Beyond Schizophrenia: The Role of DISC1 in Major Mental Illness

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Schizophrenia and related disorders have a major genetic component, but despite much effort and many claims, few genes have been consistently replicated and fewer have biological support. One recent exception is “Disrupted in Schizophrenia 1” (DISC1), which was identified at the breakpoint on chromosome 1 of the balanced translocation (1;11)(q42.1;q14.3) that co-segregated in a large Scottish family with a wide spectrum of major mental illnesses. Since then, genetic analysis has implicated DISC1 in schizophrenia, schizoaffective disorder, bipolar affective disorder, and major depression. Importantly, evidence is emerging from genetic studies for a causal relationship between DISC1 and directly measurable trait variables such as working memory, cognitive aging, and decreased gray matter volume in the prefrontal cortex, abnormalities in hippocampal structure and function, and reduction in the amplitude of the P300 event-related potential. Further, DISC1 binds a number of proteins known to be involved in essential processes of neuronal function, including neuronal migration, neurite outgrowth, cytoskeletal modulation, and signal transduction. Thus, both genetic and functional data provide evidence for a critical role for DISC1 in schizophrenia and related disorders, supporting the neurodevelopmental hypothesis for the molecular pathogenesis of these devastating illnesses.

Key words: genetics/animal models/neuroimaging/expression studies/neurodevelopment

Genetic analysis of schizophrenia has been ongoing for a number of decades, often with rather disappointing results. Most initial observations have not been successfully independently replicated. Recent encouraging exceptions are DTNBP1 and NRGI.1,2 Here we focus on a third example, DISC1, which was thrown into the limelight when it was included as part of Science magazine’s nominations for the “Scientific Breakthroughs of the Year, 2005.”3 The DISC1 story has captured not just the attention of geneticists but also of investigators in a number of other disciplines, including cell biology, animal models, and neuroimaging. This work has highlighted the possible involvement of DISC1 in predisposing individuals to a wide range of psychiatric conditions, psychological traits, and biological phenotypes. A number of key central nervous system proteins have also been identified as interacting partners, introducing the concept of the DISC1 pathway in normal and disturbed brain development and function.

Family Evidence

DISC1 was first identified in genetic studies of a large Scottish family in which a chromosomal translocation was found to segregate with mental illness. Microdissection of the translocated chromosomes identified the breakpoint on chromosome 1 at 1q42.2,4 and subsequent analysis identified 2 genes directly disrupted by the translocation, Disrupted in Schizophrenia 1 and 2 (DISC1 and DISC2).5,6 Initially, 77 members of the translocation family were available for cytogenetic analysis, and 34 carried the balanced translocation between chromosomes 1 and 11, t(1;11). The translocation segregated with a broad range of diagnoses, with the maximum LOD score of 4.3 being reached when schizophrenia, schizoaffective disorder, recurrent major depression, adolescent conduct disorder, and emotional disorders were used as a broad diagnostic class in the model.7 Long-term follow-up of the family has identified additional cases of major psychiatric illness among translocation carriers, which continues to support the hypothesis that the translocation is sufficient in its own right to cause major psychiatric illness within this family.8,9 The individuals continue to display a range of diagnoses: 7 individuals are affected with schizophrenia, 1 individual with bipolar disorder, 10 with recurrent major depression, 2 with adolescent conduct and emotional disorder, and 1 case of minor depression. The follow-up has increased the LOD score to 7.1 when those individuals with schizophrenia, bipolar disorder, and recurrent major depression are included. None of
the family members with a normal karyotype have a major psychiatric diagnosis. Family members with a psychiatric diagnosis are not distinguishable from unrelated individuals of the same diagnosis and have no concurrent physical, neurological, or dysmorphic conditions.8 Neither do the translocation carriers differ from non–translocation carriers in intelligence quotient (IQ), measured using the National Adult Reading Test.8

Measurements of auditory P300 event-related potential (ERP) in family members indicate a direct involvement of the translocation as a risk factor for the development of psychiatric illness. Auditory P300 is known to be abnormal in patients with schizophrenia and their first-degree relatives and has been proposed as a trait marker of risk for schizophrenia.10–12 Translocation carriers showed significant reduction in the amplitude of the P300 ERP compared with family members without the translocation and unrelated controls, but similar to unrelated schizophrenics.8 The abnormality of P300 ERP was independent of psychiatric symptoms, with 2 translocation carriers without diagnosis showing amplitude reductions of less than 2 standard deviations below the control mean. The genetic model of schizophrenia within the t(1;11) family is most consistent with a dominant model with reduced penetrance.9 Consistent with this, levels of DISC1 protein are approximately halved in t(1;11) lymphoblastoid cell lines.13

To date, no other family has been identified with a translocation in DISCI, but this is not unexpected due to the rarity of such events. However, a frameshift mutation in DISCI was recently reported in an American family.14 The frameshift was identified in an individual with schizophrenia and was also present in 2 siblings, one with schizophrenia and the other with schizoaffective disorder, and the unaffected father. By contrast with the t(1;11) mutation, this frameshift mutation does not segregate consistently with major mental illness. It was not present in 1 sibling with schizotypal personality disorder or 2 with major depression. Of 2 more distant family members diagnosed with schizophrenia, one is from the maternal side and therefore very unlikely to carry the frameshift, and the second was unavailable for testing. The link between this frameshift mutation and schizophrenia thus remains unclear, although if a stable, truncated protein were expressed in the brain (not tested), then it would be predicted to reduce the capacity for specific DISC1 protein interactions.

Population-Based Genetic Evidence

Despite the fact that the translocation breakpoint in the large Scottish family provided convincing evidence for the involvement of 1q42 and DISCI in the etiology of major mental illness, the outstanding question was whether DISCI had any relevance to the “at-risk” population at large. The studies performed in Finland were the first to provide such support and have been a continual and up-to-date source of evidence for DISCI since.

Finland offers an ideal framework for studies of complex disorders by virtue of its relative genetic and environmental homogeneity, the existence of comprehensive health registries, and the consistency of medical training.15,16 A number of linkage-based studies have been published at various stages in the Finnish sample collection, with chromosome 1q linkage and association being the most consistent observation. Prior to the discovery of DISCI, Hovatta and colleagues published the finding of a haplotype linked to schizophrenia (Zmax = 3.82) that spanned from 1q32.2 to 1q41 in an internal subsisolate of Finland.17 Two years later Ekelund and colleagues reported on a fine-mapping study of chromosome 1, using families ascertainment from all over Finland.18 The DISCI intragenic marker DISCI709 showed evidence for linkage to schizophrenia in the whole population of Finland (Zmax = 2.71), with the strongest evidence being from those families not originating from the internal subsisolate (Zmax = 3.21).18 Since then, the Finnish family sample has been expanded with more families participating in the study. This enabled Ekelund and colleagues to revisit the findings on chromosome 1 with the use of a completely independent, but identically ascertainment, sample. Once again, linkage was observed with a marker intragenic of DISCI, this time with a single nucleotide polymorphism (SNP) marker (rs1000731, LOD = 2.70),19 at a level that surpasses the threshold for replication set in Lander and Kruglyak’s seminal paper.20 This was followed up with an association analysis, which identified a 3 SNP haplotype that was overtransmitted to affected individuals in these families.19

Chronologically after, but published before this finding, a follow-up study monitored the allelic diversity of the 1q42 region in what was then the largest Finnish family cohort, consisting of 495 nuclear families. Hennah and colleagues reported the identification of 4 restricted loci, named HEP haplotypes, which associated with a broad diagnostic criterion that consisted primarily of schizophrenia, but also included individuals affected with other schizophrenia spectrum diagnoses, as well as affective disorders.21 The most statistically robust among the 4 observed haplotypes was the HEP3 haplotype, which consisted of 2 DISCI SNPs, including the nonsynonymous rs3738401 (Arg264Gln) located in DISCI exon 2.21 Intriguingly, this observation was for significant undertransmission of the haplotype to affected female individuals.

Dichotomized traits based on factor analysis of the Operational Criteria Checklist of Psychotic Illness22 were used to further the association study in Finnish families. The HEP3 haplotype was found to be associated to traits representing negative symptoms, and delusions and hallucinations.21 Parallel studies in 2 independent Finnish study samples further refined the interpretation of the
DISC1 “risk” phenotype. Gasperoni and colleagues analyzed the markers within the “Hovatta” haplotype in a sample of twins, containing concordant and discordant pairs with schizophrenia and a set of unaffected pairs. The most telomeric (1q41) markers provided increasing evidence of association to neurocognitive endophenotypes of schizophrenia that represent spatial and visual working memory. When Paunio and colleagues performed genome-wide analyses for neurocognitive traits in a subset of the Finnish families, evidence of linkage (LOD > 1.5) was noted at the 1q41-q42 locus for 3 traits representative of verbal memory functions. On direct testing for association to these neurocognitive endophenotypes of schizophrenia in Finnish families, the HEP3 haplotype was observed to associate with poorer performance in males for a task representative of visual working memory. The apparent paradox—between this observed poorer performances in males compared with the original undertransmission to females—led Hennah and colleagues to reevaluate their original finding using a population-based control sample. They concluded that the schizophrenia family sample has an overrepresentation of the HEP3 allelic haplotype, which resulted in the observation of the epiphenomenon of undertransmission to affected females, when there was really overtransmission to affected males. The HEP haplotypes were also analyzed in the twin sample for association to neurocognitive traits and neuroimaging-based phenotypes. Cannon and colleagues observed that the haplotypes displayed association toward spatial and visual working memory functions and to reduced gray matter volume in the dorsolateral prefrontal cortex.

The next general question was whether linkage and association would be seen for DISC1 in populations other than Finland and, if so, to which traits. Linkage for 1q42 has now been reported in other populations for schizophrenia, schizoaffective disorder, and bipolar affective disorder. Likewise, association for DISC1 has been observed to schizophrenia, schizoaffective disorder, bipolar affective disorder, and major depression, working memory functions, cognition and cognitive aging, and abnormalities in hippocampal structure and function. Consequently, DISC1 is now regarded as one of the best replicated genetic findings with biological plausibility for major mental illness. To date, there have been 2 negative reports, with independent groups utilizing the Japanese population not observing any association between the SNPs they tested and schizophrenia. However, 1 of these studies only looked at 5 SNPs in the DISC1 promoter region and did not attempt to define the allelic spectrum of the 1q42 locus. A visual summary of the published findings for the DISC1 region on 1q is presented in Figure 1.

Interestingly, many of these studies report a sex-dependent effect. In addition to the observations with HEP3 in the Finnish families, before their reevaluation,
Human DISC1 is widely expressed in tissues including the brain, heart, liver, kidney, placenta, and limb.\(^6,45\) Within the brain, expression is strongest in the hippocampus within the granule cells of the dentate gyrus and pyramidal cells.\(^43\) Quantitative PCR from human hippocampal mRNA detects only the L and L\(_v\) transcripts with no amplification detected for the Es or S forms.\(^30\) This suggests that these 2 long isoforms, containing the binding sites of the C-terminus, are the predominant transcripts in the adult hippocampus. Interestingly, both the mutated DISC1 genes so far identified in families would affect these binding sites. In rodents, the expression of the L transcript appears to be developmentally regulated.\(^33,31\) Expression of mouse full-length Disc1 peaks at E13.5, consistent with neurogenesis and cellular migration in the brain, and postnatally at P35, consistent with the onset of puberty in mice.\(^31\) This would suggest a role for DISC1 in corticogenesis and synaptic remodeling, again consistent with the high expression of DISC1 in the dentate gyrus and the olfactory bulb, as these are sites of adult neurogenesis.\(^51,52\)

DISC1 involvement in neurite extension has been demonstrated in experiments both with full-length DISC1 and truncated DISC1.\(^42,53\) DISC1 enhanced neurite extension through an up regulation of its interaction with FEZ1.\(^43\) Despite indications from DISC1 interacting proteins, until recently the involvement of DISC1 in neuronal migration had not been demonstrated. However, RNAi experiments in mouse embryonic brains have clearly shown delays in neuronal migration and reduced dendritic arborization when DISC1 is down regulated.\(^53\) Many of these biological functions are consistent with the psychological\(^25,26,35,36,37\) and neuroimaging\(^26,33\) phenotypes observed to associate with DISC1 in genetic analysis. Indeed recently, it was reported that the 129S6/SvEv strain of mouse is homozygous for a 2 base pair (bp) Disc1 deletion, which introduces a premature stop codon in exon 7.\(^7,54\) Initial examination showed no gross brain structural differences, but when the 129 Disc1 variant was bred onto a C57BL/6 genetic background, the Disc1 mutant mice performed poorly in tests of spatial working memory compared to C57 controls. The 129 strain is the most common genetic background used for making knock-out mice. These are then typically bred onto another genetic background, but the phenotypes ascribed to, for example Ndel1\(^55\) and L11\(^56\) knock-outs should be reevaluated in the light of this new knowledge with respect to Disc1 status.

To summarize, not only is DISC1 expressed in regions of the brain of relevance to psychiatric illness,\(^57\) but also perturbation of DISC1 function results in phenotypes consistent with current theories relating to mental illness. Furthermore, studies of DISC1 may allow us to determine the mechanisms through which psychiatric medications work, or to devise new ones. It has been shown, for example, that the expression of DISC1 is increased in the
hippocampus and frontal cortex in mice treated with atypical antipsychotic medication.\textsuperscript{58} The sites of interaction between DISC1 and its binding partners could be targeted using small molecules or affinity reagents to modulate these interactions.

**Parallel Evidence: The DISC1 Pathway**

Currently, the functions ascribed to DISC1 are largely inferences from the known functions of the proteins that interact with DISC1. It is therefore suggested to play a role in neuronal migration, neurite outgrowth, signal transduction, cyclic adenosine monophosphate (cAMP) signaling, cytoskeleton modulation, and translational regulation (Table 1). The interaction with DISC1 appears to be crucial to the activity of at least some of these proteins, with studies showing that binding to DISC1 modulates the function of FEZ1, NDEL1, and PDE4B.\textsuperscript{13,42,59} Future investigations will hopefully elucidate the molecular mechanism by which DISC1 regulates the activity of these protein-binding partners, leading to a better understanding of the role of DISC1 at the cellular level and ultimately at the level of brain function.

Even at this stage of partial knowledge, a reasonable hypothesis would be that disruption of other components of the DISC1 pathway could influence susceptibility to schizophrenia and related disorders. Support for this hypothesis comes from initial evidence from human and animal studies. FEZ1 was observed to associate with schizophrenia for homozygous carriers of 2 rare SNPs in the Japanese population.\textsuperscript{60} PDE4B has been found to be disrupted by a translocation breakpoint in 2 related individuals with psychosis in Scotland.\textsuperscript{13} Most recently, NDE1 has been observed to be overtransmitted to affected females with a broad spectrum of schizophrenia-related illnesses in the same Finnish families that originally highlighted DISC1 (Hennah et al., meeting abstract, *Am J Med Genet B Neuropsychiatr Genet.* 2005; 138B:123). The LIS1, NDE1, and NDEL1 genes are involved in neuronal migration. Knock-out models of these genes display disruptions of cortical and hippocampal organization,\textsuperscript{55,56,61,62} lending credence to the genetic findings linking DISC1 to gray matter volume in the dorsolateral prefrontal cortex\textsuperscript{26} and abnormalities in the hippocampus in humans.\textsuperscript{33} A recent expression study compared mRNA levels between the postmortem tissue of patients with schizophrenia and controls. Although

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<th>Gene\textsuperscript{a}</th>
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*Note:* This table shows DISC1 binding partners, their function, and evidence for a possible role in mental illness. The functions ascribed to DISC1 are largely through interpretation based on the known functions of these proteins.

\textsuperscript{a}See\textsuperscript{35} unless otherwise stated.

\textsuperscript{b}DLPFC = dorsolateral prefrontal cortex.
the researchers were unable to observe a significant difference in the DISC1 mRNA expression, their analysis of transcript levels of 3 DISC1 binding partners showed such a difference. The steady state transcript levels of NDEL1, LIS1, and FEZ1 all showed reduced quantities in the hippocampus, with FEZ1 also showing reduction of expression in the dorsolateral prefrontal cortex.\(^\text{50}\) Lipska and colleagues also state that this reduced expression is associated with the rs821616 (Ser704Cys) polymorphism in the DISC1 gene.\(^\text{50}\) However, the data presented is unclear as to whether this is an epiphenomenon of the fact that both the polymorphism and expression levels associate with schizophrenia, since similar association was not observed in the control samples.

Further, DISC1 has been shown to interact dynamically in a cAMP dependent manner with Phosphodiesterase 4B (PDE4B), which is the sole mechanism for inactivation of cellular cAMP, a key signaling molecule in the brain. Additionally, PDE4 is the pharmacological target for the antidepressant Rolipram.\(^\text{13}\) PDE4B and PDE4D are homologs of the fruit fly dunce gene, null mutations that give rise to a profound learning and memory deficit.\(^\text{63}\) Mouse mutants of PDE4B and PDE4D display behaviors that mimic the effects of antidepressants on normal mice.\(^\text{64,65}\) These observations provide a potential mechanistic link of DISC1-PDE4B to learning and memory and an etiological link between schizophrenia and bipolar disorder.\(^\text{13}\)

Although the recent focus of research in psychiatric genetics has been on DISC1, it is now clear from the emerging biology that this should be broadened to consider the wider DISC1 pathway.

**Conclusions**

Genetic associations with DISC1 have been demonstrated for multiple psychiatric illnesses, with certain psychological traits, and with aspects of brain physiology and anatomy. DISC1 has also been shown to interact with multiple proteins involved in functions thought to be highly relevant to the development of mental illness. The evidence is that DISC1 and a number of interacting proteins function in neuronal migration, cortical layering during fetal brain development, hippocampal formation, and probably adult neurogenesis in the dentate gyrus, all of which is consistent with the neurodevelopmental hypothesis of schizophrenia. It seems clear that the interacting proteins of the DISC1 pathway are functional candidates for involvement in neurodevelopmental and psychiatric disorders, for which there is already some supporting genetic evidence. If, as now appears likely, the DISC1 pathway is critical for normal brain development, then it will be of great interest to test this in pediatric and adolescent brain developmental and psychiatric disorders. Further, the dynamic interaction between DISC1 and PDE4 suggests a role in synaptic remodeling and learning and memory, an imbalance of which may also underlie fundamental features of schizophrenia and related disorders in adults. The role of DISC1 at these 2 key time points in the development of many mental illnesses is emphasized through the evidence that its expression levels peak at the equivalent developmental stages in mice.\(^\text{51}\)

To conclude, the evidence for DISC1 being a causal factor in major mental illness is strongly supported by a raft of independent genetic studies and by the growing evidence from biological studies. That said, with the exception of the t(1;11), the data for explanatory functional variants in the gene and protein are still lacking. Much still needs to be understood about the biology of DISC1 and of DISC1 interacting partners, in human and other species. However, the DISC1 pathway currently offers avenues for exploring the molecular etiology of both normal and abnormal brain development. Such studies have the potential to produce new levels of understanding and possibly more effective interventions for disorders that are among the most common and debilitating of human conditions, major mental illness.

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