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Beyond Schizophrenia: The Role of *DISC1* in Major Mental Illness

William Hennah[1,2], Pippa Thomson[1,3], Leena Peltonen[2,4,5], and David Porteous[3]

[2]Department of Molecular Medicine, National Public Health Institute, Helsinki, Finland; [3]Medical Genetics Section, University of Edinburgh, Edinburgh, Scotland; [4]Department of Medical Genetics, University of Helsinki, Helsinki, Finland; [5]The Broad Institute, Massachusetts Institute of Technology, Boston, MA, USA

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 *NRG1*.[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

[1]To whom correspondence should be addressed; e-mail: william.hennah@ktl.fi or pippa.thomson@ed.ac.uk.

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 familial 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 *DISC1*, but this is not unexpected due to the rarity of such events. However, a frameshift mutation in *DISC1* 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 *DISC1* in the etiology of major mental illness, the outstanding question was whether *DISC1* 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 *DISC1* 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 *DISC1*, Hovatta and colleagues published the finding of a haplotype linked to schizophrenia ($Z_{max} = 3.82$) that spanned from 1q32.2 to 1q41 in an internal subisolate of Finland.[17] Two years later Ekelund and colleagues reported on a fine-mapping study of chromosome 1, using families ascertained from all over Finland.[18] The *DISC1* intragenic marker *D1S2709* showed evidence for linkage to schizophrenia in the whole population of Finland ($Z_{max} = 2.71$), with the strongest evidence being from those families not originating from the internal subisolate ($Z_{max} = 3.21$).[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 ascertained, sample. Once again, linkage was observed with a marker intragenic of *DISC1*, 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 *DISC1* SNPs, including the nonsynonymous rs3738401 (Arg264Gln) located in *DISC1* 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 Illness[22] 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.[23] 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.[24] 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.[25] 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.[25] 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.[26]

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,[27] schizoaffective disorder,[28] and bipolar affective disorder.[29–31] Likewise, association for *DISC1* has been observed to schizophrenia, schizoaffective disorder, bipolar affective disorder, and major depression,[32–35] working memory functions,[36] cognition and cognitive aging,[33,37] and abnormalities in hippocampal structure and function.[33] Consequently, *DISC1* is now regarded as one of the best replicated genetic findings with biological plausibility for major mental illness.[38] To date, there have been 2 negative reports,[39,40] 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.[39] 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,

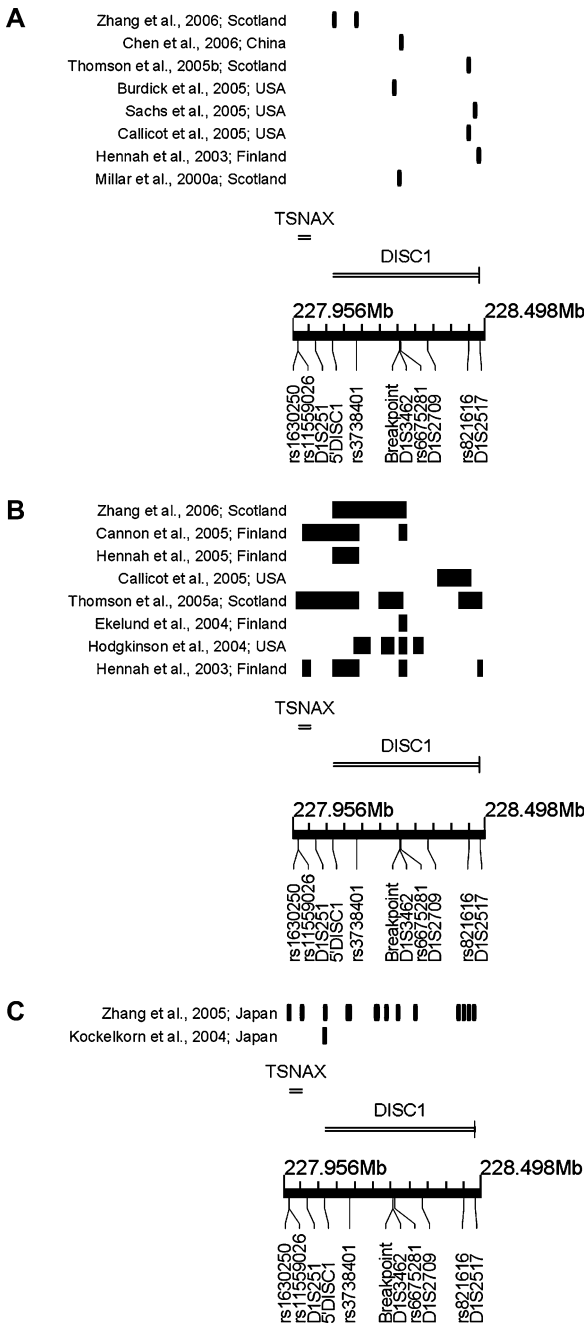

Fig. 1. Overview of the Published Findings on *DISC1* and *TSNAX* (*TRAX*), Produced Using the LocusView Program (Petryshen T, Kirby A, Ainscow M., unpublished software) and Edited. (a) Reported findings at single loci. (b) Reported findings based on haplotypes. (c) The location of the markers used for analysis in the two studies that have not observed association to this region. The markers named at the bottom of each figure are to show the locations of the microsatellite markers and the nonsynonymous SNPs within the region, as well as the location of the original translocation breakpoint.

the undertransmission to females of the same HEP3 allelic haplotype was reported in an American sample using a case-control study design.[32] Further, Thomson and colleagues[35] described 3 restricted regions of the 1q42 locus that associate with either schizophrenia or bipolar disorder in Scottish sample material. In each region sex differences were observed, region 1 being male-specific, region 2 being female-specific, and region 3 showing a variable pattern, depending on the allelic haplotype tested.[35] Analysis of the relationship between *DISC1* and cognitive aging in an elderly Scottish cohort again showed sex-specific affects, the genotype of T/T at rs821616 (Ser704Cys) appearing to be protective in males, but detrimental in females, for a task of verbal reasoning.[37] Most recently, in a genome-wide scan focusing on schizoaffective disorder, Hamshere and colleagues reported that their observed linkage on 1q42.2 increased when sex was taken as a covariate, noting that allele sharing was increased at this locus between male-male and female-female siblings when compared with male-female siblings.[28]

Although there seems to be plenty of genetic evidence for the involvement of *DISC1,* observations have been to multiple allelic variations from restricted regions located throughout the 1q42 locus. The primary reason for this is that the association studies reported to date have selected different SNP sets for typing. In those studies that do report association with a single SNP, it is either weak,[41] rare,[21] surpassed by haplotype observations,[33–35] or only 1 SNP has been tested.[37] Systematic analysis of the locus, to capture the full extent of genetic variation at the *DISC1* locus, needs to be performed in a large study sample to be able to define the specific allele(s) or variants associated with psychiatric disorders or their trait components in different populations.

The Biology of *DISC1*

Human *DISC1* is a large gene containing 13 exons spanning over 410 kilobase pairs of genomic DNA. The N-terminal region of the protein is predicted to form 1 or more globular head domains, while the C-terminal contains regions of coiled-coil forming potential.[5] A bipartite nuclear localization signal (NLS) and 3 leucine zipper motifs are also present. Analysis of human transcripts has identified 4 *DISC1* isoforms (long, L; long variant, Lv; short, S; and extra short, Es), resulting in multiple protein isoforms. The proteins predicted from these transcripts contain some, but not all, of the known binding sites for DISC1 interacting molecules, perhaps indicating different functional roles. The relationship between the transcripts and protein isoforms has not been formally identified.

Immunostaining with DISC1 antibodies has shown that DISC1 occupies multiple subcellular locations, including mitochondria, cytoplasmic puncta/stress granules, the nucleus, centrosome, and actin filaments.[42–49] 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.[45] Quantitative PCR from human hippocampal mRNA detects only the L and Lv transcripts with no amplification detected for the Es or S forms.[50] 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.[43,51] 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.[51] 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[25,26,33,36,37] 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 25 base pair (bp) *Disc1* deletion, which introduces a premature stop codon in exon 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 *Lis1*[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.[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.[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.[60] *PDE4B* has been found to be disrupted by a translocation breakpoint in 2 related individuals with psychosis in Scotland.[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,[55,56,61,62] lending credence to the genetic findings linking *DISC1* to gray matter volume in the dorsolateral prefrontal cortex[26] and abnormalities in the hippocampus in humans.[33] A recent expression study compared mRNA levels between the postmortem tissue of patients with schizophrenia and controls. Although

Table 1. DISC1 Interacting Partners

Gene[#]	Location	Function	Genetic Evidence	Animal Model	Expression Evidence[50]
PDE4B[13]	1p31.2	cAMP signaling	Millar et al. (2005)[13]	Learning and memory[63]	
MIP-T3	2q37.3	Signal transduction			
PDE4D[13]	5q11.2-q12.1	cAMP signaling		Learning and memory[63]	
FEZ1	11q24.2	Neurite outgrowth	Yamada et al. (2004)[60]		Decreased in DLPFC[^] and hippocampus
MAP1A	15q15.3	Neurite outgrowth			
NDE1	16p13	Neuronal migration	Hennah et al. (2005) meeting abstract	Disordered cortex[62]	
LIS1	17p13.3	Neuronal migration		Learning and memory;[61] Neuronal migration deficits[56]	Decreased in hippocampus
NDEL1	17p13.1	Neuronal migration		Neuronal migration deficits[55]	Decreased in hippocampus
ATF5	19q13.33	Signal transduction			
PCNT2	21q22.3	Cytoskeletal modulation			
ATF4	22q13.1	Signal transduction			
Dynactin[53]	multiple	Neuronal migration			
Dynein[53]	multiple	Neuronal migration			
eIF3[47]	multiple	Translational regulation			
tubulin	multiple	Cytoskeletal Modulation			

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.
[#]See[35] unless otherwise stated.
[^]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.[50] Lipska and colleagues also state that this reduced expression is associated with the rs821616 (Ser704Cys) polymorphism in the *DISC1* gene.[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.[13] *PDE4B* and *PDE4D* are homologs of the fruit fly dunce gene, null mutations that give rise to a profound learning and memory deficit.[63] Mouse mutants of *PDE4B* and *PDE4D* display behaviors that mimic the effects of antidepressants on normal mice.[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.[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.[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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