71 quality-controlled cohort-level results files. The included GWAS data are restricted to individuals of European descent.

Statistical analysis

We applied MiXeR v1.3 [31] to quantify polygenic overlap between ASD and cognitive traits irrespective of genetic correlation using GWAS summary statistics. This method estimates the total number of shared and trait-specific 'causal' SNPs and SNP-based heritability (h^2_{snp}) for each trait, based on the distribution of z-scores and detailed modelling of LD structure. Polygenicity estimates included the number of 'causal' variants required to explain 90% h^2_{snp} to prevent extrapolating model parameters into variants with infinitesimally small effects. Results were presented as Venn diagrams displaying the proportion of trait-specific and shared 'causal' SNPs. Dice coefficient as calculated by MiXeR was used to estimate the similarity between genetic architecture of two phenotypes. Model fit was evaluated based on predicted versus observed conditional quantile-quantile (Q-Q) plots, the Akaike Information Criterion (AIC) and log-likelihood plots (Supplementary Methods). A positive AIC indicates adequate discrimination between modelled fit and the comparative model. A negative AIC indicates inadequate discrimination between modelled fit and the comparative model. We also calculated linkage disequilibrium score regression (LDSR)-based genetic correlations (r_g) [45].

We next applied conditional(cond)/conjunctional(conj)FDR, which leverages polygenic overlap between two traits to boost statistical power to identify loci associated with a single trait (condFDR) and loci jointly associated with two traits (conjFDR) [33]. Cross-trait enrichment of SNP associations between ASD and each cognitive trait, and *vice-versa,* was visualized using conditional Q-Q plots. The condFDR value of each SNP was computed for ASD conditional on cognitive traits and *vice versa*. CondFDR represents the probability that a SNP is not associated with the primary trait

given that the p-values in the primary and conditional trait are as small as or smaller than the observed p-values. Next, the conjFDR value for each SNP was calculated as the maximum of the two condFDR values (i.e., ASD conditional on INT and *vice versa*). This represents a conservative estimate of the FDR for the association between each SNP with both traits. SNPs with a condFDR <0.01 or conjFDR<0.05 were assigned statistical significance. Since the complex correlations in regions with intricate linkage disequilibrium [46] can bias FDR estimation, all cond/conjFDR analyses were performed after excluding the following SNPs regions from the FDR fitting procedures: the extended major histocompatibility complex (MHC) region (chromosome 6: 25119106-33854733), chromosome 8: 7242715-12483982 and chromosome 17: 40000000 –47000000. However, they were not excluded from our discovery analysis. All chromosome locations are derived from genome build hg19. We further evaluated the directional effects of the shared loci by comparing their z-scores from original GWAS. We also identified previously reported GWAS associations in the NHGRI-EBI catalog [47] overlapping with the identified loci. For more details about the statistical genetics tools, see Supplementary Methods and the original publications [31, 48].

Genetic loci definition and effect direction

We defined independent genetic loci according to the FUMA protocol [37]. We evaluated the directional effects of shared loci by comparing *z* scores from the respective GWAS summary statistics.

Functional annotation

Positional and functional annotation of all candidate SNPs, in the genomic loci with a conjFDR value < 0.1 having an LD $r^2 \geq 0.6$ with one of the independent significant SNPs, was performed using multiple tools, implemented in FUMA. In addition, we linked lead SNPs to genes using three gene-mapping strategies: 1) positional mapping to align SNPs to genes based on their physical proximity, 2) expression quantitative trait locus (eQTL) mapping to match cis-eQTL SNPs to genes whose expression is associated with allelic variation at the SNP level, and 3) chromatin interaction mapping to link SNPs to genes based on three-dimensional DNA–DNA interactions between each SNP's genomic region and nearby or distant genes. All gene-mapping strategies were limited to brain tissues all other default settings in FUMA were used. Finally, we queried SNPs for known QTLs in brain tissues using the GTEx portal (GTEx, version 8) [49]. If the gene annotation of a specific SNP was marked as 'NA', we search for information in the dbSNP database.

Results

Shared genetic architecture (MiXeR)

MiXeR revealed substantial shared 'causal' variants between ASD&INT and ASD&EDU. As shown in the Venn diagram (Fig. 1), the estimated number of shared 'causal' variants between ASD and INT was 11.1k (SD=0.7k), with 1.6k (1.2k) unique ASD variants and 0.6k (0.7k) unique INT variants. The Dice coefficient was 0.91 for variants shared between ASD and INT (Table S15). MiXeR estimated 12.0k (1.3k) shared 'causal' variants between ASD and EDU, with 0.7k (0.7k) unique ASD variants and 1.7k (1.4k) unique EDU variants. The Dice coefficient was 0.90 for variants shared between ASD and EDU (Table S15). The proportion of shared 'causal' variants with concordant effects for ASD&INT was 0.58 (SD=0.004) and 0.58 (SD=0.005) for ASD&EDU.

Enrichment

In the conditional Q–Q plots, we observed SNP enrichment for ASD as a function of the significance of SNP associations with EDU (Fig. 2a) and INT (Fig. 2b). The reverse conditional Q–Q plots also demonstrate consistent enrichment in ASD given associations with INT and EDU, indicating polygenic overlap between the phenotypes (Fig S1a and S1b).

Log likelihood plots are shown in Fig S1a and Fig S1b. The AIC values (Table S15) were positive when comparing modelled estimates to minimum overlap, but negative compared to maximum overlap for both ASD/INT and ASD/EDU analysis. This indicates that the MiXeR-predicted overlap is not distinguishable from maximum possible overlap, suggesting caution in interpreting the estimates from MiXeR. ASD and INT have LDSR-based genome-wide genetic correlation of r_g=0.22 (SD=0.032, p= 4.60e-12) and MiXeR-estimated genetic correlation of shared variants of ρβ=0.24 (SD=0.01). For ASD and EDU, those values are respectively r_g=0.21 (SD=0.028, p=2.17e-13) and ρβ=0.25 (SD=0.02). This pattern of extensive genetic overlap but weak genetic correlation is indicative of mixed effect directions, supported by the MiXeR-estimated proportion of shared 'causal' variants with concordant effects of 0.58 for both ASD&INT and ASD&EDU.

Identification of shared genetic loci (cond/conjFDR)

CondFDR: We leveraged this pleiotropic enrichment using condFDR analysis and re-ranked the ASD SNPs conditional on their association with EDU or INT, and *vice versa.* At condFDR <0.01, there were 9 loci associated with ASD conditional on INT (Table S1), of which two loci were not found in the original ASD GWAS (Table S1). We identified 12 loci associated with ASD conditional on EDU (Table S2), of which four were not in identified the original ASD GWAS (Table S2).

ConjFDR: The conjFDR Manhattan plots are shown in Fig 3a and 3b. At conjFDR <0.05, we detected 19 genetic loci jointly associated with ASD and INT (Table S3), and among them, 11 are unique for ASD and INT. We detected 32 distinct genetic loci jointly associated with ASD and EDU (Table S4), of which 24 are unique for ASD and EDU. Eight loci were common for both ASD and EDU and ASD and INT, yielding a total of 43 distinct loci at conjFDR <0.05. Of these SNPs, 18 were intronic, 13 intergenic, 11 non-coding RNA intronic and 1 exonic (See Tables S3 and S4).

Evaluation of allelic effect directions: As denoted by the sign of the effect, 68% (13/19) of the shared loci between ASD and INT had concordant allelic effect directions (Table S3) and 59% (19/32) of the shared loci between ASD and EDU possessed concordant allelic effect directions (Table S4).

Novel ASD loci: As seen in table S3, 11 of 19 the lead SNPS jointly associated with ASD and INT at conjFDR <0.05, were not identified in the original ASD GWAS [11], and as seen in table S4, 21 of the 32 loci jointly associated ASD and EDU were also novel. Five of these loci were overlapping both with EDU and INT, which yielded a total of 27 novel ASD loci, which are presented in Table 2.

Functional annotation: We did functional annotation of all SNPs with a conjFDR value <0.1 within loci shared between ASD & INT and ASD & EDU, which included 2356 candidate SNPs jointly associated with ASD and INT and 1782 SNPs candidate SNPs jointly associated with ASD and EDU.

Gene-mapping: By using three different methods (positional, eQTL, and chromatin interaction) we mapped 104 genes from candidate SNPs within loci shared between ASD and INT (see Table S7) and 132 genes for ASD and EDU (see Table S8). Analyses indicated that there were 10 genes for ASD and EDU and 16 genes for ASD and INT which were credible by all three methods.

Gene-set enrichment and molecular function analysis (FUMA)

Gene expression in different tissues: Heatmaps of all genes based on candidate SNPs are shown in Fig S4a (ASD and EDU) and Fig S5a (ASD and INT). As seen in FS4b and FS5b, candidate genes from ASD and EDU had significantly upregulated differentially expressed genes (DEGs) in four of 54 different tissues namely, brain cortex/frontal cortex and brain cerebellum/cerebellum hemispheres (Fig S4b), while and candidate genes from ASD and INT had significant upregulated DEGs two tissues: cerebellum /cerebellar hemisphere.

Gene expression during brain development periods: Candidate genes tended to have upregulated expression during early prenatal period and late infancy (Fig S3c and Fig S4c) but these differences were not significant.

Gene set enrichments: GO biological processes molecular function (tables S9 and S10): Enrichment was found in 43 different gene sets, including positive regulation of central nervous system development, midbrain development, neuronal differentiation, synaptic signaling, neuron death, gliogenesis, astrocyte development, mitochondrion organization, synapse plasticity and more general pathways as inositol phosphate and response to reactive oxygen species,

Transcription factors: Candidate genes were enriched in the pathways of 100 transcription factors, of them HIF1 (hypoxia inducible factor 1), NFR1 (nuclear respiratory factor 1) and vitamin D receptor.

Immunologic signatures: Candidate genes were enrichments in 23 immune related gene sets for ASD and EDU, among them, Interleukin -2 and Interleukin-10 pathways, Macrophage Stimulating 1 (MSP1) pathway, EBNA1 anticorrelated, and development of regulatory T cells (Tregs).

GWAS gene sets: As seen in Table S9 and S10, enrichment was seen in 100 different gene sets including ASD related social behaviors (attendance at social groups, helping behavior, birth), gene sets for cognitive function, mental disorders (short sleep duration, alcohol abuse, mood instability, schizophrenia, depression, neuroticism), intracranial volume, neurologic diseases, inflammatory bowel diseases cardiovascular measures, lung function/pulmonary fibrosis and endocrine measures.

FUMA of concordant loci are shown in Fig S6 – S7 and tables S11 and S13. Tissue expression (fig S6b and S7b) analyses showed that DEGs were significantly different in 13 tissues for ASD and INT, with highest in frontal cortex. Similar results were found concordant genes for ASD and EDU, were DEGs were significantly less expressed in amygdala, hippocampus, basal ganglia, and substantia nigra. Highest upregulation (non-significant) was found in brain frontal cortex and cerebellum (fig S7b). Heatmaps of concordant candidate genes for ASD and EDU, and ASD and INT, are shown in Fig S6c and Fig S7c. The concordant genes were enriched in gene sets for extremely high intelligence, social traits (attending social groups and helping behavior), psychiatric disorders, inflammatory bowel diseases and immunological signatures (Table S11 and S13).

FUMA of discordant loci are shown in Fig S8 – S9 and tables S12 and S14. Analysis of tissue expression showed that discordant genes had significantly upregulated DEGs only in cerebellum/cerebellar hemisphere (Fig S8b and Fig S9b). Heatmaps of discordant candidate genes for ASD and EDU, and ASD and INT, are shown in Fig S8a and Fig S9a. Gene set enrichment analysis showed enrichment in several gene sets, including neurodegenerative diseases (incl. Alzheimer's disease and Parkinson's disease), chronic pain, alcohol use disorder and craniofacial macrosomia (small head and face).

Discussion

The main finding of the current study is an extensive genetic overlap between ASD and cognitive traits INT and EDU with a mixture of positive and negative effect directions of the overlapping genetic loci. We identified 43 loci jointly associated with ASD and INT or EDU, of which 27 were novel, providing new insight into the overlapping molecular mechanisms. By dissecting the overlapping genetic architecture and quantifying the shared and unique genetic factors for ASD versus cognitive traits beyond genetic correlations, we show that common genetic variants can underlie both better and worse cognitive functioning across the ASD spectrum. These findings can also contribute to better patient stratification, outcome prediction and drug discovery

The current findings of bidirectional genetic overlap between ASD and cognitive traits INT and EDU, as revealed with the MiXeR method, has not been shown before. The genetic overlap estimated by Dice similarity coefficient was 0.90–0.91 which is substantial, taking into account the relatively low genetic correlation we found between ASD and INT (r_g=0.22), in line with previous findings [11]. It is noteworthy that the genetic correlation is only present if the bulk of variants associated with both ASD and INT or EDU have consistent direction of effects (concordant or discordant) but not mixed [50]. Among the 43 loci shared between ASD and EDU or INT revealed by conjFDR, n = 27 (63%) had concordant effect directions with INT and EDU. Thus, the main fraction of common variants shared with ASD is associated with higher INT and EDU. These variants may shed light on mechanisms underlying better cognition in ASD patients [11, 51, 52] and provide support for high functioning ASD as a “neurodiversity” rather than a disorder [6] .

A high genetic overlap between ASD and cognitive traits INT and EDU is consistent with genetic overlap between INT and EDU and other mental disorders as schizophrenia (SCH) [28, 53], bipolar disorder (BP)[28], major depression (MD) [30] and attention deficit hyperactivity disorder (ADHD) [29], although the overlap between ASD and INT is larger than between INT and SCH, BP, ADHD and MD [28–30]. However, the overall concordant effect direction with INT contrasts findings in SCH and ADHD where the majority of variants shared with INT are associated with poorer cognitive performance [28, 29]. The results also differ from MD and BP which have a more balanced mixture of directional effects among the loci shared with INT [28, 30]. A potential clinical implication of the current result is to improve ASD polygenic risk scores that can stratify ASD according to cognitive difficulties and thus help to target interventions and treatment programs in ASD.

Analyses of brain tissue expression of all candidate genes, including both concordant and discordant showed that they are significantly upregulated in two brain tissues in frontal cortex and cerebellum, which is in line with a recent meta-analysis of post-mortem studies in ASD [21]. In recent years the interest in cerebellum’s role in language and social behavior has increased [54] and it has emerged as key for ASD pathology [55, 56]. The increased expression in cerebellum was only significant for discordant genes. This seems in line with the association between motor impairments and cognitive impairments in ASD [57]. Concordant genes did not have significantly upregulated DEGs in any of the brain tissues investigated, suggesting that they are not especially important for these brain regions. Associated genes were however enriched in the pathways for midbrain development, a region not included in the tissue analysis. Still, its relevance in ASD is supported by a genetic overlap between determinants of midbrain volume and ASD [58], and the concordant gene *RHOA* has been targeted for improved learning and memory in ASD animal models [59]. As expected, associated genes were enriched in several gene sets important for neurodevelopment, and with gene sets reflecting social function, as e.g., helping behavior and participating in social groups. These enrichments suggest that the associated genes are of relevance for ASD.

Genes associated with concordant loci were in contrast to discordant loci overlapping with pathway for extremely high INT [60] including creatine kinase brain type (*CKB*), which is known as a cognitive enhancer [61], while creatine

deficiency is a rare cause of ASD [62]. Concordant genes were also enriched in many immune pathways, in line with inflammation being implicated in ASD [63]. One of these was *MST1*, a gene also found in the extremely high intelligence-pathway. *MST1* plays a role in infections, cancer and autoimmunity [64], while animal studies implicate a role in depression behavior [65]. Concordant genes were also enriched in the pathway of vitamin D receptor, which may be relevant for the association between ASD and cognitive function [66, 67].

Discordant genes were enriched in gene sets for neurodegenerative diseases which may be related to the increased risk of dementia in ASD [68]. Among genes enriched in the neurodegenerative pathway are *CRHR1, KANSL1* and *WNT3*. *CRHR1* encodes a corticotrophin releasing hormone receptor implicated in social behavior [69, 70] and stress-induced cognitive deficits [71]. *KANSL1* has been associated with autistic traits [72] and cognitive difficulties in 17.q21.31 deletion syndrome [73]. *WNT3* is a Wnt-signalling gene involved in neurogenesis [74], as well as for behavioral and cognitive deficits [74]. It has been suggested that the Wnt-pathway may be of importance for understanding the high phenotypical heterogeneity of ASD [75]. Together, the discordant genes could be involved in the cognitive difficulties in ASD.

A limitation of our study is that the sample of UK-biobank consists mainly of persons of European ancestries. Another limitation is that the study does not include rare pathogenic variants causing ASD, only common variants are included into the analyses. Furthermore, the results are based on a common factor for INT, which is not exactly similar with a full IQ score. Furthermore, EDU is not purely a cognitive trait, but it is also influenced by other factors, including socioeconomic status.

In conclusion, the current findings show extensive bidirectional genetic overlap between ASD and cognitive traits, with a majority of loci for ASD associated with better cognitive performance. The mixture of effect directions is in line with the large variation in cognitive abilities in ASD. Together, these findings suggest that genetic factors explain some of the large variation in cognitive performance in ASD, and highlight molecular mechanisms involved in the two cognitive subgroups within the ASD spectrum.

Declarations

Data and code availability

Data supporting the findings of this study are openly available from an online repository or are available on request from study authors. The dataset regarding ASD is available in repositories of GWASs: ASD2019: https://www.med.unc.edu/pgc/download-results/.

Please refer to Supplementary Methods for further details. All codes are freely available at https://github.com/precimed and https://github.com/bulik/ldsc. Analyses were conducted in Python v3.5, Matlab R2020b. Locus definition, functional annotation, and gene-set analysis were performed using FUMA (https://fuma.ctglab.nl/).

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Conflicts of interests

Dr. Dale is a Founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by UCSD in accordance with its conflict of interest policies. Dr. Andreassen is a consultant for HealthLytix and received speakers honorarium from Lundbeck and Sunovion. The remaining authors have no competing interest.

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Tables

Table 1: GWAS characteristic

Sample	Sample Size (N)	Age Group	Reference
ASD	46,350 (ASD = 18,381, CON=27,969)	Adult and Children	Grove et al., 2019
INT	269,867	Adult and Children	Savage et al., 2018
EDU	766,345	Adult	Lee et al., 2018

Abbreviations: Autism Spectrum Disorder (ASD), Intelligence (INT), Educational attainment (EDU)

Table 2. Novel shared SNP's between ASD and INT, and ASD and EDU found through cond/conjFDR. The last column marks overlapping SNP's between INT and EDU.

				ASD		Trait			
Chr	Min-max BPs	Lead SNPs	conjFDR	Z-score	p-value	Z-score	p-value	Concordant	Overlapping
ASD and INT									
3	16843737-16879208	rs7625233	0.042	3.9	1.14E-04	-4.88	1.07E-06	No	Yes
3	48564209-50239012	rs73073015	0.020	4.1	3.51E-05	6.28	3.43E-10	Yes	Yes
5	81261923-81679914	rs73134709	0.041	-3.9	9.58E-05	-3.86	1.16E-04	Yes	No
5	92488009-92574385	rs4242244	0.036	-3.9	8.64E-05	-5.48	4.16E-08	Yes	Yes
5	113837198-113995764	rs414517	0.016	-4.23	2.30E-05	-4.25	2.18E-05	Yes	No
8	87754626-87783335	rs1982564	0.038	3.90	9.62E-05	-4.01	6.14E-05	No	Yes
10	106563924-106830537	rs6584649	0.046	-3.82	1.33E-04	3.88	1.05E-04	No	No
10	133729181-133815530	rs34473884	0.018	4.17	3.03E-05	5.26	1.48E-07	Yes	Yes
14	29396922-29677464	rs140802584	0.034	4.02	5.87E-05	-3.93	8.42E-05	No	No
17	43463493-44865603	rs7207582	0.002	4.71	2.44E-06	-4.91	9.22E-07	No	No
21	40553845-40741068	rs2249666	0.039	3.89	9.89E-05	4.06	4.99E-05	Yes	No
ASD and EDU									
1	45797505-46021556	rs12049503	0.050	3.77	1.63E-04	4.10	4.12E-05	Yes	No
2	104056454-104387855	rs6543224	0.015	4.26	2.05E-05	5.01	5.32E-07	Yes	No
2	159340038-159553686	rs3771643	0.049	3.80	1.46E-04	3.97	7.29E-05	Yes	No
2	215361613-215406125	rs12467438	0.044	-3.84	1.25E-04	4.28	1.85E-05	NO	No
3	16843737-16879208	rs7625233	0.042	3.86	1.14E-04	-6.37	1.83E-10	No	Yes
3	48564209-50239012	rs73073015	0.021	4.14	3.51E-05	7.25	4.14E-13	Yes	Yes
3	70252572-70291268	rs73116288	0.019	4.18	2.93E-05	4.53	5.89E-06	Yes	No
3	157829953-158284861	rs7630176	0.050	-3.77	1.63E-04	4.13	3.58E-05	No	No

4	105319081-105414222	rs7665487	0.037	3.91	9.27E-05	-4.28	1.84E-05	No	No
5	87792844-87932809	rs4916723	0.002	4.76	1.92E-06	-7.09	1.32E-12	No	No
5	92488009-92574385	rs4242244	0.036	-3.93	8.64E-05	-5.04	4.75E-07	Yes	Yes
5	113788755-113995764	rs13188074	0.004	4.67	3.04E-06	5.30	1.18E-07	Yes	No
6	19211776-19358341	rs7762189	0.048	3.79	1.51E-04	-4.60	4.25E-06	No	No
6	26341301-26341301	rs9467715	0.049	-3.78	1.60E-04	-5.42	5.98E-08	Yes	No
7	24526039-24536700	rs6461809	0.012	4.33	1.48E-05	6.04	1.55E-09	Yes	No
8	87754626-87783335	rs1982564	0.038	3.90	9.62E-05	-5.46	4.75E-08	No	Yes
10	133729181-133815530	rs34473884	0.020	4.17	3.03E-05	7.40	1.32E-13	Yes	Yes
11	17804998-17852452	rs2237944	0.042	3.85	1.18E-04	4.69	2.69E-06	Yes	No
13	58746132-59167198	rs77146055	0.044	3.83	1.26E-04	-4.02	5.90E-05	No	No
17	2295405-2296014	rs2447091	0.041	3.87	1.09E-04	-4.68	2.89E-06	No	No
17	43463493-44865603	rs55915917	0.004	4.64	3.55E-06	-8.39	4.93E-17	No	No

Abbreviations: Chromosome (Chr), Minimum-Maximum Base Pairs (Min-max BPs), Lead SNPs, Conjunctional False Discovery Rate (conjFDR), Autism Spectrum Disorder (ASD), Intelligence (INT), Educational attainment (EDU).

Figures

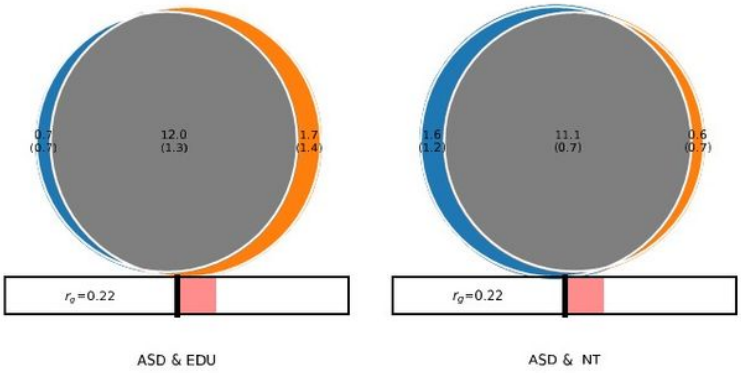

Figure 1

MiXeR-modelled genome-wide genetic overlap and genetic correlation between autism spectrum disorder (ASD) and educational attainment (EDU) and intelligence (INT). MiXeR Venn diagrams showing the number of shared and trait-specific 'causal' variants in thousands for each pair of traits. r_g is MiXeR estimated genome-wide genetic correlation. The DICE coefficient for ASD & EDU was 0.90 and for ASD & INT Dice was 0.91. Both analyses had positive AIC values when comparing modelled estimates to minimum possible overlap but negative compared to maximum possible overlap, indicating that the estimates may underestimate genetic overlap.

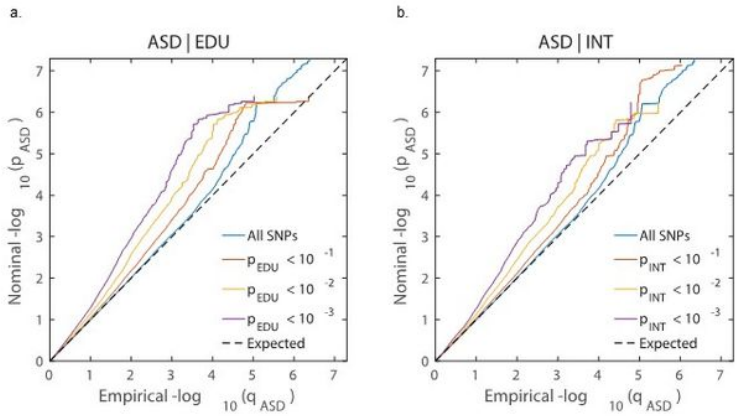

Figure 2

Conditional Q-Q plots. Conditional QQ plots of observed versus expected -log10 p-values in the primary trait as a function of significance of association with the secondary trait at the level of $p \leq 0.1$ (red lines), $p \leq 0.01$ (yellow lines) and $p \leq 0.001$ (purple lines). Blue lines indicate all SNPs. Black dotted line is the expected Q-Q plot under the null hypothesis (no SNPs associated with the trait).

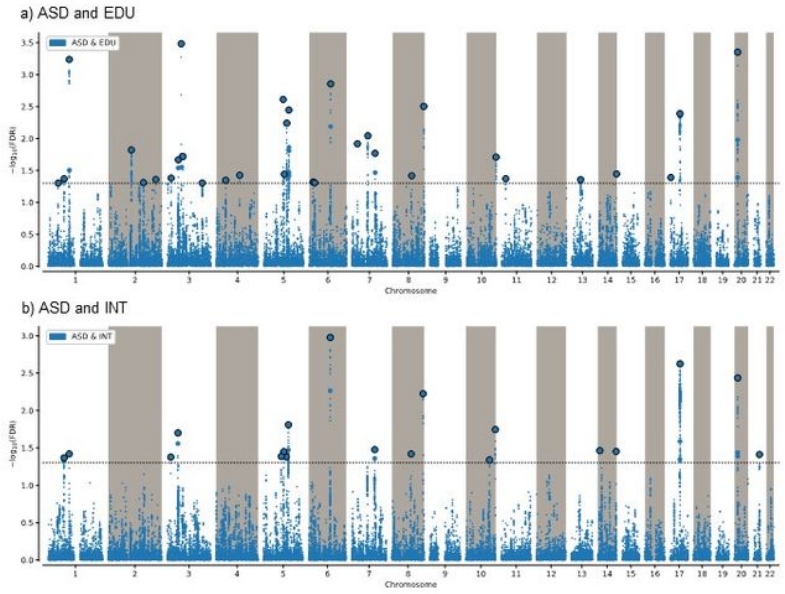

Figure 3

Manhattan plots of common genetic variants jointly associated with ASD and EDU (a) and ASD and INT (b). Common genetic variants jointly associated with ASD, INT and EDU at conjunctional false discovery rate (conjFDR) < 0.05 Manhattan plot showing the −log10 transformed conjFDR values for each SNP on the y axis and chromosomal positions along the x axis. The black dotted horizontal line represents the threshold for significant shared associations (conjFDR < 0.05, i.e., −log10 (conjFDR) > 1.3. Independent lead SNPs are encircled in black.

Supplementary Files

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