Published in final edited form as:
Front Biol (Beijing). 2013 February 1; 8(1): 1–31. doi:10.1007/s11515-012-1254-7.

DISC1 genetics, biology and psychiatric illness

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Abstract

Psychiatric disorders are highly heritable, and in many individuals likely arise from the combined effects of genes and the environment. A substantial body of evidence points towards DISC1 being one of the genes that influence risk of schizophrenia, bipolar disorder and depression, and functional studies of DISC1 consequently have the potential to reveal much about the pathways that lead to major mental illness. Here, we review the evidence that DISC1 influences disease risk through effects upon multiple critical pathways in the developing and adult brain.

Keywords

DISC1; schizophrenia; depression; genetics; neural pathways

1 Introduction

Schizophrenia and bipolar disorder jointly affect approximately 2% of the world's population and, together with depression, account for three of the top ten leading causes of disability (measured as missed days at work) (Lopez and Murray, 1998). These disorders are devastating for the affected individual and their family, and they impact upon society as a whole at many levels. Indeed, in terms of financial burden, the cost of schizophrenia alone was estimated to be >$60 billion in the United States in 2002 (McEvoy, 2007). Consequently, significant effort has been put into understanding the causes of major mental illness and finding effective treatments. Schizophrenia, bipolar disorder and depression are highly heritable, thus one approach towards understanding the underlying disease mechanisms is to identify the genes that influence disease risk. For psychiatric illness, this is proving extremely difficult, likely due to interplay between the effects of multiple genes plus environmental influences. In fact, psychiatric disorders are considered to be common complex genetic disorders, with polygenic or even oligogenic causation in some individuals (Porteous, 2008;Gershon et al., 2011;Sullivan et al., 2012). However, a small number of genes are emerging as convincing risk factors, at least in some patients, including Disrupted In Schizophrenia 1 (DISC1). In this review we will discuss the evidence supporting the role of DISC1 in risk of major mental illness. We will then go on to review what functional

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studies of DISC1 have revealed about its role in the brain, and hence the molecular events that may underlie psychiatric illness (Figure 1).

2 The t(1;11)(q42.1,q14.3) translocation

In 1970 a survey of chromosomal rearrangements in samples referred for clinical cytogenetic analysis identified a reciprocal chromosomal t(1:11) translocation in an individual with adolescent conduct disorder. Investigation of the extended family generated a genome-wide significant linkage score for co-segregation of the translocation with multiple cases of schizophrenia and major depressive disorder and a single case of bipolar disorder (logarithm of the odds ratio (LOD) = 7.1). The linkage to schizophrenia alone also reached genome-wide significance (LOD= 3.6), as did linkage to affective disorders (LOD=4.5) (Blackwood et al., 2001). Inheritance of the translocation thus confers significantly increased risk of developing these disorders. However, it should be noted that penetrance is incomplete and there are family members with a normal karyotype who have been diagnosed with a psychiatric disorder, although none with major mental illness (Blackwood et al., 2001). This translocation is unique to this one Scottish family, and is one of the most convincing causative mutations identified for major mental illness to date. Studying the effects of this translocation therefore has the potential to reveal much about the pathways underlying psychiatric disorders.

The P300 event-related potential (ERP), a measure of the speed and efficiency of information processing, has been examined in multiple members of the t(1;11) family because it is believed to provide a measure of brain function that is independent of the environmental influences that affect disease penetrance and presentation. Translocation carriers were found to have significantly reduced P300 amplitude and latency, similar to subjects with schizophrenia, but different from karyotypically normal family members and unrelated controls (Blackwood et al., 2001). Furthermore, the translocation carriers in the study included individuals with no psychiatric diagnosis, indicating that inheritance of the translocation results in subtle disturbances of brain function in all individuals, even though it only leads to major psychiatric illness in a subgroup. A major unanswered question then, is how this mutation has such variable penetrance and presentation.

We demonstrated that on chromosome 1 the translocation directly disrupts the Disrupted In Schizophrenia 1 (DISC1) gene, and its non-coding antisense partner DISC2 (Millar et al., 2000b), and that DISC1 expression is reduced by approximately 50% at the transcript and protein level in lymphoblastoid cell lines derived from t(1;11) translocation carriers (Millar et al., 2005b). DISC1 haploinsufficiency is thus likely to be a major component of the mechanism by which the translocation increases disease risk. This is unlikely to be the only factor however, because DISC2, like DISC1, is brain-expressed (Millar et al., 2000b). Moreover, there is a third disrupted gene, DISC1 Fusion Partner 1 (DISC1FP1, also known as Boymaw) on chromosome 11 (Zhou et al., 2008b;Eykelenboom et al., 2012). Like DISC2, DISC1FP1 is non-coding and brain-expressed (Zhou et al., 2010). Loss of normal function of all three genes may thus contribute to the disease mechanism. However, unlike the DISC locus on chromosome 1 (see later), there is limited independent genetic evidence for involvement of DISC1FP1 in psychiatric disorders, although association with a nearby Single Nucleotide Polymorphism (SNP), rs2509382, has been reported in male patients diagnosed with schizophrenia (Debono et al., 2012). Analysis of the Psychiatric Genetics Consortium Genome-Wide Association Study (GWAS) data using Ricopili (www.broadinstitute.org/mpg/ricopili/) revealed that there is weak additional evidence for association of DISC1FP1 with schizophrenia (p=0.00096 with rs10501738), bipolar disorder (p=0.00052 with rs56163) and major depressive disorder (p=0.001 with rs4635043),

although this did not reach genome-wide significance. This suggests that more associations may be found if this region is examined in detail.

The disease mechanism may be complicated still further by the fusion of the DISC1 and DISC1FP1 genes as a result of the translocation. Zhou et al speculated that this would result in production of chimeric transcripts (Zhou et al., 2008b), and indeed we demonstrated experimentally that this is the case (Eykelenboom et al., 2012). In lymphoblastoid cell lines derived from t(1;11) carriers at least four distinct chimeric transcripts are detectable. One, directed by the DISC1FP1 promoter on the derived 11 chromosome, encodes a C-terminal fragment of DISC1, but this is unlikely to be translated. Three, directed by the DISC1 promoter on the derived 1 chromosome, encode DISC1 amino acids 1-597 plus 1, 60 or 69 amino acids arising from translation of the normally non-coding DISC1FP1 sequence, and have been named CP1, CP60 and CP69, respectively (Eykelenboom et al., 2012). Notably, CP1 is almost equivalent to $DISC1^{1-597}$, a truncated species examined in many functional studies prior to discovery of the chimeric transcripts. The additional 69 novel amino acids in CP69 result in structural alterations and all three proteins behave aberrantly when exogenously overexpressed (Zhou et al., 2010;Eykelenboom et al., 2012). It is therefore likely that if expressed in the brains of t(1;11) translocation carriers the chimeric proteins would have multiple effects. However, while there is no obvious reason why the chimeric transcripts should not be brain-expressed (this cannot currently be tested due to lack of access to suitable tissue), we have been unable to demonstrate that the endogenous chimeric transcripts are translated in lymphoblastoid cell lines derived from translocation carriers (Eykelenboom et al., 2012). Thus it is not yet clear whether these chimeric transcripts and putative chimeric proteins contribute to the disease mechanism in translocation carriers. In the future it will be possible to address these issues using neural/glial material generated using induced pluripotent stem cells derived from t(1;11) translocation carriers.

3 Independent genetic evidence that the DISC locus is involved in risk of major mental illness

Evidence for independent linkage and association of the DISC locus to schizophrenia, schizoaffective disorder, schizophrenia spectrum, bipolar disorder, Asperger's syndrome and autism spectrum disorder was summarised in a review by Chubb et al. in 2008 (Chubb et al., 2008). This review will cover the genetic studies published since Chubb et al., highlighting the evolving areas of interest. Following Chubb et al., recent candidate gene studies focussed on the DISC locus have reported significant findings for the psychiatric diagnoses schizophrenia (Saetre et al., 2008;Song et al., 2008;Rastogi et al., 2009;Hotta et al., 2011), schizoaffective spectrum (Green et al., 2011), bipolar disorder (Hennah et al., 2009;Schosser et al., 2010;Ram Murthy et al., 2012), bipolar spectrum disorder (Song et al., 2010), depression (Schosser et al., 2010;Carless et al., 2011;Thomson et al., 2012), autism (Zheng et al., 2011), and the related traits of age of onset for depression (Thomson et al., 2012) and depression, anxiety and emotional stability (Harris et al., 2010). However genome-wide approaches have identified no clear association between DISC locus variants and schizophrenia, bipolar disorder or recurrent major depression, indicating that no common variants at this locus act independently to substantially increase risk of developing these mental illnesses. Indeed, meta-analysis of all common variants within the DISC locus, from a total of 11626 cases and 15237 controls, and testing 1241 SNPs found no evidence that common variants at the DISC locus are significantly associated with schizophrenia (Mathieson et al., 2012). The lack of signal may result from the heterogeneity/oligogenic variation that is being revealed by the current genome-wide analyses, and the DISC locus continues to feature strongly in attempts to assess genome-wide association results in terms of networks (Jia et al., 2012) or in combination with known biology (Le-Niculescu et al., 2009;Ayalew et al., 2012;Tiwary, 2012).

Despite failing to show clear association of the DISC locus with psychiatric disorders, GWAS studies have found association between variation at the DISC locus and the neurodegenerative disorders late-onset Alzheimer's disease (Beecham et al., 2009) and susceptibility to sporadic amyotrophic lateral sclerosis (OR = 0.499) (Landers et al., 2009). Although, neither of these results has been replicated, this further widens the potential effects of DISC1 variants. Intriguingly, there is biochemical evidence in support of the potential link between DISC1 and Alzheimers disease (Young-Pearse et al., 2010) which will be discussed later in this review.

For psychiatric illness, the focus has shifted to next generation sequencing approaches, with five studies reporting large-scale exon sequencing results. None of these studies identified major causative variants in DISC1, although there is evidence for rare sequence changes that influence disease risk (Song et al., 2008;Song et al., 2010;Green et al., 2011;Moens et al., 2011;Crowley et al., 2012). Song et al. reported increased burden of rare structural variants in both schizophrenia and bipolar disorder. Similarly, Green et al. reported an increase in exon 11 rare variants in a sample of schizoaffective disorder, bipolar type. Finally, Moens et al. used pooled sequencing to examine the burden of rare missense mutations in DISC1 and identified elevated burden, particularly in schizophrenic patients with a young onset age. By contrast, Crowley et al. reported no evidence for evidence for increased burden of rare variants in schizophrenia. It therefore remains to be seen whether surveying the regulatory/intronic regions of DISC1, or examining epistatic interactions within the gene, will uncover the variants underlying the previous reports of haplotypic associations derived from candidate gene studies.

GWAS and sequencing have highlighted the importance of rare genomic events such as the t(1;11) translocation and rare copy number variants (CNVs) in major mental illness, and a number of CNVs involving the DISC locus have now been identified. Subsequent to the identification of DISC1, a rare four base pair deletion at the 3′ end of DISC1 exon 12 was reported in a family with schizoaffective disorder (Sachs et al., 2005). This deletion exhibits incomplete segregation with psychiatric illness within this family and was subsequently identified in unaffected individuals (Green et al., 2006). Its relevance to psychiatric illness therefore remains equivocal, although it is likely to have functional consequences as it is predicted to result in expression of a C-terminally truncated protein (Sachs et al., 2005). In addition to this small deletion, a number of CNVs affecting the DISC locus have been reported. Duplications in the region of the DISC locus have been detected in three individuals, one affected by schizophrenia and two controls drawn from the same population (Buizer-Voskamp et al., 2011). A 2 Mb duplication encompassing seven genes, including DISC1 and DISC2, has also been described in two brothers with autism, ADHD and mild mental retardation (Crepel et al., 2010), although the clinical picture in this family is confused by the appearance of psychiatric symptoms in individuals not carrying the mutation. Additionally, a 2 Mb deletion, encompassing at least TSNAX (immediately upstream of DISC1), DISC1 and DISC2, was identified in a patient diagnosed with autism spectrum disorder (Williams et al., 2009). This deletion was inherited from the unaffected mother. An unenhanced head CT of the proband was normal at 3 years of age, but an MRI evaluation revealed multifocal scattered areas of gliosis and/or abnormal myelination in the bilateral cerebral white matter of unclear etiology. The carrier status of the child's four unaffected siblings is unknown and there is no family history of consanguinity, psychiatric disorders, or autism. Sequencing of the paternal DISC1 coding regions identified two nonsynonymous polymorphisms, L607F and E661K. E661K has not been previously reported and, since amino acid 661 is the terminal amino acid in exon 9, it may have effects on splicing. However this amino acid is poorly conserved and the effect on the protein is likely to be benign. The presence of this paternal DISC1 allele may explain the lack of effect in the mother from whom the deletion was inherited. Altogether these studies indicate that

copy number variants targeting the DISC locus may contribute to risk of mental illness, autism and other neurological disorders.

In addition to these behavioural effects, copy number variants affecting the DISC locus may also have gross effects upon brain structure, specifically, development of the corpus callosum, a fibre tract that connects the right and left hemispheres allowing communication between the two sides of the brain. Osbun et al. fine-mapped a 5.8 Mb deletion encompassing DISC1 in a mother and her two children (Osbun et al., 2011), all of whom have complete agenesis of the corpus callosum (Puthuran et al., 2005). In addition, they found a de novo 13.7 Mb deletion encompassing DISC1 in a second individual with agenesis of the corpus callosum, and four rare inherited, and potentially pathogenic, variants from a cohort of 144 well-characterised patients with this condition. One of these variants is a splice site mutation at the 5′ boundary of exon 11 that dramatically reduces expression of full-length DISC1 mRNA, but not of shorter forms. Consistent with these observations, transgenic mice expressing truncated DISC1 from a BAC exhibit partial agenesis of the corpus callosum (Shen et al., 2008). Indeed, DISC1 is highly expressed in the embryonic mouse corpus callosum at a critical time for callosal formation, suggesting that DISC1 may be critically involved in this process (Osbun et al., 2011). However other large deletions in the region that do not directly affect the DISC1 gene have also been identified in patients with this condition (Gentile et al., 2003;Filges et al., 2010), while another deletion that removes DISC1 was reported in a patient with a normal corpus callosum (Rice et al., 2006). Despite the inconsistencies, these observations are intriguing because agenesis of the corpus callosum is frequently associated with cognitive dysfunction and impaired social behaviour, both of which are present in mental illness and autism, as reviewed by Paul et al. (Paul et al., 2007).

In recent years, there has been an increase in association studies examining the effect of DISC sequence variation on brain structure, in particular grey matter and white matter volume, and cortical thickness. These studies have largely focussed on the nonsynonymous DISC1 exonic variants rs821616 (S704C) or rs6675281 (L607F), or other common variants.

Following the original observations that S704C is associated with altered grey matter volume in the hippocampus and prefrontal cortex (Callicott et al., 2005;Cannon et al., 2005), effects of variants upon grey matter volume have also been found in the prefrontal cortex with L607F (Szeszko et al., 2008), in the hippocampus with S704C (Di Giorgio et al., 2008), in the cingulate cortex with C704 (Hashimoto et al., 2006) and in the left parahippocampal gyrus and right orbitofrontal cortex with rs821597, located within intron 10 (Wei et al., 2012). In addition to the grey matter abnormalities in the prefrontal cortex, negative correlations between grey matter volume and the severity of hallucinations in patients carrying F607 compared to L/L homozygotes have been reported (Szeszko et al., 2008). Prefrontal white matter of individuals carrying the C704 allele exhibits decreased fractional anisotropy in comparison with S/S subjects (Hashimoto et al., 2006), and effects of this variant upon white matter integrity have subsequently been reported, although the allelic effects are somewhat inconsistent (Sprooten et al., 2011;Li et al., 2012).

Effects of L607F and S704C on cortical thickness have been studied and influences upon distinct cortical regions detected (Brauns et al., 2011;Raznahan et al., 2011;Chakravarty et al., 2012). In the right lateral temporal region there appears to be an additive effect of the two SNPs with L/L + C carriers exhibiting greater cortical thickness than F + C carriers (Raznahan et al., 2011). Cortical thickness in the temporal region is also reported to be affected by a SNP in intron 9, rs821589, and two SNPs in intron 1, rs11122319 and rs1417584, which also influence DISC1 expression, with differing effects in cases versus controls (Kahler et al., 2012). In the most comprehensive assessment of DISC1 variation and

cortical thickness, Carless et al. identified a number of DISC1 variants, spanning an interval from intron 1 to the 3′ UTR, associated with cortical thickness in the temporal, parietal and frontal lobes (Carless et al., 2011). However they found no evidence of association with cortical thickness and S704C.

Lateral ventricular enlargement is a consistent characteristic of schizophrenia, and there is evidence that DISC1 influences this anatomical feature. Transgenic mice expressing C-terminally truncated forms of DISC1 exhibit lateral ventricular enlargement (Hikida et al., 2007;Pletnikov et al., 2008;Shen et al., 2008). Consistent with this, SNP rs2793092 within intron 3 is associated with lateral ventricle size in first episode schizophrenics (Mata et al., 2010). However, in this study rs2793092 genotype only predicted lateral ventricular enlargement among those patients also carrying the T allele at SNP rs6994992, located within the highly supported schizophrenia risk factor Neuregulin 1 (NRG1), suggesting that DISC1 and the risk factor NRG1 act in concert to regulate lateral ventricle size. There is further biological evidence that these two genes may act in common or related pathways (Wood et al., 2009;Seshadri et al., 2010) and this will be discussed later in this review.

A number of imaging studies have also examined the effects of variants on brain activation measured by functional MRI (fMRI) of the blood oxygen level-dependent (BOLD) contrast, as a measure of brain activation, during cognitive tasks. Association of the S704 allele has been reported with increased hippocampal activation during memory encoding and greater hippocampal formation–prefrontal cortex coupling in healthy individuals (Di Giorgio et al., 2008). Similarly, the F607 allele has been associated with increased activation of the dorsolateral prefrontal cortex in healthy individuals (Brauns et al.;2011). Prata et al. examined neural activity in healthy (Prata et al., 2008) and schizophrenic or bipolar patients (Prata et al., 2011), and detected increased activation of the prefrontal cortex, cingulate cortex, striatum and thalamus in healthy S704 homozygotes, but this was not replicated in patients with schizophrenia or bipolar disorder. Similarly, the F607 allele significantly affects brain activation in controls, but not in individuals at high risk of schizophrenia or bipolar disorder (Whalley et al., 2012). Prata et al proposed that the lack of effect in their patient population may reflect interaction with other genes associated with psychiatric illness, or indeed the effect of the disorders upon brain function.

Neurocognitive traits have also been studied both as endophenotypes for schizophrenia and to determine the functional consequences of variation at the DISC locus. Independent evidence for an effect of variation upon the P300 event related potential has been reported (Shaikh et al., 2011). This study detected significant associations between P300 amplitude and latency, and polymorphisms/haplotypes in a sample of patients with schizophrenia or psychotic bipolar disorder, their unaffected relatives, and unrelated healthy controls. These results are not robust to multiple-testing correction and will require replication, but they are consistent with the P300 data obtained from the t(1;11) family (Blackwood et al., 2001).

We have reported association been S704C and IQ at age 79, and cognitive ageing between age 11 and age 79 in the Lothian Birth Cohort 1921 (Thomson et al., 2005). However the association with IQ at the slightly younger age of 70 was not replicated in the Lothian Birth Cohort 1936, and in this study replication of the effect upon cognitive aging was not attempted (Houlihan et al., 2009). Positive associations of neurocognitive traits with multiple SNPs and domains have been reported, with the strongest association observed between rs751229, within intron 1, and perseverance (Palo et al., 2007). Carless et al. (Carless et al., 2011) reported association between rs2793094, within intron 3, and spatial working memory, a trait first linked to the DISC locus by Gasperoni et al. in 2003 (Gasperoni et al., 2003).

Genetic epistasis occurs when the genetic effect of one variant is modified by another variant, within either the same or different genes. Multiple studies point to epistatic effects involving DISC1. A joint association study using 67 SNPs tagging common haplotypes across a genomic region spanning DISC1/DISC2 and the upstream gene TSNAX, found no individually significant SNP in a combined European cohort of schizophrenia and bipolar disorder (Hennah et al., 2009). However, two individual SNPs, rs1538979, within intron 4, and rs821577, within intron 9, showed association in Finnish and London samples, respectively. Conditioning the analysis on rs1538979 identified a third SNP, rs821633, within intron 11. The minor allele at rs821633 increases risk dependent on the presence of the minor allele at rs1538979 or rs821577. It is protective if the major allele is present at both other SNPs. Interplay between rs1538979, within intron 4, and r821633, within intron 11, has also been detected in a European meta-analysis of schizophrenia (Schumacher et al., 2009). These studies indicate that interactions between variants in different regions of the DISC locus impact upon disease risk.

Numerous genetic association studies have also reported sex-specific association, suggesting an interaction between sex and genotype upon diagnosis. In contrast, there are no reported interactions between brain structure or function and sex, perhaps due to small sample sizes or the better proximity to the effects of DISC locus variation to these phenotypes compared to the phenotypic outcome as measured by the diagnoses. However interaction has been noted between genotype and diagnosis for fMRI activation (Prata et al., 2008;Chakirova et al., 2011;Prata et al., 2011;Whalley et al., 2012), cortical thickness (Kahler et al., 2012), grey matter density (Wei et al., 2012), and brain morphology (Takahashi et al., 2009). In these studies the effects are either detected in cases or controls or are in the opposite directions between cases and controls. It is possible that this is the result of interaction between risk genes for psychiatric illness. Consistent with this suggestion, as already mentioned, DISC1 and NRG1 may interact genetically to affect lateral ventricular volume (Mata et al., 2010), DISC1 genetic interactions with RELN and ERBB4, two molecules that are essential for many signalling pathways in the brain, also influence regional brain volume (Andreasen et al., 2011).

If the contribution of DISC1 to mental illness does include epistatic interactions these will be difficult to unequivocally detect statistically even given the sample sizes of current meta-analyses (Zuk et al., 2012) and will likely rely on biological determination**.**

In addition to the accumulating genetic evidence for an involvement of the DISC locus in risk of major mental illness, autism spectrum disorders and others, through effects on brain structure and activation, some studies have found effects of DISC1 amino acid variants upon responses to drug treatment. It has been reported that the right medial superior frontal gyrus volume is significantly correlated with daily dosage of antipsychotic medication in S704 homozygote schizophrenia patients, suggesting this this variant may have some effect on medication induced-changes in brain morphology (Takahashi et al., 2009). Association between DISC1 and “ultra-treatment resistant schizophrenia” versus treatment-responsive schizophrenia has been reported in French Caucasian patients for missense variants Q264R and L607F, but not S704C (Mouaffak et al., 2011). However it is worth noting that a separate Japanese study failed to find evidence of association between S704C, and three other variants, and treatment-resistant schizophrenia versus treatment responsive cases (Hotta et al., 2011).

4 Regulation of DISC1 expression

DISC1 expression is extremely complex. A common alternative splicing event within exon 11 giving rise to transcripts encoding the long (L) and long variant (Lv) protein isoforms

was initially identified (Millar et al., 2000b;Taylor et al., 2003), but since then more than 50 differentially spliced transcripts have been reported. It is not clear how many of the differentially spliced DISC1 transcripts identified from human brain tissue (Nakata et al., 2009) are translated, but western blot analyses indicate that there are multiple DISC1 protein species. The alternative transcripts arise principally from use of alternative terminal exons following exons 3 and 9, to encode extremely short (Es) or short (S) isoforms respectively, or from exon skipping, although there is also evidence for use of alternative exons (Taylor et al., 2003;Nakata et al., 2009). In addition we, and others, have identified several intergenic transcripts containing exons of the gene TSNAX, which has an evolutionarily conserved location upstream of the DISC1 gene (Millar et al., 2000a;Nakata et al., 2009). These intergenic transcripts lack the TSNAX terminal exon and the first exon of DISC1, and intriguingly, some contain an uninterrupted open reading frame fusing TSNAX amino acid sequence to that of DISC1. This raises the interesting possibility that TSNAX/DISC1 fusion proteins are biologically relevant, although the existence of such proteins has yet to be demonstrated.

In general, the abundance of human DISC1 transcripts in brain decreases with age, exhibiting greatest expression during development, decreasing at birth, and continuing to decline throughout adult life, with the Δ7Δ8, Δ3 and Esv1 forms found at particularly low abundance in adulthood (Nakata et al., 2009). This expression pattern is paralleled by DISC1 protein expression in rodents which peaks at early postnatal stages, followed by a gradual decline (Austin et al., 2004;Honda et al., 2004;Kuroda et al., 2011).

Notably, hippocampal expression of the Δ7Δ8, Δ3, Esv1 and Lv transcripts is reported to be elevated in patients diagnosed with schizophrenia (Nakata et al., 2009). Moreover, expression of Δ3 transcripts is associated with the intronic SNP rs821597 that influences grey matter volume (Wei et al., 2012), while expression of Δ7Δ8 transcripts is associated with the common disease-associated DISC1 variants L607F and S704C (Nakata et al., 2009). Additional evidence for disturbed DISC1 expression levels in psychiatric patients comes from a study that reported reduced DISC1 transcript levels in lymphoblastoid cell lines derived from patients diagnosed with bipolar disorder (Maeda et al., 2006), and our own demonstration that DISC1 expression, at the transcript and protein level, is reduced by approximately half in lymphoblastoid cell lines derived from carriers of the t(1;11) translocation (Millar et al., 2005b). Moreover, DISC1 transcript levels are increased by clinically relevant doses of the atypical antipsychotic drugs olanzapine and risperidone in mouse frontal cortex and hippocampus (Chiba et al., 2006) and there is preliminary evidence from peripheral blood mononuclear cells that downregulation of DISC1 isoforms may be correlated with treatment response (Olincy et al., 2011). This suggests that some of the drugs used to treat schizophrenia may exert their effects, in part, through modulation of DISC1 expression, and this may underlie the genetic effects described above.

A number of studies thus highlight altered DISC1 expression levels as a potential disease mechanism, indicating the importance of understanding the processes that govern DISC1 transcription and translation. Multiple SNPs across the 5′ region of DISC1 are associated with DISC1 expression levels (Hennah and Porteous, 2009;Carless et al., 2011). The pattern of linkage disequilibrium between these variants suggests that they identify a haplotype block encompassing a variant(s) that affects DISC1 expression level. Moreover, a region 300-177 nucleotides upstream of the transcription start site (TSS) has been identified as the core DISC1 promoter (Walker et al., 2012). However an additional region, 982-301 nucleotides upstream of the TSS, negatively regulates promoter activity (Walker et al., 2012). There are putative transcription factor FOXP2 binding sites within the core *DISC1* promoter region (Spiteri et al., 2007;Rosenbloom et al., 2010) and, consistent with this, FOXP2 inhibits DISC1 promoter activity and protein expression (Walker et al., 2012).

Intriguingly, this negative effect of FOXP2 is counteracted by two distinct FOXP2 mutations, R553H and R328X, that are associated with developmental verbal dyspraxia, a speech and language disorder (Vernes et al., 2006). It will be interesting to now discover whether FOXP2 regulates DISC1 expression *in vivo*, and whether the mutant FOXP2-induced clinical phenotype, which may include an element of cognitive deficit, is related to the predicted resultant increase in DISC1 expression.

There is also evidence that DISC1 expression is regulated by Neuregulins (Seshadri et al., 2010), which may provide a direct functional link between two of the best supported risk factors for major mental illness. Treatment with NRG1 or NRG2 increases expression of a novel 130 kDa DISC1 antibody-immunoreactive species in HEK293 cells, an effect that was observed using two independent antibodies. There is no effect, however, upon other DISC1 isoforms at 100-105 kDa. This effect is mediated by the neuregulin receptors ErbB2 and ErbB3 (but not ErbB4) and activation of PI3K/Akt. A corresponding decrease in the 130 kDa species, but not the 100-105 kDa species, was observed in NRG1 knockout mice, and in BACE1 knockout mice which exhibit dysregulated NRG1 signalling (Seshadri et al., 2010). Moreover, expression of human DISC1$^{1\text{-}597}$ in mouse forebrain influences expression of NRG1, and ErbB3 and ErbB4, and induces abnormalities in oligodendrocyte differentiation and function (Katsel et al., 2011). These observations are consistent with both the evidence for genetic epistasis between the DISC1 and NRG1 genes (Mata et al., 2010), and with the observation that DISC1 and NRG1 apparently function within a common pathway in developing neurons and oligodendrocytes in zebrafish (Wood et al., 2009).

5 DISC1 protein structure

Based upon bioinformatics analysis, the “long” full-length DISC1 sequence (854 amino acids) has been suggested to consist of two regions: (i) an N-terminal “head” region spanning amino acid residues ~1–325, that lacks secondary structure elements and is predicted to contain large stretches of disorder (Soares et al., 2011), but which contains two notable regions of sequence conservation corresponding to a nuclear localization signal motif (Ma et al., 2002) and a serine-phenylalanine-rich motif (Taylor et al., 2003); and (ii) an alpha-helix containing C-terminal coiled-coil domain (spanning ~326–854) that shows greater conservation among orthologues than the N-terminus (Millar et al., 2000b;Ma et al., 2002;Taylor et al., 2003;Chubb et al., 2008;Soares et al., 2011).

Initial insight into DISC1 oligomerisation was provided by Brandon et al. (Brandon et al., 2004a), who noted that DISC1 forms large (≥250 kDa) species that they believed to be DISC1 dimers, or higher order oligomers. A region spanning residues 403–504 of DISC1 was later shown to be a self-association domain by pull-down experiments with deletion mutants (Kamiya et al., 2005). Early attempts at biophysical characterisation focussed on truncated C-terminal constructs (Leliveld et al., 2008;Leliveld et al., 2009). This was in part due to an inherent difficulty in expressing and purifying folded full-length DISC1 protein. From these studies it emerged that the C-terminal regions of DISC1 harbour oligomerisation domains that facilitate formation of dimers, octamers, and multimeric species. Interestingly, the authors noted that only the octameric state is required for functional interaction with nuclear distribution protein E homologue like-1 (NDEL1) indicating that an oligomerisation optimum is necessary for interaction between the two proteins. Size-exclusion chromatography analysis of another C-terminal truncated fragment showed that the common disease-associated C704 variant form of DISC1 adopts a moderately higher fraction of oligomers than the S704 form.

The first biophysical characterisation of full-length native DISC1 was recently published (Narayanan et al., 2011), and confirmed the findings from the C-terminal fragment studies.

Utilising size-exclusion chromatography and analytical ultracentrifugation, the authors observed that native DISC1 forms octamers via dimers. The authors confirmed that NDEL1 interacts with an octamer of DISC1. Narayanan et al. also evaluated the structural consequence of the DISC1 common variant S704C and noted that compared to wild-type DISC1, the DISC1-C704 protein exhibits a greater than 9mer-sized oligomeric state (Narayanan et al., 2011). Despite this improper oligomeric assembly, there is no influence upon the interaction of DISC1-C704 with NDEL1. Our laboratory (Eykelenboom et al., 2012) investigated a truncated central fragment in the C-terminus of DISC1 (amino acids 326-597), the region up to the translocation breakpoint. This fragment was compared with another fragment, DISC1 amino acids 326-597 plus the additional 69 amino acids in CP69, one of the putative aberrant chimeric proteins arising from the t(1;11) translocation (Eykelenboom et al., 2012). We found that on average, the fusion protein exhibited a higher oligomerisation propensity by dynamic light scattering experiments, with greater thermal stability, and that the additional 69 amino acids possess additional alpha-helical content by circular dichroism. Leliveld et al. demonstrated that detergent-insoluble DISC1 could be seen by immunoreactivity in ~20% of post-mortem brains of patients with chronic mental diseases, but not in healthy controls (Leliveld et al., 2008). These DISC1 aggregates did not bind NDEL1, whereas insoluble DISC1 (316–854) aggregates did co-purify with dysbindin, in brains of a subset of patients with mental illness, but not in healthy controls (Ottis et al., 2011). More recently, Atkin et al. (Atkin et al., 2012) showed that DISC1 forms large perinuclear aggregates and conclusively identified these structures as aggresomes. These findings highlight the potential of DISC1 protein aggregation and recruitment of binding partners as a biological mechanism in a subset of mental illness cases (Korth, 2009;2012).

A key remaining question is how common and rare amino acid sequence variants in DISC1 affect its structure, stability, oligomeric state and aggregation propensity, and ultimately how this might relate to protein interactions and phenotypic consequences. For further details on this see our earlier review (Soares et al., 2011). Additionally, while numerous DISC1 protein interaction partners have been confirmed, little is known about stoichiometry and thermodynamics of these interactions, precise interaction sites, or whether these interactions are competitive or co-operative. These, in addition to obtaining high resolution structural data on DISC1 (and of DISC1 in complex with its interaction partners) will be the next key goals from a biochemical and biophysical standpoint. This detailed knowledge of the structure-function relationships of DISC1 will be critical in understanding its role in disease and translating this knowledge for therapeutic benefit.

6 Mouse behavioural phenotypes

Several DISC1 mouse models have been generated. The first to be described carries a modified DISC1 allele from the mouse strain 129 that consists of a natural 25 nucleotide deletion in exon 6 resulting in a premature stop codon, plus targeted premature transcription termination and polyadenylation sites in intron 8 (Koike et al., 2006). This was followed by investigation of the effects of ethyl-nitrosourea (ENU)-generated point mutations, L100P or Q31L, within exon 2 of the endogenous gene (Clapcote et al., 2007). Three transgenic models express C-terminally truncated DISC1 species, truncated at the position of the t(1;11) translocation breakpoint, and thus referred to hereafter as $DISC1^{1-597}$. These mice constitutively (Hikida et al., 2007) or inducibly (Pletnikov et al., 2008) express truncated human cDNA under control of the CAMKII promoter, or express mouse transcripts from a truncated mouse BAC under control of the natural mouse DISC1 promoter (Shen et al., 2008). Expression of a C-terminal DISC1 fragment has also been described (Li et al., 2007). These models and their phenotypes were recently discussed in an excellent review by Brandon & Sawa (Brandon and Sawa, 2011) and will therefore not be reviewed in detail here. In general these mouse models exhibit overlapping phenotypes, including cognitive

and behavioural abnormalities, and deficits in sensorimotor gating (PPI), working memory and latent inhibition, consistent with some characteristics of schizophrenia in humans (Brandon and Sawa, 2011), thus adding further weight to the evidence for involvement of DISC1 in mental illness. However it should be noted that a recent independent study (Shoji et al., 2012) failed to confirm the behavioural alterations reported in the missense mutant mice (Clapcote et al., 2007). This may be due to strain differences, backcrossing, or may even reflect differences in laboratory housing/testing conditions (Crabbe et al., 1999;Papaleo et al., 2012).

Following on from these models, a targeted mouse model lacking DISC1 exons 2 and 3 (Δ2-3) was recently reported (Kuroda et al., 2011). Removal of these exons was designed to abolish DISC1 expression, which was convincingly demonstrated using two new DISC1 antibodies directed against the N- or C-termini. However there is increasing evidence for expression of a myriad of additional isoforms (see section 4), some of which lack exons 2 and/or 3 (Nakata et al., 2009) and it thus remains to be seen whether this mouse is in fact a complete knockout. This deletion mouse model showed no overt brain developmental defect, but there were behavioural abnormalities, some of which could be rescued pharmacologically (Kuroda et al., 2011). Another recently generated mouse model allows inducible expression of human DISC1$^{1\text{-}597}$ in astrocytes (Ma et al., 2012). These mice exhibit heightened responses to the NMDA receptor antagonist MK-801 in open field and prepulse inhibition tests, consistent with NMDA receptor hypofunction, which is considered to be a major characteristic of schizophrenia (Kristiansen et al., 2007). Thus, these mice are useful additions to the growing number now available. Each of these models needs to be used and interpreted with caution as none precisely mimic the t(1;11) translocation event, nor any of the clinically associated DISC1 variants since reported.

A number of these mouse models have been used to study gene-environment interactions. Poly I:C is an immunostimulant that is frequently used to mimic the innate immune response to viral infection. When administered during pregnancy (gestation day 9) to mice inducibly expressing human DISC1$^{1\text{-}597}$, the resulting offspring exhibit increased anxiety and depressive-like symptoms, and decreased sociability, which may be related to effects of mutant DISC1 expression upon production of cytokines in response to Poly I:C (Abazyan et al., 2010). Postnatal Poly I:C treatment of mice constitutively expressing human DISC1$^{1\text{-}597}$ demonstrated combined action to produce cognitive impairment, and effects upon hippocampus-dependent fear memory, social interaction and hyperactivity in response to treatment with the NMDA antagonist MK-801 (Ibi et al., 2010). In addition, Poly I:C treatment of these mice reduces the number of parvalbumin-positive interneurons in the medial prefrontal cortex (Ibi et al., 2010). Consistent with the genetic data indicating a role in responses to drug treatment (see section 3), cognitive impairment in these mice is rescued by treatment with the antipsychotic clozapine, while their hyper-responsiveness to MK-801, but not their social interaction deficit, is reversed by clozapine or haloperidol (Nagai et al., 2011). Chronic social defeat, another environmental stressor, may also interact with DISC1 to influence behavior (Haque et al., 2012). When tested in several behavioural paradigms relevant to schizophrenia, the 31L mutation was found to interact with social defeat in hereozygous mice (Haque et al., 2012). These studies in mice indicate that environmental factors can interact with the effects of mutant DISC1 expression to induce or exacerbate behavioural deficits.

7 DISC1 brain function – neural precursor proliferation

A number of key studies demonstrate that DISC1 is critically involved in several stages of neurogenesis, the process by which newborn neurons are generated within the developing and adult brain. This process is widespread in the developing brain, but in adult brain is

restricted essentially to the subventricular zone (SVZ) and subgranular zone of the hippocampal dentate gyrus.

In embryonic mouse brain DISC1 expression peaks at E14-E15, and then declines as development progresses (Mao et al., 2009). This peak of expression coincides with a period of active neurogenesis in the developing cortex, where DISC1 is prominent within neural progenitors in the ventricular zone (VZ) and SVZ at this time (Mao et al., 2009). DISC1 is also expressed in neural progenitors of the hippocampal dentate gyrus in adult mouse brain (Mao et al., 2009). Together these observations suggested a role for DISC1 in neurogenesis, and indeed, DISC1 RNAi in isolated adult hippocampal progenitor cells decreases their rate of proliferation, while DISC1 overexpression has the opposite effect (Mao et al., 2009). Consistent with these observations, DISC1 knock down *in utero* at E13 reduces proliferation within the SVZ, while overexpression increases proliferation (Mao et al., 2009). Moreover, reducing DISC1 expression leads to premature cell cycle exit and differentiation of neural progenitors within the VZ/SVZ (Mao et al., 2009). Altogether this results in depletion of the progenitor cell pool and, at least shortly after the treatment, overproduction of neurons (Mao et al., 2009). Neural progenitor proliferation and maintenance of the progenitor cell pool is controlled, in part, by the canonical Wnt signalling pathway, in which β-catenin modulates transcription of a set of genes that are critically required for cell proliferation (Wu and Pan, 2010). DISC1 regulates this process through direct binding to, and inhibition of, the kinase GSK3β (Mao et al., 2009), which in turn phosphorylates β-catenin to direct its degradation (Wu and Pan, 2010). Thus, DISC1 knockdown results in increased GSK3β activity, followed by increased β-catenin phosphorylation and degradation, which in turn inhibits cell proliferation while promoting differentiation, while DISC1 overexpression reduces GSK3β activity to stabilise β-catenin and stimulate gene transcription and cell proliferation (Mao et al., 2009). DIXDC1 is another DISC1 interactor involved in this process (Singh et al., 2010). Together with DISC1, DIXDC1 co-regulates Wnt-GSK3β/β-catenin signalling and cortical neural progenitor proliferation (Singh et al., 2010).

Consistent with the studies by Mao et al. and Singh et al., neurogenesis defects have also been observed in DISC1 mutant mice i) carrying the modified 129 allele (Koike et al., 2006;Kvajo et al., 2008), ii) expressing $DISC^{1-597}$ fused to EGFP (Shen et al., 2008), and iii) carrying ENU-induced point mutations, 31L and 100P, in the endogenous gene (Clapcote et al., 2007;Lee et al., 2011).

The studies by Mao et al and Singh et al clearly demonstrate DISC1 involvement in neural progenitor proliferation and provide a mechanism for its regulatory action via GSK3β, β-catenin and DIXDC1 (Mao et al., 2009;Singh et al., 2010). Intriguingly, however, the DISC1 interactors LIS1 and NDE1 (Brandon et al., 2004b;Burdick et al., 2008;Bradshaw et al., 2009) are also directly involved in regulation of neurogenesis. LIS1 and NDE1 (or its paralogue NDEL1) complex together to regulate many cytoskeleton-related functions through their effects upon the motor protein dynein (Lam et al., 2010). LIS1 deficiency affects neural progenitor cell proliferation in the VZ through disruption of the orientation of cleavage (Yingling et al., 2008). This determines the symmetry of division, distribution of cell fate determinants, and thus the fate of the daughter cells, such that asymmetric division increases neuronal differentiation at the expense of the progenitor pool. This consequence of LIS1 deficiency is likely due to multiple deleterious effects on microtubule function which can be rescued by overexpression of NDEL1 (Yingling et al., 2008). NDE1 is enriched within progenitor cells of the VZ, where, like LIS1, it regulates the plane of progenitor cell division, cell fate and maintenance of the progenitor pool (Feng and Walsh, 2004). NDE1 mutant mice also display mitotic delay/arrest, chromosome mispositioning and other abnormalities that affect progenitor cell proliferation (Feng and Walsh, 2004). NDEL1 is however, largely absent from the embryonic cortical progenitors (Feng and Walsh, 2004),

suggesting that it does not have a significant role in progenitor proliferation. It will be of interest to discover whether DISC1 modulates neural progenitor proliferation through interaction with LIS1 and NDE1, in addition to its regulatory role via GSK3β and β-catenin, and DIXDC1, and indeed whether these pathways are related.

The disease-associated variants R264Q, L607F and a novel rare variant, A83V, all impact upon DISC1 binding to GSK3β, and fail to activate canonical Wnt signalling (Singh et al., 2011). Intriguingly, these three variants also impact upon neural progenitor cell proliferation *in vivo* (Singh et al., 2011). Importantly, GSK3β is a major target of Lithium, in clinical use as a mood stabiliser for treatment of bipolar disorder patients (Serretti et al., 2009), which suggests that clinical symptoms in psychiatric patients may arise from aberrantly high GSK3β activity. Silencing DISC1 in the adult mouse dentate gyrus results in novelty-induced hyperlocomotion and increased immobility in the forced swim test, both of which are reversed through treatment with the specific GSK3β inhibitor SB-216763 (Mao et al., 2009). It is also reported that both the 31L and 100P mouse mutations reduce DISC1/GSK3β interaction, and that treatment with GSK3 inhibitors can rescue aspects of their behavioural phenotypes (Lipina et al., 2011;Lipina et al., 2012). Altogether these studies highlight reduced DISC1/GSK3β interaction, increased GSK3β activity, reduced canonical Wnt signalling and decreased neural progenitor proliferation as possible disease mechanisms in psychiatric illness. However it is worth pointing out that GSK3β performs multiple additional regulatory functions *in vivo*. Indeed, in zebrafish it has been demonstrated that DISC1, through interaction with GSK3β, has extensive effects upon brain development via canonical Wnt signalling, but also via a non-canonical Wnt pathway (De Rienzo et al., 2011). While these additional effects upon the brain could also influence disease risk if they occur in humans, it is notable that production of new neurons in the adult dentate gyrus is downregulated in response to stress. Since stress is a major trigger for psychiatric illness it is possible that reduced hippocampal neurogenesis is a contributory factor (Hanson et al., 2011;Lee et al., 2012). Moreover, there is evidence that antidepressant treatment may exert its effects, at least in some cases, through upregulation of neurogenesis in the subgranular zone. Hippocampal neurogenesis may thus be fundamentally involved in both the causation and treatment of mental illness, although this remains to be conclusively proven (Hanson et al., 2011).

8 DISC1 brain function - neuronal migration

In the developing cortex, pyramidal neurons produced in the VZ/SVZ migrate radially, along guide fibres provided by radial glia, to their final destination in an inside-out manner, where they become integrated into functional neuronal networks. Interneurons, however, migrate tangentially, independent of radial glia (Kriegstein and Noctor, 2004). Neuronal migration also proceeds in other developing brain regions including the hippocampus, where granule cells produced near the dentate notch migrate to the developing dentate gyrus, while pyramidal cells populate the hippocampus in an inside-out fashion. In the adult brain neuronal migration is restricted to neural precursors moving from the subgranular zone to the granular zone of the hippocampus, and from the SVZ to the olfactory bulbs via the rostral migratory stream. The migration process involves extension of the leading edge of the cell. This is followed by migration of the nucleus (nucleokinesis), and finally, retraction of the trailing edge of the cell.

Silencing DISC1 in the developing cortex inhibits radial migration to the cortical plate, an effect that is recapitulated by overexpression of $DISC1^{1-597}$ (Kamiya et al., 2005;Duan et al., 2007;Kubo et al., 2010;Young-Pearse et al., 2010). DISC1 is also required for migration of cortical interneurons in the embryonic brain, with DISC1 knockdown inhibiting migration of neurons from the medial ganglionic eminence (Steinecke et al., 2012). Migrating

interneurons extend a long branched leading process that detects guidance cues (Valiente and Martini, 2009), and this leading process is abnormal in cells where DISC1 expression has been silenced. Such cells exhibit abnormally extended processes with fewer branches (Steinecke et al., 2012). In the developing hippocampus DISC1 knockdown inhibits granule cell migration (Meyer and Morris, 2009), while there are conflicting reports about whether DISC1 is required for migration of CA1 pyramidal cells (Meyer and Morris, 2009;Tomita et al., 2011). In postnatal brain DISC1 is reported not to be involved in neuroblast migration via the rostral migratory stream (Wang et al., 2011b), while intriguingly, in the adult dentate gyrus, DISC1 RNA interference results in overextended migration, with newborn neurons from the subgranular zone migrating beyond their intended destination within the granular zone (Duan et al., 2007). The reason for this apparent discrepancy in the effect of DISC1 RNA interference in developing cortex and adult hippocampus is unknown, but it may be related to the different organisation of these two structures, with cortical layers laid down in ‘inside-out’ fashion while hippocampal layers are established in an ‘outside-in’ sequence (Duan et al., 2007). It has thus been suggested that DISC1 knockdown compromises the ability of the neuron to recognise the cues that guide its migration (Duan et al., 2007), and these cues may exhibit temporal and spatial specificity in cortex versus hippocampus. Intriguingly, in the adult hippocampus there is evidence that DISC1 acts in concert with NMDA receptors to modulate neuronal migration (Namba et al., 2011), Consistent with these studies revealing involvement of DISC1 in neuronal migration, evidence of disrupted radial migration was found in the neocortex of the 100P and the 31L DISC1 mutant mice (Lee et al., 2011).

The DISC1 interactors LIS1 and NDEL1 are known to be critically involved in neuronal migration (Sasaki et al., 2000), with mutations in LIS1 causing the neuronal migration disorder lissencephaly (Wynshaw-Boris, 2007). The DISC1 interactor DIXDC1 is also required for neuronal migration in the developing cortex, and intriguingly this requires both DISC1/DIXDC1 interaction, and CDK5-dependent recruitment of NDEL1 to DIXDC1, to which it also binds (Singh et al., 2010). Unlike their role in regulating neural progenitor proliferation, the role of DISC1 and DIXDC1 in neuronal migration is, however, independent of the Wnt-GSK3β/β-catenin pathway (Singh et al., 2010). Thus, in the absence of NDEL1 binding, DISC1/DIXDC1 direct neural progenitor proliferation via Wnt-GSK3β/β-catenin, while upon recruitment of NDEL1 the function of this protein complex shifts to neuronal migration.

There is an additional important mechanism that mediates the functional transition of DISC1 from activator of neural progenitor proliferation to promoter of newborn neuron migration in the developing cortex (Ishizuka et al., 2011). This switch is triggered by DISC1 phosphorylation at mouse S710 or its human equivalent S713, which abolishes DISC1 binding to, and inhibition of GSK3β, consequently inhibiting DISC1’s activity as a positive regulator of wnt/β-catenin signalling (Ishizuka et al., 2011). While losing interaction with GSK3β, DISC1 phosphorylated at S710 (DISC1 pS710) becomes enriched at the centrosome and displays markedly increased affinity for (Bardet-Biedl Syndrome) BBS1, leading to enhanced recruitment of this protein to the centrosome (Ishizuka et al., 2011). This is thought to be an important step in the transition from neural progenitor proliferation to migration, because the DISC1-mediated recruitment of BBS proteins to the centrosome is an established mechanism underlying neuronal migration in the developing cortex (Kamiya et al., 2008). Consistent with the proposed role of DISC1 S710 phosphorylation in the transition from neural progenitor proliferation to migration, DISC1 pS710 is predominantly enriched in the cortical plate and intermediate zone of the developing mouse cortex, where most migrating neurons are found, and is virtually absent in the ventricular and subventricular zones, sites of active cell proliferation (Ishizuka et al., 2011). Most strikingly, neuronal migration defects induced by DISC1 knock-down in the developing mouse cortex

can be rescued by expression of wild-type DISC1 or phospho-mimic mutant DISC1 E710, but not by phospho-dead mutant DISC1 A710, whereas the opposite is true for progenitor proliferation deficits induced by DISC1 silencing (Ishizuka et al., 2011).

The common disease-associated S704C DISC1 variant influences the role of DISC1 in neuronal migration, with the C variant inhibiting migration in the developing cortex (Singh et al., 2011). Notably, the other variants tested, A83V, R264Q and L607F, do not affect cortical migration (Singh et al., 2011). Moreover, these variants, but not S704C, influence Wnt-GSK3β/β-catenin signalling, which again demonstrates that the role of DISC1 in cortical neuronal migration is independent of this pathway (Singh et al., 2011).

The Alzheimer's disease risk factor amyloid precursor protein (APP) is also required for neuronal migration (Young-Pearse et al., 2007). Intriguingly, APP knockdown in mouse results in cortical migration defects that are rescued by overexpression of DISC1 (Young-Pearse et al., 2010). DISC1 and APP interact (Young-Pearse et al., 2010), therefore they likely function together during neuronal migration. This study thus provides a biochemical link between risk factors for psychiatric illness and Alzheimers disease, which suggests the possibility of overlapping pathological mechanisms.

DISC1's role in migration has also been examined in zebrafish, where DISC1 knockdown dysregulates cranial neural crest cell migration (Drerup et al., 2009). The migration defect correlates with increased expression of the transcription factors FOXD3 and SOX10, leading to a suggested mechanism whereby DISC1 indirectly modulates migration through transcriptional repression of transcription factors with a known role in development (Stuhlmiller and Garcia-Castro, 2012).

9 DISC1 brain function - neuronal integration and maturation

As well as regulating production and migration of neurons, DISC1 is also required for neuronal integration (Duan et al., 2007). Silencing DISC1 in the adult mouse dentate gyrus affects the morphogenesis of newborn granule cells, with these cells exhibiting enlarged cell bodies, ectopic dendrites, increased dendritic length and branching, and accelerated acquisition of intrinsic excitability and synapse formation (Duan et al., 2007). Moreover, DISC1 knockdown results in aberrant axonal targeting to hippocampal subfield CA3 (Faulkner et al., 2008). DISC1 has thus been suggested to act as a 'master regulator', controlling the timing of neuronal integration through its many stages (Duan et al., 2007). Functional effects upon neurons in the adult mouse hippocampus have also been reported in mice carrying the endogenous modified 129 allele (Koike et al., 2006). Within the dentate gyrus of these mice there is neuronal mispositioning providing further evidence of overextended migration, and abnormal dendritic morphology. However, in contrast to the RNA interference experiments reported by Duan et al, these mice exhibit impaired dendritic growth, suggesting that newborn neurons may be unable to fully integrate into circuits within the dentate gyrus (Kvajo et al., 2008). Similar impairment of dendritic development has been reported in frontal cortical neurons of mice carrying 31L and 100P missense mutations (Lee et al., 2011). Mice carrying the modified 129 allele also exhibit altered axonal projections to CA3, and have short-term plasticity deficits at hippocampal CA3/CA1 synapses (Kvajo et al., 2011). Consistent with the observations in these mice, when heterologously expressed in *C. elegans*, mouse DISC1 induces axon guidance defects via activation of UNC-73/TRIO-RAC-PAK signalling (Chen et al., 2011). Finally, in addition to these effects upon neuronal positioning, morphology and axon pathfinding, when DISC1 is knocked down in pyramidal neurons of the prefrontal cortex early in development, maturation of dopaminergic neurons is defective, with consequent effects upon neural circuitry (Niwa et al., 2010).

DISC1 co-operates with its binding partners NDEL1 and FEZ1 in regulating many aspects of neuronal development in the adult hippocampus (Duan et al., 2007;Kang et al., 2011), but the most detailed analysis of underlying pathways involves Girdin, otherwise known as KIAA1212. Girdin activates the kinase AKT, however DISC1 interaction with Girdin blocks its ability to bind and activate AKT (Kim et al., 2009), thus DISC1 indirectly modulates activity of this important kinase. Overexpression of Girdin or a constitutively active form of AKT recapitulates many, but not all, of the effects of DISC1 knockdown upon granule cell development (Kim et al., 2009;Enomoto, 2011), indicating that these three proteins function in a common pathway to regulate maturation of newborn granule cells. Intriguingly, the effects of DISC1 knockdown or Girdin overexpression can be rescued by treatment with the mTOR inhibitor rapamycin, but not by inhibition of GSK3β (Kim et al., 2009). Moreover Girdin is weakly expressed in proliferating neural progenitors in the subgranular zone of the adult hippocampus, suggesting that it does not have a significant role in progenitor proliferation (Kim et al., 2009;Enomoto, 2011). Together these observations point towards a mechanism whereby DISC1 regulates the role of Girdin and AKT in neuronal maturation via the mTOR pathway (Kim et al., 2009). AKT also directly regulates GSK3β activity via inhibitory phosphorylation of S9 on GSK3β, but this kinase does not seem to be involved in the neuronal integration function of DISC1 (Kim et al., 2009).

The role of DISC1 in adult hippocampal neuronal maturation is also dependent upon the extrinsic factor GABA, via NKCC1, an ion transporter involved in GABA responses (Kim et al., 2012). In adult hippocampus NKCC1 knockdown rescues the dendritic growth defects in newborn neurons that result from DISC1 knockdown and knocking down the $GABA_A$ receptor γ2 subunit has a similar effect. Moreover, both treatments inhibit the effect of DISC1 knockdown upon the AKT/mTOR pathway. Thus this study provides evidence that, in adult hippocampal neuronal maturation/integration, DISC1 and GABA signalling synergise in regulating dendritic outgrowth via the AKT/mTOR pathway (Kim et al., 2012). DISC1 knockdown has no apparent effect upon early postnatal hippocampal neuronal maturation/integration, until mice are subjected to maternal deprivation stress, whereupon the same spectrum of deficits occurs as in adult hippocampus (Kim et al., 2012). Moreover, knockdown of NKCC1 suppresses the dendritic abnormalities and soma hypertrophy observed under these conditions at early postnatal stages (Kim et al., 2012). Similarly, treatment with rapamycin also reverses the defects induced by DISC1 knockdown plus stress (Kim et al., 2012). These intriguing observations indicate that early postnatal hippocampal neuronal maturation and integration may be particularly sensitive to the combined effects of aberrant DISC1 expression, as may occur in some psychiatric patients such as t(1;11) translocation carriers, and environmental stress, such as maternal deprivation.

There is evidence that cAMP signalling is another pathway that modulates neuronal maturation. DISC1 is known to function in the cAMP pathway through interaction with the phosphodiesterase 4 family of proteins (Millar et al., 2005b). PDE4s hydrolyse cAMP to terminate, and thus regulate, cAMP signalling in a compartmentalised manner (Houslay and Adams, 2003). Mammalian PDE4s are orthologues of Drosophila Dunce, so-called because of its role in cognition and synaptic plasticity (Houslay and Adams, 2003), and are specifically inhibited by drugs such as rolipram which have antidepressant and antipsychotic activity (Houslay and Adams, 2003;Siuciak et al., 2007). In a negative feedback loop, catalytic activity of certain PDE4 isoforms is induced by upregulation of cellular cAMP, resulting in cAMP hydrolysis and termination of the signalling cascade (Houslay and Adams, 2003). We have shown that DISC1 binds to PDE4s in a cAMP-dependent manner (Millar et al., 2005b;Murdoch et al., 2007), and have provided evidence that DISC1 inhibits the induction of PDE4 activity that normally occurs in response to elevated cAMP levels (Carlyle et al., 2011). Mice carrying the modified 129 DISC1 allele exhibit decreased PDE4

activity in the hippocampus, with expression of many PDE4B and PDE4D isoforms decreased at the protein level (Kvajo et al., 2011). Consistent with this, cAMP levels in the granular zone of the dentate gyrus are increased. This increase in cAMP leads to increased activation of the cAMP-dependent transcription factor CREB and dysregulated expression of molecules required for axon guidance and dendritic growth (Kvajo et al., 2011). In primary culture, mutant neurons exhibit altered axon pathfinding and dendritic branching defects, both of which are rescued by treatment with an adenylyl cyclase inhibitor to reduce cAMP levels (Kvajo et al., 2011). Consistent with these effects on PDE4 activity and cAMP signalling, we have observed decreased DISC1/PDE4 interaction in mice carrying 31L and 100P mutations, with the 31L mutation resulting in reduced total brain PDE4 activity (Clapcote et al., 2007), although it is not yet known how this relates to the anatomical defects that have been reported in these mice (Lee et al., 2011).

Altogether then, DISC1 regulates neurogenesis at many levels, including proliferation of neural progenitors via Wnt-GSK3β/β-catenin and DIXDC1, migration of neurons to their final destination via DIXDC1-NDEL1, BBS1 and APP, and possibly also through effects upon expression of transcription factors FOXD3 and SOX10, and maturation/integration into existing neural circuitry via AKT/mTOR/GABA, PDE4/cAMP, NDEL1 and FEZ1.

10 DISC1 brain function - neurosignalling

Several studies report that DISC1 is present at synapses. We (Bradshaw et al., 2008), and others (Hayashi-Takagi et al., 2010), have shown that, when overexpressed in primary cultured rodent neurons, DISC1 locates to dendritic spines where it co-localises with PSD-95 (Bradshaw et al., 2008), a marker of the post-synaptic density. At the ultrastructural level, endogenous DISC1 localises to the post-synaptic density in human frontal and parietal cortices (Kirkpatrick et al., 2006), rat hippocampus (Wang et al., 2011a), mouse striatum (Ramsey et al., 2011) and monkey prefrontal cortex (Paspalas et al., 2012), using three independent antibodies. This location is further confirmed by subcellular fractionation studies which show that DISC1 is loosely associated with the post-synaptic density (Hayashi-Takagi et al.;Clapcote et al., 2007;Wang et al., 2011a), again using three different antibodies. Finally, DISC1 co-immunoprecipitates from mature neurons with PSD-95, CIT and Kal-7, all core post-synaptic density components (Hayashi-Takagi et al.).

Intriguingly, DISC1 modulates the size and density of dendritic spines via interaction with Kal-7 (Hayashi-Takagi et al., 2010). Essentially, DISC1 dissociates Kal-7 interaction with RAC1, for which Kal-7 is a GDP/GTP exchange factor (GEF), and RAC1 activity is reduced as a result. DISC1 may thus inhibit activation of RAC1 by sequestering its GEF, Kal-7. This likely underlies DISC1's effect upon spine morphology and density because RAC1 is an established modulator of dendritic spines (Hayashi-Takagi et al., 2010). These effects appear to be dependent upon NMDA receptor activity (Hayashi-Takagi et al., 2010), suggesting that DISC1 may play an important role in activity-dependent spine remodelling. There is also evidence that DISC1 modulates glutamatergic synapse composition via its interaction with the kinase TNIK at the post-synaptic density (Wang et al., 2011a). TNIK protein expression and phosphorylation are apparently glutamate receptor activity-dependent and TNIK may therefore be involved in synaptic signal transduction (Wang et al., 2011a). Inhibition of TNIK activity using a peptide derived from the TNIK binding site on DISC1 decreases synaptic expression of PSD-95, the AMPA receptor subunit GluR1 and the AMPA receptor regulator stargazin through protein degradation (Wang et al., 2011a). Altogether these data suggest that DISC1 mediates activity-dependent glutamatergic synapse remodelling. It is now apparent from these two studies that DISC1 may be a key modulator of some of the activity-dependent changes that underlie synaptic plasticity. In a separate study, it was demonstrated that mice carrying a DISC1 point mutation, 100P, display altered

expression profiles of transcripts encoding the synaptic proteins NRXN1 and NRXN3 (Brown et al., 2011). How this occurs is not yet known, but it is likely to be independent of TNIK and synaptic proteolysis, and indicates that there must also be a transcriptional mechanism by which DISC1 regulates synapse composition.

We have demonstrated that a number of additional DISC1 interactors localise to the post-synaptic density, including the phosphodiesterase (PDE4) family of proteins (Bradshaw et al., 2008). While the role of synaptic PDE4 is currently unknown, its presence at the post-synaptic density suggests a role in modulation of cAMP signalling events downstream of receptor activation, a role that is likely to be modulated by DISC1.

In addition to its post-synaptic density localisation, within dendritic spines DISC1 is also present at perisynaptic and extrasynaptic sites in monkey prefrontal cortex, where it associates with Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels (Paspalas et al., 2012). HCN channel activation is modulated by cAMP to regulate, for example, neuronal excitability, so it is notable that they also associate with the dopamine D1 receptor and with PDE4A within spines (Paspalas et al., 2012). Dopamine D1 receptor stimulation induces cAMP synthesis, thus within spines the HCN channels, PDE4A and DISC1 are strategically placed to respond to these cAMP signalling events. It has been suggested that the location of this ‘cAMP signalplex’ may render prefrontal neuronal networks particularly sensitive to dysregulated cAMP signalling (Paspalas et al., 2012).

There is also evidence that DISC1 functions presynaptically. Using optogenetics to stimulate presynaptic neurons, it has been demonstrated that DISC1 overexpression enhances the probability of glutamate release at the synapse, while DISC1 RNA interference has the opposite effect (Maher and LoTurco, 2012). Additionally, expression of $DISC1^{1-597}$ disrupts the synchronous nature of glutamate release (Maher and LoTurco, 2012). This is consistent with a report that DISC1 knockdown or expression of $DISC1^{1-597}$ reduces synaptic vesicle transport (Flores et al., 2011), while mice expressing the modified 129 allele have smaller synaptic vesicles (Kvajo et al., 2011). It is thus possible that the effect of DISC1 expression upon glutamate release at the synapse is related to its role in transporting vesicles to the synapse.

Because DISC1 has multiple roles at the synapse, and no doubt more have still to be uncovered, it is intriguing that synaptic expression of DISC1 is altered in mice mutant for synaptic proteins. The first study investigated Densin, a post-synaptic density scaffold molecule that regulates function of metabotropic glutamate receptors (mGluRs) and Calmodulin Kinase II (CAMKII) at the synapse (Carlisle et al., 2011). Knockout of Densin in mice leads to selective reduction of mGlur5 and DISC1 at the post-synaptic density (Carlisle et al., 2011). The second study used mice which express NMDA receptors at only 10% of the normal level. In these mice synaptic DISC1 and its binding partner 14-3-3Epsilon are reduced in striatum in an age-dependent manner (Ramsey et al., 2011). Moreover treatment of wild-type mice with NMDA receptor antagonists also reduces DISC1 levels (Namba et al., 2011;Ramsey et al., 2011). Together, these studies suggest that DISC1 expression is synaptic activity-dependent.

DISC1 may also modulate synaptic transmission via interaction with serine racemase (Ma et al., 2012). This enzyme generates D-serine, an NMDA receptor co-agonist. $DISC1^{1-597}$ cannot interact with serine racemase, and expression of this aberrant form of DISC1 decreases serine racemase expression via its ubiquitination and subsequent degradation (Ma et al., 2012). Expression of $DISC1^{1-597}$ may thus lead to impaired NMDA receptor transmission, consistent with the behavioural phenotype of mice expressing this form of DISC1, as discussed earlier. Aberrant DISC1 expression also influences dopamine D2

receptor expression (see section 13) (Lipina et al., 2010;Pogorelov et al., 2012). DISC1 thus modulates neurosignalling at many levels, including effects upon NMDA receptors and dopamine D2 receptors, which are involved in the actions of psychotropic drugs such as phencyclidine, and antipsychotic drugs respectively, and therefore strongly implicated in the pathophysiology of schizophrenia (Kristiansen et al., 2007;da Silva Alves et al., 2008).

11 DISC1 at the subcellular level - nucleus

DISC1 is involved in multiple functions at the subcellular level, via localisation to several compartments and interaction with an ever-increasing number of binding partners. Any/all of these locales and binding partners could contribute to its roles in neurogenesis and neurosignalling.

Multiple lines of evidence support a direct involvement of DISC1 in nuclear transcriptional regulation. DISC1 partially distributes to the nucleus (Sawamura et al., 2005;Malavasi et al., 2012), and here it can be prominently detected within promyelocytic leukaemia (PML) nuclear bodies, sites of active transcription (Sawamura et al., 2008). DISC1 nuclear targeting is mediated by at least two well conserved cis-acting elements in the protein: a classic tetra-arginine nuclear localisation motif at positions 35-RRRR-38 (NLS1) and a putative leucine zipper spanning residues 607-628, encoded by DISC1 exon 9 (LZ9) (Sawamura et al., 2008). In *Drosophyla melanogaster* the nucleus-restricted expression of full-length but not $DISC1^{1-597}$induces sleep homeostasis disturbances, supporting a potential role for nuclear DISC1 in the regulation of sleep/wake cycles (Sawamura et al., 2008). These findings must be cautiously interpreted, since it has not been established that invertebrates naturally express DISC1. However the possibility that nuclear DISC1 might be directly involved in regulation of sleep homeostasis is particularly intriguing because this process is often disturbed in psychiatric patients (Schulz and Steimer, 2009;Wulff et al., 2009;Wulff et al., 2012) and is partly regulated by cAMP signalling (Zimmerman et al., 2008), a pathway in which DISC1 is involved by virtue of its modulatory interaction with PDE4 (Millar et al., 2005b;Carlyle et al., 2011). A study conducted on human post-mortem brains also hinted at the potential clinical relevance of altered nuclear DISC1 function (Sawamura et al., 2005). In this study, increased nuclear expression of a 75-85kDa DISC1 protein species was detected in brains from patients diagnosed with schizophrenia or depression (Sawamura et al., 2005). While this effect was correlated with drug abuse in patients with major depression, none of the common brain-associated confounding factors explained the nuclear enrichment of DISC1 in brain tissue from schizophrenic patients, suggesting aberrant DISC1 nuclear targeting as a potential pathogenic mechanism (Sawamura et al., 2005). Additional evidence supporting the potential contribution of aberrant nuclear DISC1 expression to psychopathogenesis came from a recent study from our group, which revealed that the putatively causal amino acid substitution 37W (Song et al., 2008) located within DISC1 Nuclear Localisation Signal 1 (NLS1), and the disease-associated variant 607F located within DISC1 Leucine Zipper 9 (LZ9), significantly decrease DISC1 nuclear expression in a dominant-negative fashion (Malavasi et al., 2012). Interestingly, nuclear targeting of $DISC1^{1-597}$, which retains NLS1 but lacks LZ9, is also significantly decreased (Sawamura et al., 2008).

Two highly related members of the ATF/CREB family of transcription factors, ATF4 and ATF5, are DISC1 interactors (Millar et al., 2003;Morris et al., 2003;Ozeki et al., 2003;Bradshaw et al., 2008;Sawamura et al., 2008;Malavasi et al., 2012). ATF4 and ATF5 are preferentially translated in response to a variety of environmental insults, including nutrient deprivation, endoplasmic reticulum stress, viral infections and oxidative stress, and in turn govern the transcriptional responses to these damaging stimuli (Ameri and Harris, 2008;Watatani et al., 2008;Zhou et al., 2008a). ATF4 and ATF5 are also key regulators of

the transition from neuroprogenitor cell proliferation to neuronal differentiation in the developing cortex (Greene et al., 2009;Frank et al., 2010). Moreover, ATF4, is a central controller of the transcriptional events governing establishment of long-term memory (Karpinski et al., 1992;Bartsch et al., 1995;Chen et al., 2003;Lee et al., 2003;Costa-Mattioli and Sonenberg, 2006;Costa-Mattioli et al., 2007), and is additionally involved in regulation of emotional behaviour (Green et al., 2008) and behavioural flexibility (Trinh et al., 2012) in rodent models. Collectively, these observations support the hypothesis that ATF4 dysregulation may contribute to the pathophysiology of schizophrenia, characteristics of which include impaired emotional behaviour and cognition, and for which various environmental stressors are believed to contribute significantly to risk, (Trinh et al., 2012). We, and others, have carried out *in vitro* reporter assays (Sawamura et al., 2008;Malavasi et al., 2012) which have established that DISC1 regulates the transcriptional activity of both exogenously expressed, and endogenous stress-induced, ATF4 on different promoter elements, and may thus be potentially involved in regulation of multiple ATF4-dependent transcriptional events. Both ATF4 and ATF5 expression is subject to circadian regulation (Igarashi et al., 2007;Lemos et al., 2007;Koyanagi et al., 2011), and a direct involvement in the control of circadian pathways has been demonstrated for ATF4 (Koyanagi et al., 2011;Ushijima et al., 2012), suggesting a potential mechanism linking nuclear DISC1 expression to altered sleep/wake cycles in the fruit fly (Sawamura et al., 2008). Since DISC1 is also capable of binding the nuclear receptor co-repressor NCoR, a transcriptional co-repressor that recruits histone deacetylase to the transcriptional machinery (Jepsen and Rosenfeld, 2002), it was hypothesised that DISC1 may act by recruiting this factor to the ATF4-containing complex on DNA (Sawamura et al., 2008). Intriguingly, and consistent with their detrimental effect on DISC1 nuclear expression, we recently demonstrated that amino acid substitutions 37W and 607F significantly impair DISC1's ability to regulate ATF4-dependent transcription *in vitro* (Malavasi et al., 2012), suggesting that these DISC1 variants may contribute to susceptibility to psychiatric illness, at least in part, by affecting the DISC1-dependent regulation of ATF4 transcriptional activity.

12 DISC1 at the subcellular level - centrosome

In actively dividing animal cells, microtubules nucleate from the centrosome, which functions as the main microtubule-organising center (MTOC)(Nigg and Raff, 2009). The centrosome consists of a pair of microtubule-based structures, the centrioles, embedded in an amorphous protein matrix, the pericentriolar matrix (PCM) (Nigg and Raff, 2009). As well as being essential for the process of cell division, it is well established that the centrosome plays important roles throughout neurodevelopment. In proliferating neural progenitors, the centrosome regulates asymmetrical distribution of cell fate factors to daughter cells, thus determining whether they will continue dividing, or begin differentiating (Higginbotham and Gleeson, 2007). Moreover, correct positioning of the centrosome is necessary for establishment of cell polarity in newborn neurons, and for migration of developing neurons to their final destinations in the brain (Kuijpers and Hoogenraad, 2011).

Various centrosomal proteins, including NDE1, NDEL1, LIS1, PCM1, CAMDI, PCNT (also known as Kendrin) and multiple BBS proteins are DISC1 binding partners (Morris et al., 2003;Ozeki et al., 2003;Brandon et al., 2004a;Miyoshi et al., 2004;Camargo et al., 2007;Shinoda et al., 2007;Kamiya et al., 2008;Fukuda et al., 2010). All these proteins have well-established roles in centrosome-dependent aspects of neural development, and some of them cause severe brain development defects when mutated. For example, as previously mentioned, mutations affecting LIS1 are associated with lissencephaly, a condition arising from defective neuronal migration and characterised by lack of cortical folds, severe mental retardation and seizures (Reiner et al., 1993). On the other hand, mutations in PCNT result in primordial dwarfism and microcephaly (small brain size) (Rauch et al., 2008), mutations

in NDE1 cause microcephaly and microlissencephaly (Alkuraya et al., 2011;Bakircioglu et al., 2011;Guven et al., 2012), whereas BBS4 mutations are associated with Bardet-Biedl syndrome, a pleiotropic disorder that is often accompanied by mental retardation (Mykytyn et al., 2001).

A number of studies independently reported localisation of DISC1 to the centrosome in cultured cell lines and primary neurons (Morris et al., 2003;Miyoshi et al., 2004;Kamiya et al., 2005;Bradshaw et al., 2008;Kamiya et al., 2008). DISC1's centrosomal localisation requires interaction with Kendrin (Miyoshi et al., 2004;Shimizu et al., 2008). Disruption of DISC1-Kendrin binding prevents DISC1 recruitment to the centrosome and impedes microtubule aster formation, highlighting the importance of this interaction for correct centrosomal function (Shimizu et al., 2008). Further studies established that centrosomal DISC1 is involved in the recruitment and anchoring of several other essential centrosomal proteins to this organelle. For example, DISC1 cooperates with its interactor BBS4 to tether PCM1 to the centrosome (Kamiya et al., 2008). Here, PCM1 is in turn necessary for the correct localisation of other centrosomal proteins, including Kendrin (Kamiya et al., 2008), and for the correct organisation of microtubule arrays (Dammermann and Merdes, 2002). Interestingly, studies in cell models and post-mortem human brains have evidenced an influence of risk-conferring DISC1 amino acid substitutions L607F and S704C on PCM1 centrosomal recruitment (Eastwood et al., 2009;Eastwood et al., 2010). Exogenous expression of DISC1-607F in a neural cell line is associated with reduced centrosomal immunoreactivity of endogenous PCM1 compared to cells expressing DISC1-607L (Eastwood et al., 2009). Consistent with findings in cultured cells, analysis of brain tissue from DISC1 607F homozygotes revealed a trend towards reduced centrosomal PCM1 immunoreactivity in glial cells, and the same was observed in tissue from DISC1-704C carriers (Eastwood et al., 2010). Moreover, a potential cumulative effect between the two DISC1 variants was observed, whereby PCM1 centrosomal abundance was lowest in brain tissue from 607F homozygotes that were also 704C carriers (Eastwood et al., 2010). The molecular mechanism behind the effects of DISC1 amino acid substitutions L607F and S704C on PCM1 localisation is not known, but it is possible that these amino acid substitutions might directly disrupt DISC1 binding to PCM1 and/or reduce DISC1 localisation to the centrosome, perhaps by reducing its binding to Kendrin. Like PCM1, CAMDI is recruited to the centrosome in a DISC1-dependent manner (Fukuda et al., 2010).

Importantly, centrosomal DISC1 is also necessary for anchoring the dynein microtubule motor complex (Kamiya et al., 2005). Overexpression of $DISC1^{1-597}$ displaces endogenous wild-type DISC1 from the centrosome and prevents the DISC1-mediated recruitment of the dynein motor complex to the centrosome, which is consequently unable to organise the microtubule network (Kamiya et al., 2005). Failure of DISC1-dependent recruitment of the dynein motor complex to the centrosome has been suggested to underlie the neurite outgrowth and cortical migration defects observed in neurons after DISC1 knock-down or overexpression of $DISC1^{1-597}$(Kamiya et al., 2005). This hypothesis is supported by the observation that DISC1 knock-down in cortical neurons significantly increases the distance between the centrosome and the nucleus, which is one of the proposed mechanisms accounting for the migration defects (Kamiya et al., 2005).

The dynein motor complex also contains NDE1, NDEL1 and LIS1, which together regulate either cargo recruitment or dynein processivity (Lam et al., 2010). This complex is essential for the correct organisation and function of microtubule networks during neurite outgrowth and neuronal migration (Wynshaw-Boris and Gambello, 2001). Our work showing that the cAMP phosphodiesterase PDE4 co-localises with DISC1 at the centrosome, together with LIS1, NDEL1 and its paralogue NDE1, suggests a potential role for cAMP and DISC1/PDE4 in regulation of the NDE1/NDEL1/LIS1 complex at this location (Bradshaw et al.,

2008). Indeed, we demonstrated that two NDE1 residues, S306 and T131, can be phosphorylated by PKA and that this is regulated by DISC1 and PDE4 (Bradshaw et al., 2011). NDE1 phosphorylation at T131 inhibits its binding to LIS1 while promoting its interaction with NDEL1 (Bradshaw et al., 2008;Bradshaw et al., 2011). Moreover PDE4 itself binds directly to NDEL1 to promote NDEL1/NDEL1 self-association, and this interaction is ablated by cAMP (Collins et al., 2008). PDE4 also binds directly to LIS1, an interaction that is augmented by cAMP (Murdoch et al., 2011). Cyclic AMP, via DISC1 and PDE4, thus substantially redistributes interactions within the LIS1/NDE1/NDEL1 complex. Critically, these effects of cAMP are accompanied by decreased LIS1 interaction with dynein and loss of dynein function (Murdoch et al., 2011).

13 DISC1 at the subcellular level – primary cilium

The observation that exogenous DISC1 localises at the base of primary cilia in NIH3T3 cells and primary striatal neurons, supports its potential involvement in the establishment and/or function of this structure (Marley and von Zastrow, 2010). Primary cilia are single immotile filamentous protrusions found on virtually all cell types, including neurons and glia (Louvi and Grove, 2011). They consist of a long membrane-enveloped axoneme projecting from a basal body or mother centriole, which is structurally indistinguishable from the one that originates the centrosome (Nigg and Raff, 2009). The basal body has the dual function of anchoring the cilium to the cell surface and organising the movement of cargo molecules along ciliary microtubules to and from the cytoplasm, in a process known as intraflagellar transport (IFT) (Nigg and Raff, 2009). The motor proteins Kinesin and Dynein are necessary for IFT which is, in turn, essential for the establishment and maintenance of primary cilia (Nigg and Raff, 2009), while NDE1 knockdown promotes ciliogenesis (Kim et al., 2011). Ciliogenesis additionally depends on the transport of membrane vesicles required for ciliary membrane assembly, a process mediated by a large complex of BBS proteins (the BBSome) located at the basal body (Nigg and Raff, 2009). Primary cilia are multifunctional organelles that act as sensors for both mechanical and extracellular stimuli, and they are additionally involved in the regulation of key developmental signalling pathways. Primary cilia also act as regulators of canonical and non-canonical wnt signalling, and mutations that prevent the development of primary cilia in mice result in markedly increased β-catenin levels, suggesting that primary cilia normally inhibit wnt signalling (Berbari et al., 2009). Loss-of-function mutations of proteins required for normal ciliogenesis, including BBS proteins, result in a broad spectrum of developmental and degenerative disorders collectively described as ciliopathies (Hildebrandt et al., 2011). Several ciliopathies, including Bardet-Biedl syndrome and Joubert syndrome, present neurodevelopmental and/or cognitive defects as part of their clinical spectrum (Louvi and Grove, 2011). Consistently, genetic ablation of ciliogenesis in mouse models causes brain development defects, and it also inhibits adult hippocampal neurogenesis by decreasing the formation, expansion and maintenance of the pool of proliferating neural progenitor cells (Breunig et al., 2008;Han et al., 2008;Amador-Arjona et al., 2011) while inhibiting the morphological and functional maturation of newborn neurons in the adult dentate gyrus (Kumamoto et al., 2012). Intriguingly, DISC1 knock-down in NIH3T3 cells or primary striatal neurons reduces the number of primary cilia to a similar extent as depletion of IFT88, a protein essential for ciliogenesis (Marley and von Zastrow, 2010). Moreover, the ciliogenesis defects induced by DISC1 knockdown in NIH3T3 cells and striatal neurons can be fully rescued by exogenous expression of GPF-DISC1, strongly supporting a central role of DISC1 in ciliogenesis in both neuronal and non-neuronal cells (Marley and von Zastrow, 2010). Interestingly, several neuroreceptors, including dopamine receptors 1, 2 and 5, serotonin receptor 6 and somatostatin receptor 3, are prominently or exclusively expressed in neuronal primary cilia, strongly implicating this organelle in neurotransmission (Handel et al., 1999;Marley and von Zastrow, 2010;Domire et al., 2011). In mice, the ENU-induced DISC1 single amino acid substitution L100P is

associated with a behavioural phenotype related to characteristics of schizophrenia (Clapcote et al., 2007). DISC1 100P mice display hypersensitivity to the psychostimulant effects of amphetamine, which induces dopamine release, coupled to an increased proportion of high-affinity functional D2 receptors in the striatum (Lipina et al., 2010). Conversely, inducible expression of human DISC1$^{1\text{-}597}$ is linked to altered responses to the amphetamine analogue methamphetamine, and decreased D2 receptor expression (Pogorelov et al., 2012). Collectively, these findings raise the intriguing possibility that, besides being directly involved in the formation and maintenance of primary cilia, where D2 receptors are primarily expressed, DISC1 might also contribute to the trafficking and/or functional modulation of ciliary D2 receptors. It would thus be interesting to examine if and how the 100P mutation, as well as clinically relevant DISC1 mutations, affect the development and function of primary cilia in relevant neuronal populations.

14 DISC1 at the subcellular level - mitochondria

Mitochondria are the major source of ATP, through oxidative phosphorylation, but they also perform additional functions, including calcium homeostasis. Of all the organs in the body, the brain is particularly sensitive to mitochondrial dysfunction, in part due to its extremely high energy requirements, approximately 20% of total body energy consumption at rest. The majority of this energy consumption is due to neurotransmission. Neuronal action potential firing results in influx of sodium or calcium ions, among others, and neurons consequently must utilise the majority of their ATP for rebalancing the ionic gradients that are essential to maintain their excitability. Indeed, sodium and calcium transport, including mitochondrial calcium transport, are estimated to account for 40-50% or 3-7%, respectively, of ATP utilised by the brain (Ames, 2000). An estimated further 10-20% of ATP is used for additional aspects of neurotransmission, including neurotransmitter synthesis, packaging and transport to synapses (Ames, 2000).

Any factor affecting mitochondrial function and/or transport is likely to deleteriously affect neurotransmission and other cellular processes, ultimately influencing brain development/function at multiple levels. Not surprisingly then, mitochondrial dysfunction is believed to underpin a number of important neurological diseases, including Parkinson's, Alzheimer's and Huntington's diseases (Han et al.) and there is now accumulating evidence pointing towards DISC1 being another factor that induces mitochondrial dysfunction to cause brain disease, indeed network analysis indicates enrichment of Huntingtin binding partners in networks of interactors built around DISC1, including a number of mitochondrial proteins (Boxall et al., 2011).

DISC1 associates with mitochondria, where it has been detected both at mitochondrial membranes in an unspecified location (Ramsey et al., 2011;Paspalas et al., 2012) and inside the outer mitochondrial membrane (James et al., 2004;Park et al., 2010), in association with mitofilin (Park et al., 2010), a core component of the Mitochondrial Inner Membrane Organising System (MINOS), the Mitochondrial Organising Structure (MitOS) or the Mitochondrial Intermembrane space Bridging complex (MIB)(Hoppins et al., 2011;Alkhaja et al., 2012;Ott et al., 2012). These multiprotein complexes, which likely represent the same entity, attach cristae membranes to the inner mitochondrial membrane and promote assembly of respiratory chain complexes (Hoppins et al., 2011;Alkhaja et al., 2012;Ott et al., 2012). Mitofilin knockdown induces mitochondrial morphological abnormalities visible at the ultrastructural level, including disorganisation of the mitochondrial inner membrane and loss of cristae junctions (John et al., 2005).DISC1 modulates mitofilin ubiquitination and stability (Park et al., 2010) and, intriguingly, DISC1 knockdown induces similar mitochondrial membrane architecture abnormalities to mitofilin knockdown (Park et al.,

2010), suggesting that it may directly regulate mitochondrial inner membrane architecture via mitofilin.

In addition, knockdown of either DISC1 or mitofilin, or expression of $DISC1^{1-597}$, reduces the activity of mitochondrial NADH dehydrogenase, a component of the respiratory chain pathway, and consistent with this, cellular ATP levels are reduced (Park et al., 2010). Decreased mitochondrial monoamine oxidase activity and perturbed calcium dynamics also result from the same treatments (Park et al., 2010). Altogether these observations indicate that DISC1 and mitofilin influence a range of mitochondrial processes, and this may occur through effects on mitochondrial membrane organisation.In support of these observations, DISC1 and mitofilin both associate with CHCM1/CHCHD6, another protein of the inner mitochondrial membrane (An et al., 2012). Like mitofilin and DISC1, CHCM1/CHCHD6 regulates cristae morphology (An et al., 2012), and knockdown of this protein leads to reduced ATP synthesis, reduced oxygen consumption, and slowed cell growth (An et al., 2012).

As well as mitochondrial function *per se*, mitochondrial trafficking is also of critical importance to the brain because, for neuronal mitochondria to deliver their energy provision and calcium buffering to the synapse, they must be efficiently transported along axons and dendrites, which can be extremely lengthy in some cases. It is therefore notable that DISC1 expression levels influence the number of motile mitochondria within neurons, as assessed by live cell imaging (Atkin et al.;2011). The mechanism by which manipulation of DISC1 expression exerts these effects upon mitochondrial motility is not yet known, however it is possible that they are a consequence of effects on mitochondrial membrane architecture and general mitochondrial function: Mitochondrial transport is an active process that would be predicted to be affected by ATP production. Moreover, mitochondrial damage and intracellular calcium levels influence mitochondrial transport (Miller and Sheetz, 2004;Yi et al., 2004), thus the morphological and functional mitochondrial abnormalities caused by DISC1 knockdown (Park et al., 2010) could contribute to inhibition of axonal mitochondrial motility induced by the same treatment in neurons (Atkin et al.;2011). Alternatively, DISC1 may affect the mitochondrial transport process more directly (see section 15), although this possibility has yet to be investigated.

There is mounting evidence that DISC1-induced mitochondrial function and/or transport defects may contribute to disease risk. In addition to the observations discussed above, we have demonstrated that two of the aberrant DISC1 species putatively expressed by t(1;11) translocation carriers (Eykelenboom et al., 2012), CP60 and CP69, are almost exclusively mitochondrial and induce profound mitochondrial dysfunction, manifest as perinuclear mitochondrial clustering and loss of membrane potential (Eykelenboom et al., 2012). Notably, we have found that addition of GFP tags, or deletion of the C-terminal tail, also results in increased mitochondrial DISC1 expression and altered mitochondrial morphology (Millar et al., 2005a). While these latter two examples are not disease-related, they further illustrate the emerging impression that aberrant DISC1 expression frequently leads to increased mitochondrial targeting and mitochondrial dysfunction. Finally, the disease-associated DISC1 common sequence variant 607F fails to rescue the block on axonal mitochondrial transport induced by DISC1 knock down (Atkin et al., 2011). Altogether, these observations indicate that altered DISC1 expression and/or function compromises mitochondrial function and may contribute to disease risk. Consistent with this, there is evidence for mitochondrial dysfunction in schizophrenia and bipolar disorder (Rezin et al., 2009;Clay et al., 2011), and it is now essential to discover whether psychiatric patients carrying the t(1;11) translocation or the DISC1 607F variant, or otherwise exhibiting altered DISC1 expression, suffer mitochondrial dysfunction.

15 DISC1 functions at the subcellular level – motor proteins

DISC1 knockdown inhibits axonal transport of various cargoes, including mitochondria (see mitochondria section) and synaptic vesicles (Shinoda et al., 2007;Taya et al., 2007;Atkin et al., 2011;Flores et al., 2011), suggesting a general role in microtubule-based intracellular transport. This process is mediated by the co-ordinated actions of multiple molecular motors including kinesin and dynein which are respectively responsible for anterograde and retrograde microtubule-based transport. Anterograde transport is essential in all cells, but particularly so in neurons for trafficking of cargo, including newly synthesised proteins, receptors and synaptic vesicles or mitochondria, to distant regions such as axonal growth cones and synapses. Retrograde transport is required, for example, for synaptic vesicle recycling or transport of chemical messengers back to the soma, thus allowing the synapse to communicate with the cell body. Kinesin and dynein are also essential for additional functions including mitosis and nucleokinesis and thus, in the brain, are critical for processes such as neural precursor proliferation and neuronal migration.

DISC1 associates with kinesin1, and DISC1 knockdown reduces axonal transport of the proteins GRB2, LIS1, NDEL1 and 14-3-3Epsilon, which are all kinesin-associated (Shinoda et al., 2007;Taya et al., 2007), suggesting a direct role in anterograde axonal transport. Interestingly, the DISC1 interactor FEZ1 (Miyoshi et al., 2003) is also implicated in this transport process. FEZ1 complexes with kinesin 1 and tubulin to promote anterograde mitochondrial transport (Fujita et al., 2007;Ikuta et al., 2007). FEZ1 also promotes synaptic vesicle transport in association with kinesin 1, a process that is disrupted by expression of $DISC^{1-597}$ (Flores et al., 2011). In Drosophila FEZ1 acts as an intermediary between kinesin 1 and the synaptic vesicle membrane protein Synaptotagmin 1 (SYT1) (Toda et al., 2008). DISC1, but not $DISC1^{1-597}$, promotes FEZ1 interaction with SYT1, suggesting that DISC1 may facilitate recruitment of synaptic vesicles to the transport complex for trafficking to the synapse (Flores et al., 2011). Intriguingly, lithium, in clinical use as a mood stabiliser, reverses the FEZ1/SYT1 association and synaptic vesicle trafficking defects induced by expression of $DISC1^{1-597}$ (Flores et al., 2011). It is tempting to speculate that DISC1 also participates in recruiting mitochondria to kinesin/FEZ1 complexes. It will be interesting to discover whether DISC1 has a general role in recruiting cargo to kinesin transport complexes, which could help to explain its very large number of interactors.

As already discussed (see section 12), DISC1 also complexes with Dynein Intermediate Chain (DIC) and the dynein adaptor protein Dynactin ($p150^{glued}$) (Kamiya et al., 2005), and may thus be involved in retrograde intracellular transport, although this has yet to be demonstrated.

16 Involvement of DISC1-associated molecules in disease risk

There is evidence that a number of DISC1-associated proteins are themselves involved in conferring risk of psychiatric illness (summarised in Table 1 for schizophrenia) or are associated with brain-related traits (Table 2). For some of these the convergent evidence is becoming compelling. As for DISC1, we have demonstrated that the PDE4B gene is directly disrupted by a chromosomal translocation in psychiatric patients (Millar et al., 2005b) and a number of genetic studies have found evidence for involvement in schizophrenia (Table 1). The potential importance of AKT, GSK3β, NDEL1, LIS1 and 14-3-3Epsilon are all highlighted by several genetic association studies (Table 1), while NDE1 shows association with schizophrenia (Table 1) and is also targeted by a number of CNVs identified in psychiatric patients (Ingason et al., 2011). Moreover, there are recent reports of interplay/epistasis between DISC1 and its protein interactors from structural and fMRI studies (Mata et al., 2010;Nicodemus et al., 2010;Kang et al., 2011) adding to the initial reports suggesting

interaction between candidate genes for schizophrenia (Hennah et al., 2007;Burdick et al., 2008), as proposed by Meyer-Lindenberg and Weinberger (Meyer-Lindenberg and Weinberger, 2006). These reports suggest that epistatic interactions affecting genetic risk may occur between DISC1 and NDEL1/NDE1 (Hennah et al., 2007), with Ser704Cys status altering both risk of schizophrenia detected using the NDEL1/NDE1 SNPs, and NDEL1/NDE1 binding to DISC1 (Burdick et al., 2008). An interaction between DISC1 3′ UTR SNP rs1411771 and an intronic SNP in the gene encoding another DISC1 interactor, CIT, has also been shown to increase the risk of developing schizophrenia, and this was validated by fMRI (Nicodemus et al., 2010). Genetic interaction between DISC1 and PDE4B influences regional brain volume (Andreasen et al., 2011), while epistasis between Ser704Cys and FEZ1 is reported to act on the risk of developing schizophrenia, and synergistic effects of the two proteins on dendritic growth of newborn neurons in the adult mouse hippocampus are reported (Kang et al., 2011). Finally, SNPs within DISC1 and the gene encoding NKCC1 also interact (Kim et al., 2012). Altogether, these studies indicate that pathways involving DISC1 and these associated molecules may be of particular relevance to the aetiology of mental illness.

17 Summary

Although the contribution of DISC1 to total risk of mental illness remains unknown, it is apparent that rare genetic events that target the DISC locus, such as the t(1;11) translocation and CNVs, can predispose individuals to developing a major psychiatric disorder. Indeed, the unequivocal segregation of the t(1;11) translocation with schizophrenia, bipolar disorder and major depressive disorder indicates that disruption of the DISC1 gene is likely to be a major predisposing factor in this family. Thus studying DISC1 function and the effect of the translocation will inform on the disease pathways operating in translocation carriers, and likely also in unrelated psychiatric patients as a result. Such studies have highlighted critical roles for DISC1 at many stages of neurogenesis (neural precursor proliferation, neuronal migration and neuronal integration/maturation) indicating that any factor that compromises normal DISC1 function is likely to impact upon brain development and also production of new neurons in the adult brain. Importantly, DISC1 also has multiple roles at the pre- and post-synapse, indicating that neurosignalling deficits are likely to occur, in addition to developmental defects. DISC1 regulates these pathways through interaction with an extensive array of protein interactors and most likely via a complex blend of alternative splicing, distribution to multiple subcellular compartments, oligomerisation and regulation of protein phosphorylation. Intriguingly, many DISC1 interactors are themselves implicated as risk factors for mental illness, and there is evidence for epistasis between DISC1 and its interactors in disease risk. Moreover, consistent with its multiple roles in the developing and adult brain, DISC1 is now also implicated in risk of autism spectrum disorders, and there is emerging genetic and molecular evidence of overlap with molecular pathways relating to proteins involved in Alzheimer’s disease, while protein network analysis indicates possible functional overlap with Huntingtin. It will therefore be interesting to find out if DISC1 dysfunction can result in the kind of neurodegeneration that characterises Alzheimer’s or Huntington’s diseases.

An increasing number of studies are addressing the effects of missense variants upon DISC1 function, and common variants are now known to influence DISC1 oligomerisation, and nuclear targeting, with effects upon signalling pathways, nuclear transcription, centrosome composition and mitochondrial trafficking. Normal variation thus influences DISC1 function, and consequently numerous brain processes, at many levels. Notably, some of the same processes are also affected by at least one rare, putatively causal variant. Consistent with these observations, imaging studies have demonstrated effects of common DISC1 variants upon brain structure in adults, either unaffected or diagnosed with a mental

disorder. These effects upon DISC1 function and brain structure likely contribute to disease risk, as evidenced by the association of some of the common variants with psychiatric disorders. Moreover, the paradigm of interaction between genes and the environment in determining disease risk is well established for major mental illness (van Os et al., 2008), with maternal deprivation stress and maternal immune activation (for example due to viral infection) already believed to be critical environmental risk factors. It is thus intriguing that the genetic risk factor DISC1 apparently interacts with these environmental risk factors to adversely affect postnatal brain development or behavioural phenotypes in mice. DISC1 also interacts directly with transcription factors that regulate the pathways by which cells respond to a variety of environmental stressors, and may therefore directly mediate the effects of stress. Such DISC1-environment interactions may go some way towards explaining the incomplete penetrance of the t(1;11) translocation (Blackwood et al., 2001).

Studying DISC1 function has revealed much about the brain processes that are likely to be adversely affected by DISC1 dysfunction and one of the challenges now is to determine if/how these pathways involving DISC1 contribute to psychiatric disorders, and why the outcomes of DISC1 dysfunction are so variable - the t(1;11) translocation apparently causes brain dysfunction in all carriers, but some carriers are unaffected, while others suffer from schizophrenia, bipolar disorder or depression. Moreover, one of the major motivations for studying DISC1, or indeed any other risk factor for major mental illness, is ultimately to develop more effective therapeutic interventions than are currently available. DISC1 itself is not likely to be a viable drug target, but the ever-increasing information on DISC1 brain function is revealing pathways that are, or may be, druggable in patients. Another considerable challenge will therefore be to determine if/which pathways involving DISC1 can be targeted to effectively treat the symptoms of psychiatric illness. A number of DISC1 mutant mice with defined behavioural phenotypes have been generated that will aid in this process, and induced pluripotent stem cells will provide an essential complementary tool. IPSC can now be generated directly from patient-derived primary cells such as skin fibroblasts, and ultimately differentiated into neural progenitors, specified neuronal subtypes or even glial cells. Because these cells can be generated from patients and their unaffected family members it is possible to assay the effects of endogenous mutations, CNVs, common variants etc in human neural material, and importantly, against the relevant genetic background which may include genetic modifiers or other risk alleles. Such IPSC have already been generated for the four base pair deletion in exon 12 identified in one family (Chiang et al., 2011), and are in prospect for the t(1;11) translocation family.

Acknowledgments

We thank David Porteous for critical reading of this manuscript. DCS is funded by the Wellcome Trust (WT088179MA), MB is funded by an MRC studentship and EG is funded by the MRC (MR/J004367/1).

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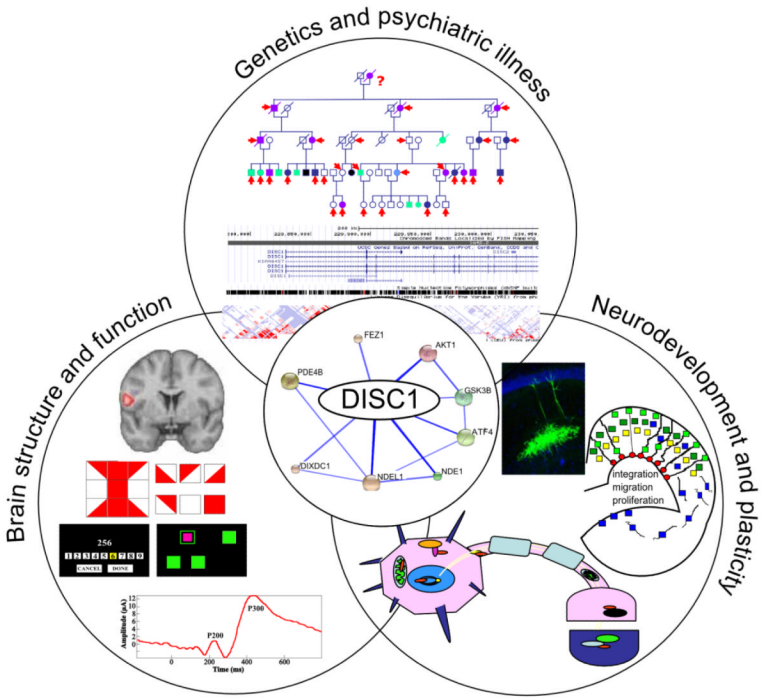

Figure 1.

DISC1 in neurodevelopment, brain functioning and psychiatric illness. DISC1 is a scaffold protein with many functional partners associated with brain development and disease. *Genetics and psychiatric illness*: The DISC1 protein network was modified from String DB (http://string-db.org/). The t(1;11) Scottish pedigree was modified, with permission, from Blackwood et al. (Blackwood et al., 2001) . A fragment of the DISC1 gene structure, SNPs and linkage disequilibrium blocks was generated using the UCSC genome browser (http://genome.ucsc.edu/). *Brain structure and function*: Examples of neurocognitive tests in which individuals carrying variants at the DISC1 locus show altered performance; differences in brain activation by DISC1 L607F genotype as measured by functional MRI (with thanks to Andrew McIntosh); the P300 event related potential, which is elicited in decision making, and shows reduced amplitude and latency in DISC1 translocation carriers. *Neurodevelopment and plasticity*: DISC1 is a multi-compartmentalised protein, present at the nucleus, centrosome, mitochondria, microtubules and synapse; DISC1 has roles in neurodevelopment and plasticity, in proliferation, migration and integration of neurons; neural stem cells are a promise in research and treatment of psychiatric and neurodegenerative disorders; GFP-labelled neural stem cells transplanted into the mouse brain can give rise to cells resembling normal hippocampal neurons (Image by Yirui Sun, Wellcome Images[cc]).

Table 1

Evidence of association to schizophrenia from candidate gene studies for selected DISC1 interactors. Evidence for association was identified using SZGene (http://www.szgene.org/, updated 23 December 2011). The table shows those found in SZGene, the total number of studies (both case-control and familial) listed in SZGene, and whether any SNP remained significant after meta-analysis. Note: Only those SNPs with published genotype data in at least four independent case-control samples eligible for analysis were subjected to meta-analysis by SZGene (see http://www.szgene.org/methods.asp for details).

gene	present in SZgene	number of studies	results	meta-analysis significant SNPs
DISC1	Y	45 studies	31 positive/9 negative/ 3 trend	rs3737597, rs999710
AKT1	Y	17 studies	9 positive/7 negative/1 trend	rs3803300
ATF4	Y	1 study	negative	
ATF5	Y	1 study	negative	
BBS1				
BBS4				
CCDC141				
CCDC88A (encodes KIAA 1212/Girdin)				
CIT	Y	1 study	positive	
DIXDC1				
FEZ1	Y	5 studies	negative	
GRB2				
GSK3β	Y	8 studies	1 positive/6 negative/1 trend	
KALRN (encodes KAL-7)				
NDE1	Y	4 studies	negative	
NDEL1	Y	7 studies	4 positive/3 negative	
PAFAH1B1 (encodes LIS1)	Y	5 studies	1 positive/4 negative	
PCM1	Y	7 studies	6 positive/1 negative	
PCNT	Y	3 studies	1 positive/1 negative/1 trend	
PDE4A				
PDE4B	Y	12 studies	9 positive/3 negative	rs910694
PDE4C				
PDE4D	Y	2 studies	positive	
SLC12A2 (encodes NKCC1)				
TNIK				
YWHAE (encodes 14-3-3s)	Y	5 studies	2 positive/3 negative	

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Table 2

Evidence of association between DISC1 interactors and brain-related traits. Evidence from genome-wide studies was downloaded from the NCBI Phenotype-Genotype Integrator (http://www.ncbi.nlm.nih.gov/gap/PheGenI) for any category or trait with p-values $p < 1 \times 10^{-5}$. Brain-related traits were identified by inspection. The full list of genes examined is given in Table 1.

trait	SNP	context	gene	p-value
neuroanatomy	rs12042938	intron	DISC1	4.00E-36
Alzheimer's disease	12044355	intron	DISC1	9.00E-06
schizophrenia	2088885	intron	TNIK	6.00E-06
neurotic disorders	702543	intron	PDE4D	2.00E-06
mental competency	295973	intron	PDE4D	7.61E-07
mental competency	295973	intron	PDE4D	7.61E-07
neuroblastoma	9892996	intergenic	SLC25A19/GRB2	2.23E-07
neuroblastoma	16967789	intron	GRB2	1.10E-06