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Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder and intelligence

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Abstract

Schizophrenia (SCZ) and bipolar disorder (BD) are severe mental disorders associated with cognitive impairment, which is considered a major determinant of functional outcome. Despite this, the etiology of the cognitive impairment is poorly understood, and no satisfactory cognitive treatments exist. Increasing evidence indicates that genetic risk for SCZ may contribute to cognitive impairment, while the genetic relationship between BD and cognitive function remains unclear. Here, we combined large genome-wide association study data on SCZ (n=82,315), BD (n=51,710) and general intelligence (n=269,867) to investigate overlap in common genetic variants using conditional false discovery rate (condFDR) analysis. We observed substantial genetic enrichment in both SCZ and BD conditional on associations with intelligence indicating polygenic

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Conflict of interest

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overlap. Using condFDR analysis, we leveraged this enrichment to increase statistical power and identified 75 distinct genomic loci associated with both SCZ and intelligence, and 12 loci associated with both BD and intelligence at conjunctional FDR<0.01. Among these loci, 20 are novel for SCZ, and four are novel for BD. Most SCZ risk alleles (61 of 75, 81%) were associated with poorer cognitive performance, whereas most BD risk alleles (9 of 12, 75%) were associated with better cognitive performance. A gene-set analysis of the loci shared between SCZ and intelligence implicated biological processes related to neurodevelopment, synaptic integrity and neurotransmission; the same analysis for BD was underpowered. Altogether, the study demonstrates that both SCZ and BD share genetic influences with intelligence, albeit in a different manner, providing new insights into their genetic architectures.

Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are severe psychiatric disorders recognized as leading causes of morbidity and mortality in the world.[1,2] SCZ and BD share many clinical features,[3] including disturbances in mood, thought, perception and social functioning, and they are often accompanied by cognitive impairment.[4,5] The cognitive deficits are consistently found to be more severe in SCZ than BD.[6–8] A wide range of cognitive domains are affected in both SCZ[6,7,9,10] and BD,[6,7,11–14] including executive function, verbal learning, processing speed, and memory, as well as general intelligence. The general factor of intelligence, denoted as *g*, is a latent trait that captures around 40–50% of the shared variance across diverse cognitive abilities.[15,16] It is noteworthy, however, that cognitive dysfunction is not a prerequisite of either SCZ or BD, at least in terms of traditional definitions of cognitive dysfunction.[8] Many individuals with SCZ and BD perform within the normal range of cognitive functioning,[6,9,17] and superior intelligence occurs among individuals with both disorders, although more frequently in BD.[18–20] Furthermore, both higher and lower premorbid cognitive performance have been linked to increased BD risk.[20–22] In SCZ, however, cognitive underperformance often precedes the onset of psychotic symptoms and subsequent diagnosis of SCZ by many years.[8,23,24] Accumulating evidence indicates that intelligence is a major determinant for many socioeconomic and health-related outcomes in the general population.[25,26] Additionally, the degree of cognitive underperformance is a key predictor of functional and treatment outcome in both SCZ[6,27] and BD.[6,28,29] Despite this, there are currently no psychiatric treatments available that effectively amend cognitive impairment,[4,5] and the limited mechanistic understanding prevents the development of novel effective therapies.

SCZ, BD and intelligence are complex, heterogeneous phenotypes under strong genetic control, with heritability estimates ranging between 0.6 and 0.8 for SCZ and BD,[30] and around 0.5 for cognitive abilities.[31] There is abundant genetic overlap between SCZ and BD, [32] in accordance with their high degree of clinical overlap.[3] Results from family and twin-studies indicate that genetic liabilities of SCZ and cognitive abilities covary,[33–35] and molecular genetic studies have implicated rare and common alleles influencing both SCZ and cognitive abilites.[36,37] Family studies have found that cognitive impairments are more common among unaffected relatives of patients with BD than in healthy controls,[13,38–40] suggesting that genetic susceptibility to BD may also contribute to cognitive dysfunction.

Yet, whereas genome-wide association studies (GWAS) analyses have consistently found significant negative genome-wide correlations between SCZ and cognitive abilities (r_g ranging between −0.2 to −0.4),[41–48] most studies have found no genome-wide correlations between BD and cognitive abilites.[41–49] One study did find a significant genome-wide correlation between BD and a measure of memory,[41] but the latter shows low test-retest correlation,[50] low single nucleotide polymorphism (SNP)-heritability$\left(h^2_{SNP} = 0.05\right)$,[51] and no genetic correlation with educational attainment,[41] suggesting that its genetic architecture may be different from that of other cognitive traits.

Here we aimed to provide further insights into the genetic relationship between SCZ, BD and intelligence by analyzing summary data from recent large GWAS on SCZ (n=82,315),[52] BD (n=51,710),[49] and general intelligence (n=269,867).[44] In these GWAS, 108 genomic loci were associated with SCZ at the genome-wide significance level,[52] 30 loci were associated with BD,[49] and 205 loci were associated with intelligence.[44] Among the loci, 24 were jointly associated with SCZ[52] and intelligence,[44] with SCZ risk linked to poorer cognitive performance at 18 loci. There was a significant moderate negative genetic correlation between SCZ and intelligence (rg=–0.21, p= 3.82×10^{-17}).[44] Four genome-wide significant loci were jointly associated with BD[49] and intelligence,[44] with BD risk linked to poorer cognitive performance at three loci. In line with prior studies,[41–48] the genetic correlation between BD and intelligence was non-significant (rg=−0.05, p=0.08).[49] Despite the success of these GWAS to uncover trait-associated variants, large fractions of the polygenic architectures underlying SCZ, BD, and intelligence still remain to be uncovered.[44,49,52] To identify additional common genetic variants jointly influencing these phenotypes, we applied a conditional false discovery rate (condFDR) approach.[53,54] This method builds on an empirical Bayesian statistical framework, and combines GWAS summary data to increase statistical power to detect SNPs that did not reach genome-wide significance.[53,54] The condFDR approach does not require a genetic correlation to improve discovery, but leverages systematic co-localization of SNP associations to prioritize likely pleiotropic SNPs.[55] To our knowledge, there are no previous conditional GWAS studies comparing BD and intelligence, while a recent condFDR study identified 21 genomic loci shared between SCZ and different cognitive abilities, where most (18 out of 21) SCZ risk alleles were associated with poorer cognitive performance.[36] Applying the same statistical approach to larger GWAS samples,[44,49,52] we here investigated polygenic overlap between SCZ, BD and intelligence.

Methods

Participant Samples

We obtained GWAS results in the form of summary statistics (p-values and z-scores).[44,49,52] Data on SCZ and BD were acquired from the Psychiatric Genomics Consortium. The SCZ dataset consisted of 49 case control samples (34,241 cases with SCZ or schizoaffective disorder and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios).[52] The BD dataset consisted of 20,352 cases and 31,358 controls from 32 cohorts.[49] Among the cases, 14,879 individuals had a diagnosis of BD type I (BD1), 3,421 had BD type II (BD2), 977 had schizoaffective disorder, bipolar type (SAB), and the

remaining unspecified BD.[49] Data on general intelligence were based on 269,867 individuals drawn from 14 cohorts, primarily consisting of data from the UK Biobank (n=195,653).[44] The cohorts contributing to the intelligence GWAS either calculated Spearman's *g* or used a primary measure of fluid intelligence that correlates highly with *g*.[44,56] All GWAS investigated in the present study were approved by the local ethics committees, and informed consent was obtained from all participants. The Norwegian Institutional Review Board for the South-East Norway Region has evaluated the current protocol and found that no additional institutional review board approval was needed because no individual data were used. For details, see Supplementary Methods and the original publications.[44,49,52]

Statistical analysis

To provide a visual pattern of overlap in SNP associations, we constructed conditional quantile-quantile (Q-Q) plots. The conditional Q-Q plots compare the association with a primary trait across all SNPs and within SNPs strata determined by their association with the secondary trait. Pleiotropic enrichment exists if the proportion of SNPs associated with a phenotype increases as a function of the strength of the association with a secondary phenotype. In conditional Q-Q plots, this enrichment is visualized as successive leftward deflections from the null distribution, and can be directly interpreted in terms of the true discovery rate (1-FDR).[53–55] To improve the discovery of genetic variants associated with SCZ, BD and intelligence, we applied a condFDR statistical framework.[53–55] The condFDR is an extension of the standard FDR, that re-ranks the test-statistics of a primary phenotype based on a *conditional* variable, in this case the strength of the association with a secondary phenotype.[53–55] Inverting the roles of primary and secondary phenotypes provides the inverse condFDR value. The conjunctional FDR (conjFDR), defined in turn as the maximum of the two condFDR values, provides a conservative estimate of the FDR for association with *both* phenotypes. P-values were corrected for inflation using a genomic inflation control procedure.[53] All code used for carrying out the described analyses is available upon request from the corresponding author. All analysis was performed after excluding SNPs in the major extended histocompatibility complex and 8p23.1 regions. For details, see Supplementary Methods.

Genomic loci definition

We defined independent genomic loci according to the FUMA[57] protocol. FUMA is an online platform for functional mapping of genetic variants (http://fuma.ctglab.nl/).[57] First, we identified *independent significant SNPs* as SNPs with condFDR<0.01 and independent from each other at r^2<0.6. A subset of these in approximate linkage equilibrium with each other at r^2<0.1 were then selected as *lead SNPs*. To define *distinct genomic loci,* we merged any physically overlapping lead SNPs (LD blocks<250kb apart). The borders of the genomic loci were defined by identifying all SNPs in LD ($r^2 \geqq 0.6$) with one of the independent significant SNPs in the locus. The region containing all of these *candidate SNPs* was considered to be a single independent genomic locus. All LD information was calculated from the 1000 Genomes Project reference panel.[58] We evaluated the directional effects of the loci shared between SCZ, BD and intelligence by comparing their z-scores and odds ratios.

Functional annotation

Using FUMA,[57] we functionally annotated all candidate SNPs in the genomic loci with a condFDR or conjFDR value <0.10 having an LD $r^2 \geqq 0.6$ with one of the independent significant SNPs. SNPs were annotated with Combined Annotation Dependent Depletion (CADD)[59] scores, which predict how deleterious the SNP effect is on protein structure/function, RegulomeDB[60] scores, which predict likelihood of regulatory functionality, and chromatin states, which predict transcription/regulatory effects from chromatin states at the SNP locus.[61,62] We also identified previously reported GWAS associations in the NHGRI-EBI catalog[63] overlapping with the identified loci. Moreover, we used FUMA[57] to evaluate gene ontology (GO)[64] gene-set enrichment for the genes nearest the identified shared loci. Finally, we used data from the genotype tissue expression (GTEx) resource,[65] to determine gene expression and assess expression quantitative trait locus (eQTL) functionality of likely regulatory lead SNPs. All analyses were corrected for multiple comparisons. For details, see Supplementary Methods.

Results

We observed successive increments of SNP enrichment for SCZ and BD as a function of the significance of the associations with intelligence (Figure 1). This indicates polygenic overlap between the phenotypes. The reverse conditional Q-Q plots demonstrate consistent enrichment in intelligence given associations with SCZ and BD (Supplementary Figure 1). To increase statistical power, we leveraged this pleiotropic enrichment using condFDR analysis and re-ranked SCZ and BD SNPs conditional on their association with intelligence, and vice versa. At condFDR<0.01, we identified 236 loci associated with SCZ and 48 loci associated with BD conditional on their association with intelligence (Supplementary Tables 1–2). Next, we identified 337 loci associated with intelligence conditional on SCZ and 283 loci conditional on BD at condFDR<0.01 (Supplementary Tables 3–4). Altogether, we identified 138 SCZ loci, 31 BD loci, and 165 intelligence loci that were not identified in the original GWAS,[44,49,52] demonstrating the improved power for SNP discovery gained by combining GWAS in a condFDR framework.

A total of 75 distinct genomic loci were jointly associated with SCZ and intelligence at conjFDR<0.01 (Figure 2A; Supplementary Table 5). 42 of these loci were not identified in the original SCZ GWAS.[52] 22 of the 42 were however reported in other SCZ GWAS according to the NHGRI-EBI catalog (Supplementary Table 6), yielding a total number of 20 novel SCZ risk loci among the shared loci.[63] Further, 37 of the top lead SNPs in these loci were associated with BD at p<0.05. As denoted by the sign of the effect sizes, most of the SCZ risk alleles (61 out of 75; Supplementary Table 5) were associated with cognitive underperformance, corroborating prior findings.[36] We also identified 12 distinct loci shared between BD and intelligence at conjFDR<0.01 (Figure 3A; Supplementary Table 7). Eight of these were not identified in the original BD GWAS.[49] Four of the eight had however been identified in prior BD GWAS (Supplementary Table 8), yielding a total of four novel BD risk loci among the shared loci.[63] Eight of the lead SNPs in these loci were associated with SCZ at p<0.05. Although SNPs near *SRPK2* on chromosome 7 reached genome-wide significance in both GWAS on BD[49] and intelligence,[44] no SNPs in this locus were jointly

associated with these phenotypes at conjFDR<0.01 but rs9655780 came close (conjFDR=0.012; Supplementary Table 9). At the shared loci, 9 out of 12 BD risk alleles were associated with higher cognitive performance (Supplementary Table 7). However, among the shared loci at conjFDR<0.05, only 40 out of 79 (51%) loci had concordant effects on BD risk and intelligence (Supplementary Table 9). To visualize the distribution of the shared variants, we constructed 'conjFDR Manhattan plots' where all SNPs without pruning are shown, and the independent significant lead SNPs are encircled in black (Figures 2A and 3A).

Functional annotation[57] of all SNPs having a conjFDR value<0.10 in the loci shared between SCZ and intelligence (n=6853; Figures 2B–D) demonstrated that these were mostly intronic and intergenic, while 2.0% were exonic (Supplementary Table 10). Of the 75 top lead SNPs in the loci shared between SCZ and intelligence, 40 were located inside a protein-coding gene and 11 inside a non-coding RNA (Supplementary Table 5). Of the 75 top lead SNPs, two SNPs (rs11695125, rs1805645) had CADD scores above 12.37, the threshold suggested to signify deleteriousness,[59] and one SNP (rs5751191) had a RegulomeDB[60] score of 1f suggesting that it was likely affecting binding sites (Supplementary Table 5). We followed up this finding using the GTEx database,[65] and found that rs5751191 was significantly associated with eQTL functionality in different brain regions for genes *CYP2D6, NAGA, WBP2NL* and *RP4–669P10.16* (Supplementary Table 11). Using GTEx[65] data, we found that the genes nearest the 75 shared loci were significantly overexpressed in multiple brain regions (Supplementary Figures 2–3). GO gene-set analysis for these genes revealed 32 significantly associated biological processes, the most strongly associated being "regulation of neuron differentiation", "regulation of cell development", "neurogenesis", "modulation of synaptic transmission", and "regulation of receptor binding" (Supplementary Table 12). Further, the genes were significantly associated with 10 cellular component gene-sets, including "neuronal projection", "the synapse", and "the anchored part of membranes", as well as six molecular function gene sets, the most strongly associated being "GABA receptor binding" (Supplementary Table 12).

We also functionally annotated all SNPs having a conjFDR value<0.10 in the loci shared between BD and intelligence (n=846; Figures 3B–D). 4.6% were exonic and most of the others were intronic or intergenic (Supplementary Table 13). Of the 12 top lead SNPs in the loci shared between BD and intelligence, seven were located inside a protein-coding gene and one inside a non-coding RNA (Supplementary Table 7). One of the top SNPs (rs60144015; intronic variant within *FOXO6)* had a CADD score of 18.65 suggesting deleteriousness (Supplementary Table 7). The genes nearest the 12 shared loci were significantly overexpressed in three tissues, all in the brain, namely "frontal cerebral cortex BA9", "nucleus accumbens" and "cerebral cortex" (Supplementary Figures 2 and 4). Gene-set analysis identified one biological process significantly associated with these genes: "long chain fatty acid metabolic process" (Bonferroni-corrected p-value 0.015; data not shown). No gene-sets for cellular components or molecular functions were significantly associated with these genes.

Discussion

In the current study, we analyzed large GWAS datasets on SCZ, BD and intelligence[44,49,52] to gain insights into their shared genetic basis. First, we showed that common genetic variants associated with SCZ and BD are enriched for associations with intelligence (Figure 1). Using conjFDR analysis we leveraged this pleiotropic enrichment and identified 75 genomic loci jointly associated with SCZ and intelligence (Figure 2A) and 12 genomic loci jointly associated with BD and intelligence (Figure 3A). Among the shared loci, 20 are novel SCZ risk loci and four are novel BD risk loci. Altogether, this study indicates that large fractions of the genomic risk architectures underlying SCZ and BD also influence intelligence, albeit in a different manner. This provides new insights into the molecular genetic underpinnings of the altered cognitive performance in these patients groups.[6–14,38] Further experimental interrogation of the identified loci may uncover biological insights that can inform the development of novel effective cognitive treatments, which remains to this day a pressing need in psychiatry.[4,8]

The GWAS power for BD (n=51,710)[49] is still trailing that of SCZ (n=82,315),[52] which limits the validity of comparing the present findings for the two disorders. Yet, the study strengthens prior genetic evidence[44,49] that SCZ and BD differ in their relation to intelligence.[8] Whereas most identified SCZ risk alleles (81%) were associated with lower cognitive performance (Supplementary Table 5), most BD risk alleles (75%) were associated with better cognitive performance (Supplementary Table 7). The discrepant results may thus highlight unique genetic effects underlying SCZ and BD, contrasting their otherwise high degree of genetic overlap.[32] Yet, 8 of 12 lead SNPs associated with both BD and intelligence were also associated with SCZ at $p<0.05$, and 37 of 75 lead SNPs associated with both SCZ and intelligence were also associated with BD at $p<0.05$. Firstly, these results suggest that many of the genetic variants do not exclusively influence SCZ or BD, although they may be more specific to one of the disorders. Secondly, the consistent effects between the disorders support the validity of the present findings, even though the genetic correlation between BD and SCZ is not perfect (r_g=0.70[49]).

To our knowledge, the finding of polygenic overlap between BD and intelligence is novel (Figure 1B, Figure 3A). Prior investigations did not find any genetic correlation between BD and cognitive abilities using LD score regression and polygenic risk scores.[41–49] However, these methods are unable to detect genetic overlap if there are no consistent effect directions among the overlapping SNPs.[66,67] Indeed, at the 79 loci associated with both BD and intelligence at a lower significance threshold (conjFDR<0.05, Supplementary Table 9), only 51% of BD risk alleles were associated with higher cognitive performance. This balanced mixture of directional effects complies with the non-significant genetic correlation between the phenotypes,[44,49] indicating that a substantial polygenic component underlying BD risk also influences intelligence. The converging genetic data does not provide an explanation for the cognitive impairments associated with BD,[6,7,11–14,38] suggesting that environmental factors or undetected rare and common genetic variants may also play a role. Our study further dissects the well-established polygenic overlap between SCZ and cognitive abilities,[36,41–47] strengthening the hypothesis that common genetic variance may contribute to cognitive dysfunction in SCZ. It is nevertheless noteworthy that SCZ risk alleles were

associated with higher cognitive performance at almost one fifth (~19%) of the shared loci. Overall, our findings suggest that the genetic relationship between SCZ, BD and intelligence is more complex than what is expressed by their genetic correlations,[44,49] which may help explain the diverse cognitive performance within these patient groups.[6,9,17–22]

Phenotypic refinement[32] may further illuminate the genetic relationship between BD, SCZ and intelligence. For example, patients with BD without a history of psychosis showed milder cognitive deficits than those with a history of psychosis,[7] while BD1 is associated with more severe cognitive deficits than BD2.[14] In the BD GWAS presently analyzed, 73% of cases had BD1, 17% of cases had BD2 and 5% of cases had SAB.[49] However, larger GWAS samples are required to clarify any genetic differences underlying these subtypes. Note that the genetic effects on intelligence were determined in individuals representative of the normal population.[44] Hence, the experimental design of the conjFDR approach ensures that the cognitive effects here linked to BD and SCZ risk alleles are not attributable to confounding known to bias neuropsychological assessment of these patient groups, such as high symptomatic load or medication.[68] Although some participants in the intelligence GWAS[44] likely suffered from psychiatric disorders, their contribution would not bias the results as they represent a minor fraction of the total GWAS sample.[44]

The genes nearest the 75 loci shared between SCZ and intelligence and the 12 loci shared between BD and intelligence were significantly overexpressed in human brain regions (Supplementary Figures 2–4). Although these genes are not necessarily the genes by which the genetic variants exert their phenotypic effect, the findings support the importance of brain- expressed genes in the shared genetic etiology underlying SCZ, BD and intelligence. The gene-set enrichment analysis implicated 32 biological processes significantly associated with the joint loci between SCZ and intelligence, converging on processes related to neurodevelopment, synaptic integrity and neurotransmission (Supplementary Table 10). These processes are previously linked to SCZ risk[5,37,69] and intelligence.[44,56] In line with these results, the gene-set analysis for cellular components revealed significant associations for neuronal projections, the synapse, and the anchored part of membranes, among others (Supplementary Table 12). The most strongly associated gene-set for molecular functions was “GABA receptor binding”, suggesting that inhibitory signaling may be affected. Intriguingly, we identified several loci shared between SCZ and intelligence previously associated with subcortical brain volumes (at *DPP4, SPATS2L, NEK4, FOXO3,* and *DCC*), [70,71] providing plausible genetic links between SCZ, intelligence and brain structure formation. At all of these loci, SCZ risk was associated with poorer cognitive performance. We identified four loci shared between BD and intelligence that had not reached genome-wide significance in the BD GWAS[49] analyzed but were identified in prior BD GWAS (at *SUMO2P2,*[72] *TENM4/ODZ4*,[73,74] *RHEBL1*,[72,73] and *NFX*[73]; Supplementary Table 8), supporting their role in BD risk. Experimental follow-up studies are needed to determine the causal variants underlying the shared associations detected here, and to detail how these variants individually and collectively affect brain function and development.

In conclusion, our study demonstrates polygenic overlap between intelligence and the psychiatric disorders SCZ and BD, providing new insights into their common genetic basis. Owing to the well-powered GWAS[44,49,52] investigated and their large degree of overlapping

associations, the number of shared loci identified here substantially exceeds that of prior condFDR studies.[36,53,54,70] Yet, the substantial pleiotropic enrichment observed suggests that many more loci shared between SCZ, BD and intelligence will be identified as GWAS samples get larger. This may have profound implications for understanding, and potentially treating, the cognitive abnormalities associated with these psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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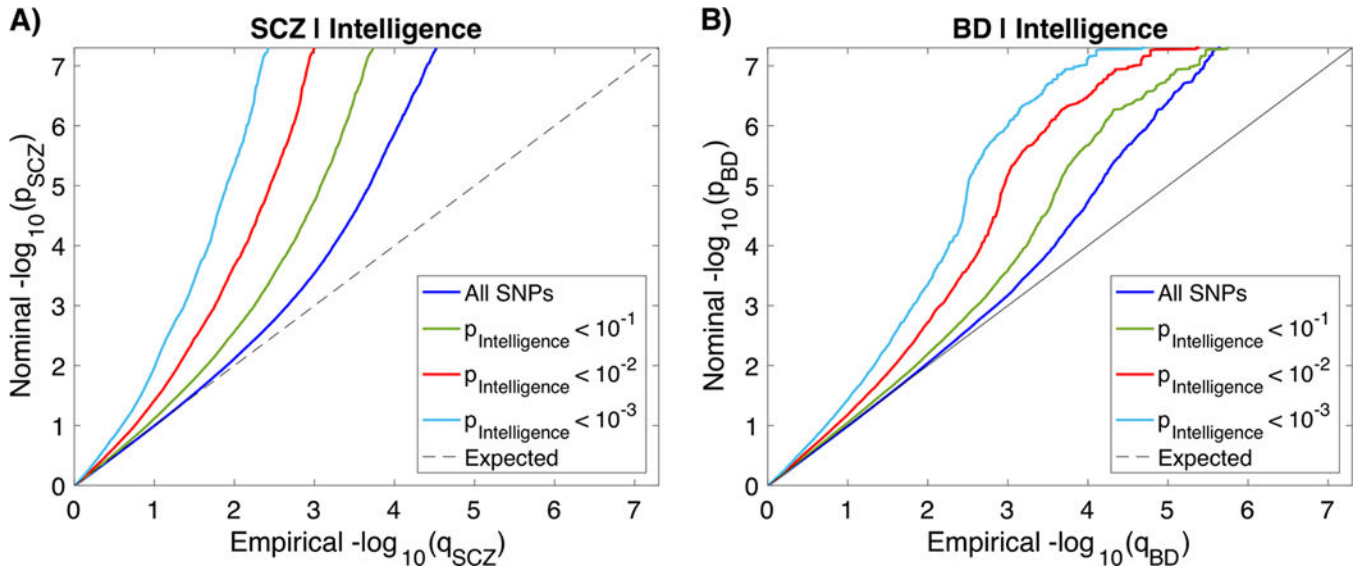

Figure 1.

Polygenic overlap between schizophrenia (SCZ), bipolar disorder (BD) and intelligence. Conditional Q-Q plots of nominal versus empirical $-\log_{10}$ p-values (corrected for inflation) in **A)** SCZ and **B)** BD below the standard GWAS threshold of $p<5\times10^{-8}$ as a function of significance of association with intelligence, at the level of $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis.

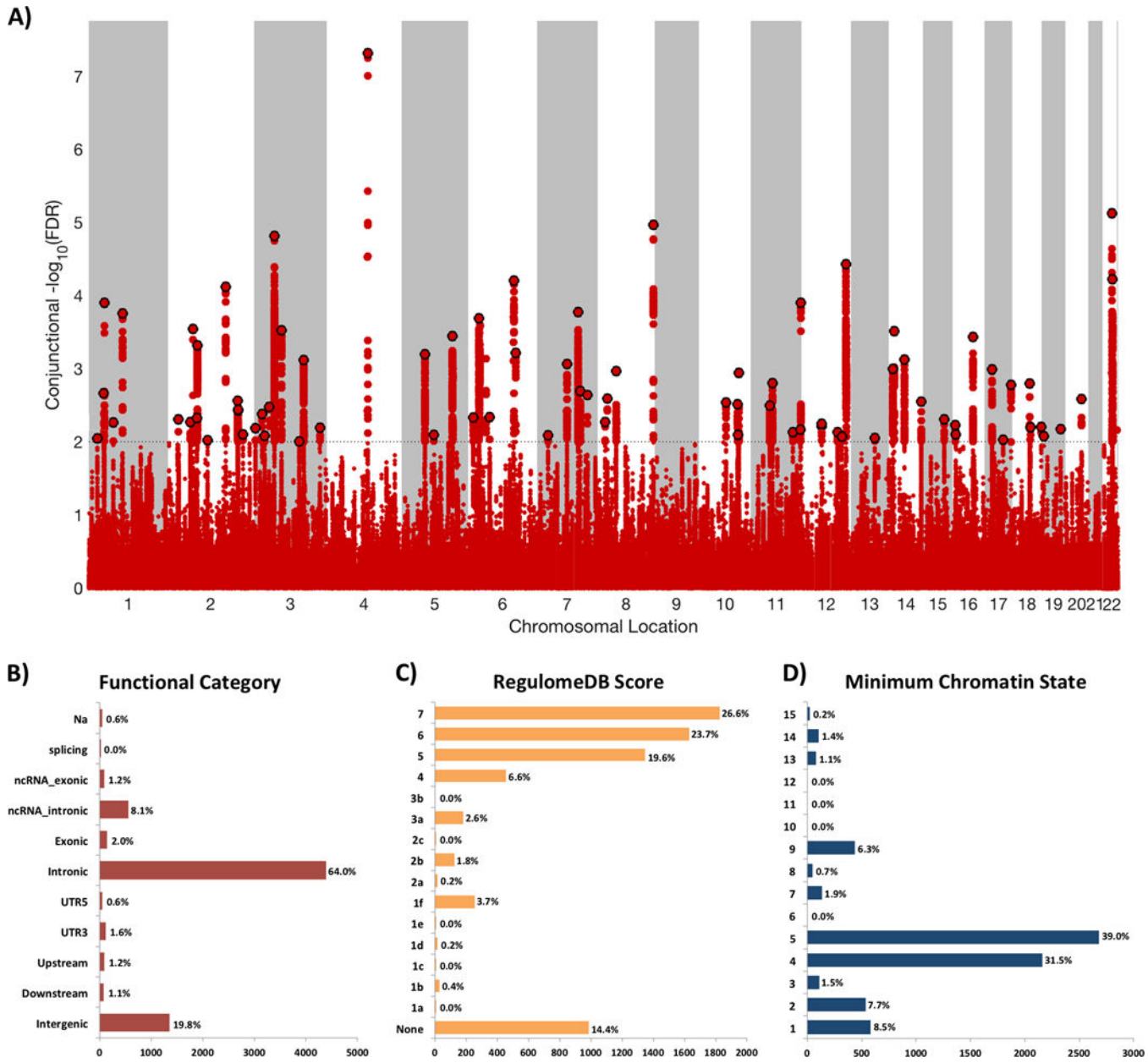

Figure 2.

A) Common genetic variants jointly associated with schizophrenia (n=82,315) and intelligence (n=269,867) at conjunctional false discovery rate (conjFDR) <0.01. Manhattan plot showing the -$\log_{10}$ transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted horizontal line represents the threshold for significant shared associations (conjFDR<0.01, ie -$\log_{10}$(conjFDR)>2.0). Independent lead SNPs are encircled in black. The significant shared signal in the major histocompatibility complex region (chr6:25119106–33854733) is represented by one independent lead SNP. Further details are provided in Supplementary Table 5. **B)** Distribution of functional consequences of SNPs in the shared genomic risk loci. **C)** Distribution of RegulomeDB score for SNPs in shared genomic loci, with a low score

indicating a higher likelihood of having a regulatory function. **D)** The minimum chromatin state across 127 tissue and cell types for SNPs in shared genomic loci, with lower states indicating higher accessibility and states 1–7 referring to open chromatin states.

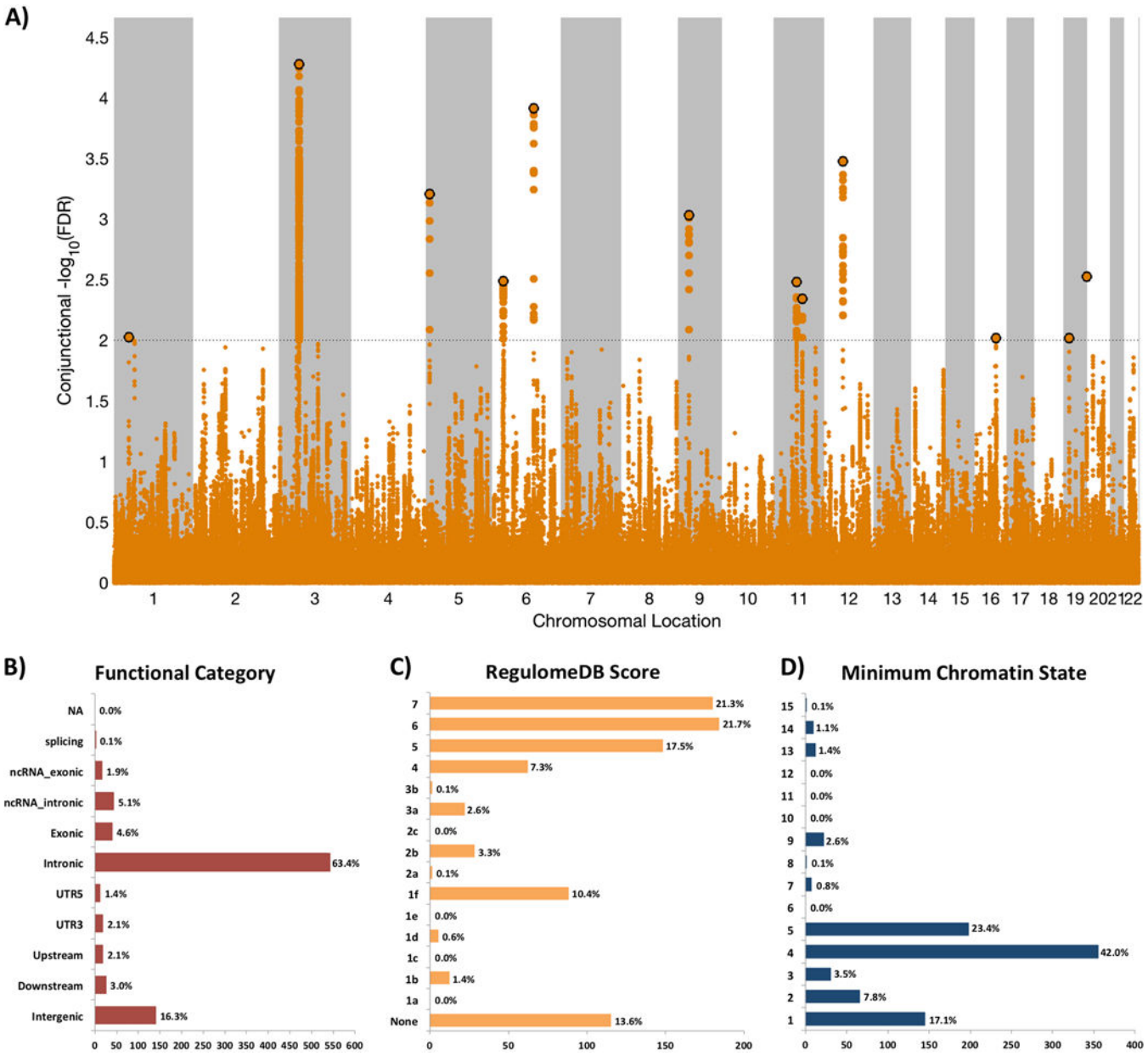

Figure 3.

A) Common genetic variants jointly associated with bipolar disorder (n=59,315) and intelligence (n=269,867) at conjunctional false discovery rate (conjFDR) <0.01. Manhattan plot showing the -$\log_{10}$ transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted horizontal line represents the threshold for significant shared associations (conjFDR<0.01, ie -$\log_{10}$ (conjFDR)>2.0). Independent lead SNPs are encircled in black. Further details are provided in Supplementary Table 7. **B)** Distribution of functional consequences of SNPs in the shared genomic risk loci. **C)** Distribution of RegulomeDB score for SNPs in shared genomic loci, with a low score indicating a higher likelihood of having a regulatory function. **D)** The minimum chromatin

state across 127 tissue and cell types for SNPs in shared genomic loci, with lower states indicating higher accessibility and states 1–7 referring to open chromatin states.