The Genetics and Biology of Disc1—An Emerging Role in Psychosis and Cognition

David J. Porteous, Pippa Thomson, Nicholas J. Brandon, and J. Kirsty Millar

In the developing field of biological psychiatry, DISC1 stands out by virtue of there being credible evidence, both genetic and biological, for a role in determining susceptibility to schizophrenia and related disorders. We highlight the methodologic paradigm that led to identification of DISC1 and review the supporting genetic and biological evidence. The original finding of DISC1 as a gene disrupted by a balanced translocation on chromosome 1q42 that segregates with schizophrenia, bipolar disorder, and recurrent major depression has sparked a number of confirmatory linkage and association studies. These indicate that DISC1 is a generalizable genetic risk factor for psychiatric illness that also influences cognition in healthy subjects. DISC1 has also been shown to interact with a number of proteins with neurobiological pedigrees, including Ndel1 (NUDEL), a key regulator of neuronal migration with endo-oligopeptidase activity, and PDE4B, a phosphodiesterase that is critical for cyclic adenosine monophosphate signaling and that is directly linked to learning, memory, and mood. Both are potential "drug" targets. DISC1 has thus emerged as a key molecular player in the etiology of major mental illness and in normal brain processes.

Key Words: Bipolar affective disorder, cognition, DISC1, NUDEL, PDE4B, schizophrenia

Abundant evidence from family, twin, and adoption studies suggests a substantial genetic contribution to the risk of developing schizophrenia, bipolar affective disorder, and related major mental illnesses, but the road to gene discovery has been rocky with several false trails. It is not the purpose of this review to consider critically alternative strategies for charting a successful course to gene discovery but rather to highlight one successful strategy that we employed to identify the DISC1 gene. Suffice to say that classical linkage studies have the power and resolution to identify loci but rarely genes, whereas candidate gene association studies and, more so, prospective whole genome association studies are problematic, not least because of multiple testing, the presence of variable extents of linkage disequilibrium, and the absence of biologically confirmed causal variants. Molecular cytogenetics is a powerful alternative genome-wide strategy to nominate candidate genes. This is how the DISC1 gene (Millar et al 2000) and others (MacIntyre et al 2003) were identified. The one fundamental presupposition is that in the proband the cytogenetic event is necessary and sufficient to predispose to the observed psychiatric phenotypes.

The Molecular Cytogenetics Strategy

In the molecular cytogenetics strategy, chromosome spreads (metaphase or interphase) are examined for evidence of cytogenetic anomalies, and promising finds are followed up using chromosome paints and thereafter probes of higher resolution (typically BAC clones) to define the rearrangement at the molecular level (Pickard et al 2005b). It is important to note, however, that no assertion is made here that cytogenetic rearrangements (chromosome translocations, inversion, deletions, and duplications) account for a substantial proportion of the trait variance or disease liability. Rather, this is a powerful discovery strategy for possibly unique or rare events that offers the possibility of a potential genetic route of causation. Once identified, these are then directly testable for their wider relevance.

Psychiatric Illness Cosegregating with a Balanced Chromosomal Translocation

The discovery of DISC1 has its roots in prescient studies of chromosomal abnormalities undertaken by the MRC Population and Cytogenetics (now Human Genetics) Unit in Edinburgh, UK (Jacobs et al 1970). St. Clair et al (1990) searched the cytogenetics database for any cases with an associated psychiatric diagnosis, followed up this case and family members, conducted a psychiatric and cytogenetic examination, and reported that the balanced translocation between chromosomes 1 and 11 originally identified in the proband (a young person with adolescent conduct disorder) was inherited and present in about half of the family members. Strikingly, the family had a high loading of major mental illness that cosegregated with the t(1;11) translocation with high statistical significance. The log of the odds (LOD) score was 3.4 when the diagnosis was restricted to schizophrenia alone. This equates with a probability of less than one in a thousand of observing this cosegregation pattern by chance. Thirty years after the proband was first identified, Blackwood et al (2001) demonstrated the enormous value of long-term clinical follow-up and the evolving nature of psychiatric illness. Of 29 individuals on whom cytogenetic analysis had confirmed the presence of the translocation, 7 had a diagnosis of schizophrenia, 1 bipolar affective disorder, and 10 recurrent major depression (or MMD). Thus, 18 of 29 (70%) translocation carriers had a diagnosis of major mental illness, whereas none of 38 nontranslocation carriers had such a diagnosis—compelling statistical evidence for a causal link between the t(1;11) and the psychiatric liability in this unique family (LOD = 7.1, or less than a 1 in 10 million probability of chance occurrence). Moreover, Blackwood et al (2001) also reported that in unaffected translocation carriers the latency and amplitude of the event related potential (ERP) P300 was indistinguishable from those of affected individuals and that as a group the translocation carriers showed the characteristic abnormal ERP P300 associated with SCZ and with BP.

To summarize, the pattern of inheritance in the t(1;11) family is consistent with a simple dominant mode of inheritance with reduced penetrance, with altered ERP P300 as a correlated endophenotype. Epidemiological, family, and twin studies all point to a high heritability for schizophrenia and for bipolar

From the Medical Genetics Section (DJP, PT, JKM), Molecular Medicine Centre, University of Edinburgh, Crewe Road South, Edinburgh; Merck Sharp and Dohme (NJB), Terlings Park, Harlow, Essex, United Kingdom.

Address reprint requests to Medical Genetics Section, Molecular Medicine Centre, University of Edinburgh, Crewe Road South, Edinburgh; E-mail: david.porteous@ed.ac.uk.

Received December 7, 2005; revised March 31, 2006; accepted April 4, 2006.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2006.04.008

© 2006 Society of Biological Psychiatry

affective disorder, with MZ concordances rates of .5–.8 (Kendler et al 1993; McGuffin et al 2003; Sullivan et al 2003). Thus, in this family the t(1;11) accounts for essentially all of the expected transmitted risk. Secondary and independently segregating genetic risk factors, variable environmental exposures, or stochastic events may influence the presence or absence of clinical signs and the specific psychiatric diagnosis. One final point worth emphasizing is that the t(1;11) apart, there were no other distinguishing clinical features of the psychiatric presentations (Blackwood et al 2001).

Positional Cloning of the DISC1 Gene

A variety of hypothetical mechanisms (long-range position effect on transcription, novel gene fusion product, etc) could be invoked to explain the causal link between the t(1;11) and psychiatric illness, but Ocam's razor suggested looking for evidence of direct disruption of a gene at the translocation breakpoints (Millar et al 2000; Muir et al 1995). There was no evidence for gene disruption on chromosome 11 but clear evidence for direct disruption of what became known as the Disrupted in Schizophrenia (DISC) locus (Millar et al 2000). In fact, the evidence was for not one but two genes disrupted. The DISC1 gene occupies approximately 415 kb of genomic DNA, comprises a 13-exon transcript of about 7.5 kb, and encodes a novel protein of 854 amino acids (Millar et al 2000). The genomic structure and amino acid sequence is conserved across primates, rodents, and fish, but there is no obvious insect or worm homologue (Taylor et al 2003). Antiparallel and antisense to DISC1 is an apparently RNA-only gene, DISC2. The DISC2 transcript is at least 15 kb long and therefore joins a small but interesting class of RNA-only genes that are thought to be negative regulators of their protein-coding counterparts (Taylor et al 2003). There is as yet nothing more concrete to say about any possible impact of DISC2 on the psychiatric phenotype, but much more can be said about DISC1.

Evidence for the DISC Locus as a Risk Factor in Psychiatric Illness and Related Traits

Independent evidence for the involvement of DISC1 in psychiatric illness has come from studies of the Finnish population. Ekelund et al (2000) reported a linkage peak (LOD = 2.65) at D1S2833, 1cM proximal to DISC1, for 134 sib pairs affected with schizophrenia and schizoaffective disorder, a result that was further refined using a microsatellite within intron 9 of DISC1, generating a LOD score of 3.21 for schizophrenia, plus schizoaffective disorder and schizophrenia spectrum (Ekelund et al 2001). This linkage has since been replicated in an independent Finnish population sample (LOD = 2.7 for a SNP in intron 9; Ekelund et al 2004). Other studies of Taiwanese, North American, Icelandic, and British subjects have all shown suggestive linkage between psychiatric illness and the 1q42 region using broad phenotype models (Table 1). Recently, a genome scan of families ascertained for schizoaffective disorder (rather than schizophrenia or bipolar disorder) generated a LOD score of 3.54 for a microsatellite in 1q42.2 (Hamshere et al 2005). Thus, as first noted in the t(1;11) family, variants at the DISC locus appear to predispose to a wide spectrum of psychiatric disorders in the general population.

Association studies have also been supportive but must be interpreted with some caution because there is likely to be a publication bias toward positive findings. Moreover, there is only partial overlap between the markers used and the phenotypes tested in these independent studies (Figure 1). Devon et al (2001) sequenced the exons and intron–exon boundaries of DISC1 and reported 15 novel polymorphisms including the common Ser704Cys polymorphism in exon 11. No evidence of single marker association was observed, but this was a preliminary study of low power designed primarily to discover and report potentially useful polymorphisms. Hennah et al (2003) reported an association study on a sample of 458 Finnish families with probands ascertained for schizophrenia, but applying a broad diagnosis of affected status to relatives (schizophrenia, schizoaffective disorder, schizotypal disorder, bipolar disorder and recurrent major depression). They found a number of associated haplotypes of which HEP3, which spans 62kb from intron 1 to exon 2, was the most statistically robust. HEP3 shows undertransmission only to affected females ($p = .00024$) implying a sex-specific effect of variants in DISC1. In females, the undertransmitted haplotype was significantly associated with delusions, hallucinations, and negative-component-traits, but not with manic or depressive symptoms. The exon 9 haplotype (HEP1) has been replicated in an independent sample from the Finnish population using the same SNPs (Ekelund et al 2004). In North American study samples, Callicott et al (2005) reported haplotype association with schizophrenia ($p = .002$), whereas Hodgkinson et al (2004) reported association to schizophrenia, to schizoaffective disorder and to bipolar disorder as discrete diagnoses ($p = .05$, $p = .0000023$, and $p < .01$, respectively). The fourth major study was performed in the same population from which the original translocation family was identified (Thomson et al 2005b). This study identified tagging SNPs monitoring haplotypes within DISC1 and tested case control samples of both schizophrenia and bipolar disorder. Consistent with the linkage results from this population (Macgregor et al 2004), the strongest association was seen with bipolar disorder ($p = .0016$), although

Table 1. Tables of Studies with Significant LOD Score in the Region of 1q42

Study	Diagnoses	Marker	LOD	Position
Blackwood et al 2001	SCZ, BP, RMD	Translocation	7.1	Intron 8
Ekelund et al 2001	SCZ, SCZAFF, SCZTYP	D1S2709	3.21	Intron 9
Ekelund et al 2004	SCZ, SCZAFF, SCZTYP	rs1000731	2.7	Intron 9
Hwu et al 2003	SCZ, SCZAFF, SCZ TYP	D1S251	1.2	1q42
Gejman et al 1993	BP, RMD, SCZAFF	D1S103	2.39	1q42
Detera-Wadleigh et al 1999	BP, RMD, SCZAFF	D1S1660-D1S1678	2.67	1q25-42
Macgregor et al 2004	BP	D1S103	2.63	1q42
Curtis et al 2003	BP	D1S251	1.1, 2.5	1q42
Hamshere et al 2005	SCZAFF, SCZ, BP	D1S2800	3.54	1q42

BP, bipolar disorder; LOD, log of the odds score; SCZ, schizophrenia; RMD, recurrent major depression; SCZAFF, schizoaffective disorder; SCZSPEC, schizophrenia spectrum; SCZTYP, schizotypal.

Download English Version:

https://daneshyari.com/en/article/4180132

Download Persian Version:

https://daneshyari.com/article/4180132

Daneshyari.com