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Impact of *DISC1* variation on neuroanatomical and neurocognitive phenotypes

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Abstract

Although *DISC1* has been implicated in many psychiatric disorders, including schizophrenia, bipolar disorder, schizoaffective disorder and major depression, its biological role in these disorders is unclear. To better understand this gene and its role in psychiatric disease, we conducted transcriptional profiling and genome-wide association analysis in 1 232 pedigreed Mexican American individuals for whom we have neuroanatomic images, neurocognitive assessments and neuropsychiatric diagnoses. SOLAR was used to determine heritability, identify gene expression patterns and perform association analyses on 188 quantitative brain-related phenotypes. We found that the *DISC1* transcript is highly heritable (h^2=0.50; p=1.97 × 10^{-22}), and that gene expression is strongly *cis*-regulated (*cis*-LOD=3.89) but is also influenced by *trans*-effects. We identified several *DISC1* polymorphisms that were associated with cortical gray-matter thickness within the parietal, temporal and frontal lobes. Associated regions affiliated with memory included the entorhinal cortex (rs821639, p=4.11 × 10^{-5}; rs2356606, p=4.71 × 10^{-4}), cingulate cortex (rs16856322, p=2.88 × 10^{-4}) and parahippocampal gyrus (rs821639, p=4.95 × 10^{-4}); those affiliated with executive and other cognitive processing included the transverse temporal gyrus (rs9661837, p=5.21 × 10^{-4}; rs17773946, p=6.23 × 10^{-4}), anterior cingulate cortex (rs2487453, p=; 4.79 × 10^{-4}; rs3738401, p= 5.43 × 10^{-4}) and medial orbitofrontal cortex (rs9661837; p=7.40 × 10^{-4}). Cognitive measures of working memory (rs2793094, p=3.38 × 10^{-4}), as well as lifetime history of depression (rs4658966, p=4.33 × 10^{-4}; rs12137417, p=4.93 × 10^{-4}) and panic (rs12137417, p=7.41 × 10^{-4}) were associated with *DISC1* sequence variation. *DISC1* has well-defined genetic regulation and clearly influences important phenotypes related to psychiatric disease.

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Conflicts of Interest

The authors declare no conflicts of interest.

Keywords

DISC1; association; neuroanatomical; neurocognitive; endophenotype; cis-regulation; depression; panic; memory; learning

Introduction

Disrupted in schizophrenia 1 (*DISC1*) is one of the few genes that have been consistently implicated in psychiatric illness, making it one of the most promising genes for understanding the biological mechanisms that drive such disorders. However, little is known about how *DISC1* is regulated and how extensively neuroanatomical and neurocognitive measures are influenced by *DISC1* genetic variation.

DISC1 was initially identified as a schizophrenia candidate gene when linkage analysis in a large Scottish family revealed co-segregation between schizophrenia and a balanced translocation (1;11)(q42.1;14.3) that disrupts the *DISC1* locus (1, 2). Further analysis revealed linkage of the *DISC1* locus to schizophrenia, bipolar disorder and/or schizoaffective disorder in families from Finland (3, 4), Scotland (5), and the United Kingdom/Ireland (6). It has been noted that both unaffected carriers of this transclocation and individuals affected with schizophrenia show reduced amplitude and latency of the auditory P300 event-related potential (7) and this in turn has been correlated with reduced gray matter volume in the left superior temporal gyrus, suggesting that *DISC1* may mediate this important trait marker for schizophrenia risk. In addition, numerous studies have provided evidence for association of various *DISC1* single nucleotide polymorphisms (SNPs) in schizophrenia (8-11), bipolar disorder (9, 10, 12, 13), depression (14) and autism and Asperger syndrome (15). Although some *DISC1* variants have been associated with brain-related phenotypes, including hippocampal gray matter volume and function (16), poor concentration (in schizophrenics) (17), recall and memory (10), verbal ability and memory (10), visuospatial ability (10), psychomotor processing (10), visual working memory (10, 18, 19) and general cognitive ability (20), these studies have examined only a few selected SNPs usually based on prior evidence for potential involvement. Furthermore, DISC1 SNPs have been associated with anxiety, depression, emotional stability and neuroticism in elderly women (21).

Composed of 13 alternatively spliced exons spanning about 415kb (NG_011681.1), *DISC1* has numerous isoforms and is expressed most highly during periods of neurogenesis (22). In the adult mammalian brain, expression levels are highest in the hippocampus and cerebral cortex (23, 24). However, the regulation of *DISC1* expression has not been well studied, with one study finding no evidence (25), and another showing only suggestive evidence for *cis*-regulation (26). DISC1 interacts with a number of binding partners to regulate neuronal development (23, 27). Notably, DISC1 plays a critical role in normal microtubular dynamics (24, 27), neurite outgrowth (23, 27, 28) and neuronal migration (27).

To improve our understanding of *DISC1* we used a combination of transcriptional profiling of lymphocytes and genome wide genotyping to investigate the genetic factors driving *DISC1* expression in a large sample of randomly ascertained individuals. Here we show that

the expression of the *DISC1* gene is heritable and highly *cis*-regulated. Furthermore, we have identified *DISC1* sequence variation that strongly influences various neuroanatomic and neurocognitive traits that commonly coincide with mental illness.

Methods

For more detailed information, please refer to online Supplementary Methods.

Population phenotypes

We utilized samples derived from individuals in the San Antonio Family Heart Study (SAFHS) (29) and San Antonio Diabetes/Gallbladder Study (SAFDGS) (30, 31), which both consist of large extended families. All study participants gave informed consent and the study was undertaken with approval by the Institutional Review Board at The University of Texas Health Science Center at San Antonio. Brain-related phenotypes were collected for up to 625 participants. Neuroanatomical images for 387 individuals have been collected using a Siemens 3T MRI scanner (Siemens, New York, NY), linearly aligned and averaged (32) and analyzed using FreeSurfer software (33). Gray-matter thickness, surface area and volume have been determined for 34 cortical regions of interest (ROI), combining left and right hemispheres and gray-matter volume has been determined for 16 subcortical regions. The South Texas Assessment of Neurocognition (STAN) neuropsychological battery (34) includes clinical and experimental tests investigating a wide range of cognitive domains, including general intellectual functioning, sensory-motor and processing speed, attention, executive functioning, working memory, long-term memory, language and social cognition. To date, 625 GOBSF individuals have received the STAN neuropsychological battery as well as the Mini-International Neuropsychiatric Interview (MINI-Plus) (35), a semi-structured interview to facilitate diagnoses of DSM-IV and ICD-10 psychiatric illnesses.

Genetic analysis

We previously generated transcriptional profiles for 1 240 individuals within the SAFHS population using Illumina® Sentrix® Whole Genome (WG-6) Version 1 BeadChips (Illumina, San Diego, CA) and utilized highly polymorphic STR markers to examine evidence of *cis*-linkage of *DISC1* gene expression (36). To examine genetic variation that might influence *DISC1* gene expression and brain-related phenotypes, we used Illumina GoldenGate technology to genotype 1 240 individuals for 125 SNPs within the 5′ UTR, 3′ UTR and *DISC1* gene, 11 of which overlapped with previously implicated *DISC1* SNPs (Supplementary Table 2). One 5′ UTR polymorphism (rs3738398), which could not effectively be incorporated into the OPA pool, was genotyped using a Taqman assay (Supplementary Table 2). Illumina HumanHap550k version 3.0 and Human1M version 1.0 BeadChips were used to assess 543 031 SNPs in 858 individuals to determine *trans*-effects on *DISC1* gene expression. There were no SNPs within the *DISC1* gene within this panel, making this genotyping platform independent of the analysis of *DISC1* gene variation.

Statistical analysis

All statistical analyses were performed using the SOLAR software package (37). Heritability was assessed using a classical approach to deconstruct the phenotypic variance

into independent genetic and environmental components and the Loki software package (38) was used to compute probabilities of multipoint identity-by-descent (IBD) allele sharing. Covariates sex, age, sex*age, age^2, and sex*age^2) were included in every analysis performed. Quantitative trait linkage analysis of DISC1 gene expression levels was performed using the likelihood ratio tests (37). Heritability and linkage analysis of *DISC1* transcript levels is based on 1 240 individuals, while our genome-wide association of *DISC1* expression is performed on a subset of 858 of these individuals. Association testing was performed by measured genotype analysis (39). All brain-related measures were performed on the same set of 625 individuals (387 for neuroanatomical measures), all were typed for each DISC1 sequence variant.

To account for multiple testing, we performed modified Bonferroni corrections adjusting for the number of effective *DISC1* SNPs (n=66) for each test (required significance $p=7.7\times10^{-4}$.

Results

DISC1 is a *cis*-regulated gene

The expression of *DISC1* was highly heritable ($h^2=0.50$; $p=1.97\times10^{-22}$). Furthermore, quantitative trait linkage analysis performed at the genetic location of *DISC1* revealed strong evidence for *cis*-regulation, (*cis*-LOD=3.89; $p=1.16\times10^{-5}$). This cis-acting QTL was estimated to account for a sizable 25.6% of the total phenotypic variation in *DISC1* expression levels suggesting that the cis effects are large.

For the 1 240 individuals that had previously undergone transcriptional profiling, we genotyped 126 known *DISC1* SNPs. A total of 1 232 individuals had complete data sets for both *DISC1* transcripts levels and *DISC1* SNP variation. The effective number of SNPs could be reduced to 66 based on linkage disequilibrium across the gene (Supplementary Figure 1). Global variation within the promoter region (Supplementary Figure 2) was significantly associated with expression of the *DISC1* transcript ($p=5.7\times10^{-34}$). To determine whether particular variants were more highly associated with expression of *DISC1*, we performed association analysis with individual SNPs using *DISC1* gene expression as a quantitative trait. Within the promoter region, 15 SNPs were significant after a Bonferroni correction for the effective number of SNPs (see Table 1, Figure 1), which is in contrast to prior studies by Hayesmoore (25) and Hennah and Porteus (26). Multivariant analysis (40) identified at least 5 independent cis-acting contributions. The best multivariant model included five SNPs (rs12042938, rs34574703, rs3738398, rs16854957, and rs16856202) and accounted for 16.6% (multivariate $p=1.07\times10^{-39}$) of the total phenotypic variation in *DISC1* expression. This estimate of the component of heritability due to cis effects confirms the importance of local sequence variation on *DISC1* regulation.

DISC1 expression is modulated by *trans*-effects

We used genome-wide association analysis employing 543 031 SNPs in 857 of these individuals to identify genomic regions harboring genes that might contribute to the modulation of *DISC1* expression. Eighteen SNPs were identified that were significantly associated with *DISC1* expression using a false discovery rate of 0.10. Of these, 15 SNPs

were *cis*-acting (as previously described) and the remaining three SNPs represented significant *trans*-effects in two genomic regions. The SNPs were within or near the *NUP210* gene at 3p25 ($p=5.5\times10^{-6}$) and *MPP6* gene at 7p15 ($p=8.1\times10^{-6}$). Although these genes may be directly responsible for regulating *DISC1* expression it is more likely that potential upstream modifiers are located within these genomic regions. To identify potential modifiers of *DISC1* expression we examined the genes within 1Mb either side of the *trans*-effects seen at 3p25 and 7p15 to determine whether quantitative expression of these genes was also genetically correlated (r_G) with *DISC1* expression. At 3p25, bivariate quantitative genetic analysis revealed several correlated genes including *PPARG* ($r_G=0.703$, $p=6.4\times10^{-4}$), *MGC2776* ($r_G=0.280$, $p=1.4\times10^{-2}$), *RAF1* ($r_G=0.252$, $p=2.9\times10^{-2}$), *RPL32* ($r_G=-0.293$, $p=4.6\times10^{-2}$), *NUP210* ($r_G=-0.219$, $p=3.2\times10^{-2}$), *HDAC11* ($r_G=-0.549$, $p=1.6\times10^{-2}$), *CHCHD4* ($r_G=0.225$, $p=2.4\times10^{-2}$), and *XPC* ($r_G=0.252$, $p=1.4\times10^{-2}$). At 7p15 these genes included *SNX10* ($r_G=0.386$, $p=4.4\times10^{-4}$), *SCAP2* ($r_G=0.387$, $p=1.4\times10^{-3}$), and *TRA2A* ($r_G=-0.294$, $p=8.8\times10^{-3}$).

DISC1 is associated with brain-related endophenotypes

In those individuals, for whom we had both genotypic and brain-related phenotypic data, we examined associations between *DISC1* variants and neuroanatomical and neurocognitive measures. Implementing a modified Bonferroni correction within phenotypes for the 66 effective SNPs, we identified 14 associations with neuroanatomical traits (Table 2), two associations with neurocognitive traits and two associations with a neuropsychiatric diagnosis of recurrent major depressive disorder. These associations and SNP locations, as well as proximity to previously implicated SNPs, are described in Figure 1. Notably, many associated SNPs are located within the 3′ end of the gene between exons 9 and 13, a fewer number of SNPs are located in intron 1, exon 2 and intron 3. Significant associations were detected with cortical thickness in the temporal, parietal and frontal lobes and in some cases specific *DISC1* variants were associated with cortical thickness in multiple regions.

Additionally, associations were detected with measures of spatial working memory (rs2793094, $p=3.38\times10^{-4}$), recurrent major depressive disorder (MDD) (rs4658966, $p=4.33\times10^{-4}$; rs12137417, $p=4.93\times10^{-4}$) and lifetime measures of panic (rs12137417, $p=7.41\times10^{-4}$).

All observed associations are obligately independent of sex and age effects which were utilized as covariates in each analysis. Additionally, there was no evidence for any correlation between age or sex and genotype for any *DISC1* sequence variant.

Discussion

The *DISC1* gene is a strong candidate gene for a number of psychiatric illnesses. Using a combination of transcriptional profiling of lymphocytes, targeted genotyping and genome wide association analysis, we show here that *DISC1* expression is heritable, highly regulated by variation within its promoter region and to a lesser extent influenced by other genomic regions (3p25, 7p15). Furthermore, variation within *DISC1* is associated with a number of neuroanatomical and neurocognitive phenotypes, most significantly cortical thickness.

One obvious caveat regarding our findings is that while we correct on a phenotype by phenotype basis for the multiple testing of *DISC1* sequence variants, we do not perform such correction across all phenotypes examined. We anticipate that replication of these observed associations for specific phenotypes will be needed to confirm our findings.

Lymphocyte-derived or lymphoblastoid-derived *DISC1* gene expression has previously shown variability in psychiatric diseases, such as bipolar disorder (41), schizophrenia and schizoaffective disorder (42), and in unaffected family members carrying the *DISC1* t(1;11) translocation (43). Further, this variability has been correlated with markers for schizophrenia risk (7). This current study supplements the increasing body of evidence that suggests transcriptional profiling of lymphocytes is a good surrogate model for diseases in which the tissue of interest is difficult to obtain (36, 44). Moreover, they suggest that *DISC1* gene expression in lymphocytes may provide a suitable marker for psychiatric disease risk.

We determined *DISC1* to be strongly *cis*-regulated. Using allelic expression analysis of a single common SNP (rs3738401) within exon 2 of *DISC1* in 148 unrelated individuals, Hayesmoore and colleagues failed to detect *cis*-regulation of *DISC1* (25). Using a significantly larger population size, we found moderate evidence for *cis*-regulation at this same SNP ($p=3.78\times10^{-10}$), although the strongest *cis*-effects were seen in intron 1 ($p=1.61\times10^{-4}$-3.51×10^{-36}) and near the 5′ end of the gene (5.69×10^{-6}-5.98×10^{-33}). Hennah, *et al*, probed existing databases for evidence of *cis*-regulation at 754 SNPs, also for a small number of samples (210 cell lines derived from the four HapMap population cohorts). They found only suggestive evidence for *cis*-regulation in three of the four populations for six SNPs, four of which were located about 4-30kb upstream of our region of significance (26). The remaining two SNPs were located at the 5′ end of our region of significance, including one (rs3738398) that we also found to be significant (26). It is possible that ethnic heterogeneity and low sample numbers contributed to an underpowered study, which was unable to detect significant *cis*-effects. Given that we investigated *cis*-effects in 1 240 ethnically similar individuals, we believe that our study was more highly powered to identify strong *cis*-regulation of the *DISC1* gene.

The DISC1 protein-protein “interactome” is a highly connected network consisting of 127 proteins and 158 interactions (45), in which DISC1 acts as a “hub” protein functioning in cAMP signaling, axon elongation and neuronal migration. We have identified two genomic regions, which may comprise genes that regulate *DISC1* gene expression. Although there are no obvious candidate genes within the 3p25 or 7p15 regions, it is possible that one or more genes within these regions may act to regulate *DISC1* expression through protein modification (e.g. *HDAC11*), cell-specific splicing (e.g. *TRA2A*), or DNA repair (e.g. *XPC*). Given the importance of DISC1 as a “hub” protein within many neurological processes, it is important to identify upstream modifiers of *DISC1* gene expression, which could potentially be targeted for therapeutic benefit. Other factors regulating *DISC1* gene or protein expression that are outside the context of this study should also be considered, such as epigenetic modifications. Recently, it was shown that enriched histone methylation occurs proximal to transcription start sites of annotated genes and that reorganization of the neuronal epigenome is correlated with age, suggesting an important role for epigenetics in the regulation of genes involved in neuronal development (46).

There is little overlap between *cis*-regulated SNPs and those that influence brain-related phenotypes, suggesting that genetic variation influencing lymphocyte-derived gene expression and functional outcome are largely independent. The 5′ region of *DISC1* contains 15 *cis*-acting SNPs, of which 11 are located within the 5′UTR or intron 1, where the strongest signal is seen. In contrast, most SNPs influencing brain structure and function are located toward the 3′ end of the *DISC1* gene, and might be more likely to influence post-transcriptional or post-translational modifications. Only two SNPs, rs3738401 and 2487453, were found to be *cis*-acting and influence brain structure, specifically thickness of the cingulate cortex. Of these, rs3738401 is part of a haplotype block (HEP3) that has previously been implicated in schizophrenia, schizoaffective disorder, bipolar disorder and MDD as well as related phenotypes of delusions/hallucinations, manic and depressive thoughts and visual memory (10, 18, 47). Findings from our study, in addition to previous studies, suggest this SNP may be extremely important in not only regulating *DISC1* gene expression, but also in eliciting a functional response the predisposes to various psychiatric disorders.

Only one other previously implicated SNP, rs2356606, was also implicated within this study and was found to be associated with thickness of the entorhinal cortex and postcentral gyrus. This SNP is within a haplotype block that has previously been associated with schizophrenia in females (48). By analyzing a large number (n=115) of previously unstudied SNPs, we have identified a number of novel associations with brain-related phenotypes, which need to be verified by follow-up studies. It is important to note that a number of SNPs that were found to be associated with brain-related phenotypes in our study are in close proximity to previously implicated SNPs (seen in Figure 1). It is therefore possible that they are in linkage disequilibrium with previously implicated SNPs, and the causal variant would likely lie somewhere within this region.

Many of the associated SNPs identified in this study are within intronic regions of the *DISC1* gene, for which we have no current evidence of a functional effect on the DISC1 protein. It is possible that these SNPs may play a role in regulation of or targeting by miRNAs, or in RNA stability or splicing efficiency, but it is perhaps more likely that associated intronic SNPs are in linkage disequilibrium with other functional SNPs. Few studies have identified functional variants of the *DISC1* gene and most have looked at the effect of the Ser704Cys variant (rs821616) on psychiatric disease. Variation at this locus has been associated with schizophrenia brain morphology (14, 49). Despite its proximity to a number of SNPs for which we have strong evidence of association with brain morphology, we have found no such association with the Ser704Cys variant. Given that we identified significant brain-related associations within multiple regions of the *DISC1* gene, we expect that additional functional analyses will likely reveal a number of polymorphisms that directly or indirectly act to influence brain structure and phenotypes associated with cognitive functioning.

Reduction in cortical thickness is well known to be associated with schizophrenia (50-52) and has been implicated in bipolar disorder (53), depression (54), posttraumatic stress disorder (55), autism spectrum disorder (56) and Alzheimers disease (57). In this study, we identified a number of brain regions in which cortical thickness is associated with *DISC1*

genetic variation, including regions of the temporal, parietal and frontal lobes and the cingulate cortex. *DISC1* gene variation was associated with cortical thickness of brain regions involved in memory (entorhinal cortex, cingulate cortex, parahippocampal gyrus) (58, 59) and emotion- and reward-based cognitive processing and learning (anterior cingulate cortex, medial orbitofrontal cortex) (60, 61). Given the inherent functions of these brain regions, it is not surprising that variation in cortical thickness of such regions has already been identified in patients with schizophrenia (parahippocampal gyrus, anterior cingulate cortex, entorhinal cortex, medial orbitofrontal cortex) (50-52); bipolar I disorder (left cingulate gyrus) (53); depression (postcentral gyrus, anterior cingulate cortex, medial orbitofrontal cortex) (54); posttraumatic stress disorder (parahippocampal gyrus) (55); autism spectrum disorder (left anterior cingulate gyrus, left parahippocampal gyrus, left medial orbitofrontal gyrus) (56, 62); and Alzheimer's disease or mild cognitive impairment (parahippocampal gyrus, entorhinal cortex, retrosplenial cortex, anterior cingulate cortex) (57, 63, 64). Furthermore, individuals at ultra high risk for psychosis and relatives of individuals affected with schizophrenia also show reduction in cortical thickness in certain brain regions (50, 65-67), suggesting a strong genetic component to regional cortical thinning, which may be progressive in nature.

The spatial working memory measure, a delayed response task, significantly associated with *DISC1* was previously shown to be sensitive to genetic liability for schizophrenia (68) and psychotic bipolar disorder (69). Furthermore, brain regions associated with *DISC1* (e.g. entorhinal cortex, cingulate cortex and parahippocampal gyrus) were engaged when healthy subjects (70) and first episode patients with schizophrenia (71) performed this task during functional MRI. Although SNPs associated with cortical thickness of regions associated with memory are located in the 3′ region of the *DISC1* gene (between exons 9 and 13), the SNP associated with working memory is located closer to the 5′ end of the gene (intron 3). It is therefore likely that the true functional SNP(s) that play a role in cortical thickness are different from those involved in spatial working memory and that multiple *DISC1* SNPs may contribute to memory functioning. Measures of lifetime panic and depression were also associated with variation in *DISC1*. Interestingly, SNPs associated with MDD and lifetime panic were located in close proximity, within intron 9 of the *DISC1* gene (Figure 1). Variation associated with the orbitofrontal cortex, previously implicated in panic disorder and MDD (72-74), was located nearby in exon 13. However, variation influencing the rostral cingulate cortex, a brain region associated with affective and anxiety disorders, was located in the 5′ region of the gene (exon 2, intron 3).

The *DISC1* gene, although well implicated in psychiatric disease, is not well understood. We have attempted here to determine factors that influence *DISC1* expression and identify *DISC1* sequence variation associated with neuroanatomical and neurocognitive traits. We found significant associations in regions of the brain associated with memory and cognitive processing, which was also reflected in associations with cognitive measures of memory, depression and panic. The results presented here suggest that variation in *DISC1* sequence and gene expression acts coordinately to affect both brain structure and cognition, specifically within phenotypes that are implicated in psychiatric disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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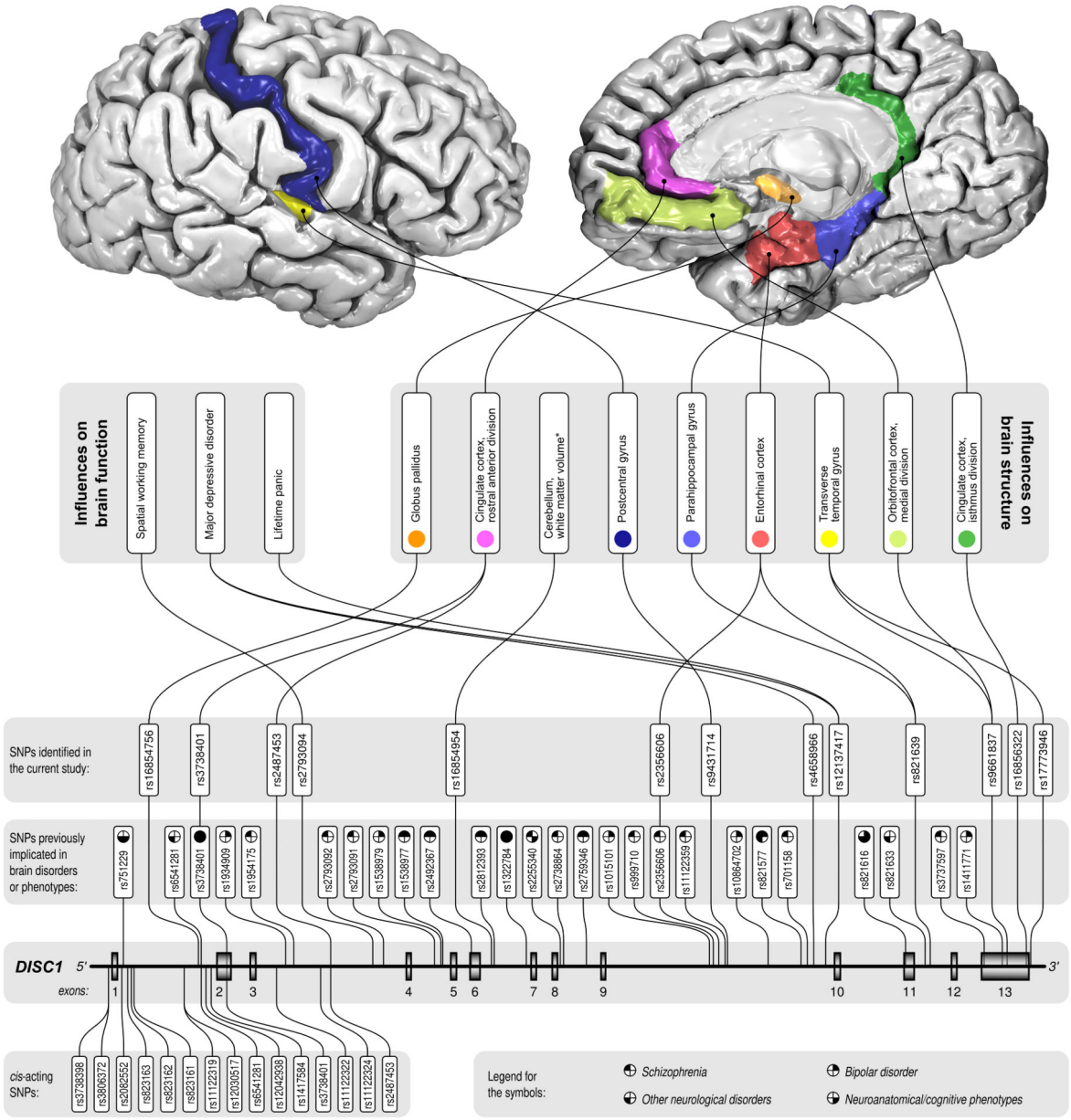

Figure 1.

Location of *DISC1* SNPs and their influence on brain structure and function. Proximity to SNPs that have been previously implicated in published studies of schizophrenia, bipolar disorder, other neurological disorders, or neuroanatomical/neurocognitive phenotypes in either single SNP or haplotype analysis, is also shown.

Table 1

DISC1 cis-acting SNPs

SNP	MAF*	Gene Region	p-value
rs12042938	0.478 (C)	Intron 1	3.51×10^{-36}
rs11122319	0.487 (A)	Intron 1	1.33×10^{-33}
rs3738398	0.424 (C)	5′ UTR	5.98×10^{-33}
rs12030517	0.444 (C)	Intron 1	3.65×10^{-31}
rs823163	0.489 (C)	Intron 1	1.49×10^{-30}
rs823161	0.486 (T)	Intron 1	3.83×10^{-30}
rs2082552	0.362 (G)	Intron 1	7.13×10^{-27}
rs6541281	0.389 (T)	Intron 1	1.89×10^{-25}
rs1417584	0.399 (A)	Intron 1	2.12×10^{-22}
rs11122322	0.361 (G)	Intron 3	3.48×10^{-11}
rs3738401	0.348 (A)	Exon 2	3.78×10^{-10}
rs11122324	0.364 (A)	Intron 3	7.06×10^{-10}
rs2487453	0.379 (A)	Intron 3	2.58×10^{-9}
rs3806372	0.081 (T)	5′ UTR	5.69×10^{-6}
rs823162	0.042 (G)	Intron 1	1.61×10^{-4}

*Minor allele listed according to the forward strand designated by dbSNP build 131

Table 2

Brain-related phenotypes associated with *DISC1* variation

Phenotype	Hemisphere	SNP	MAF*	p-value
Temporal Lobe, Medial Aspect, Entorhinal Cortex; thickness	- overall - left - left	rs821639 rs821639 rs2356606	0.277 (C) 0.136 (C)	4.11×10^{-5} 1.11×10^{-4} 4.71×10^{-4}
Left Pallidum; volume		rs16854756	0.010 (C)	2.01×10^{-4}
Cingulate Cortex, Retrosplenial Cortex; thickness		rs16856322	0.271 (T)	2.88×10^{-4}
Left Cerebellum White Matter; volume		rs16854954	0.168 (C)	4.31×10^{-4}
Temporal Lobe, Medial Aspect, Parahippocampal Gyrus; thickness	- left - overall	rs821639 rs821639	0.277 (C)	4.68×10^{-4} 4.95×10^{-4}
Cingulate Cortex, Rostral Anterior Division; thickness	- overall - overall	rs2487453 rs3738401	0.379 (A) 0.348 (A)	4.79×10^{-4} 5.43×10^{-4}
Temporal Lobe, Lateral Aspect, Transverse Temporal Cortex; thickness	- overall - right	rs9661837 rs17773946	0.009 (G) 0.012 (G)	5.21×10^{-4} 6.23×10^{-4}
Parietal Lobe, Postcentral Gyrus; thickness	- left	rs9431714	0.308 (G)	7.22×10^{-4}
Frontal Lobe, Medial Division, Orbitofrontal Cortex; thickness	- right	rs9661837	0.009 (G)	7.40×10^{-4}

*Minor allele listed according to the forward strand designated by dbSNP build 131