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DISC1-binding proteins in neural development, signalling and schizophrenia

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ABSTRACT

In the decade since *Disrupted in Schizophrenia 1* (*DISC1*) was first identified it has become one of the most convincing risk genes for major mental illness. As a multi-functional scaffold protein, DISC1 has multiple identified protein interaction partners that highlight pathologically relevant molecular pathways with potential for pharmaceutical intervention. Amongst these are proteins involved in neuronal migration (e.g. APP, Dixdc1, LIS1, NDE1, NDEL1), neural progenitor proliferation (GSK3β), neurosignalling (Girdin, GSK3β, PDE4) and synaptic function (Kal7, TNIK). Furthermore, emerging evidence of genetic association (*NDEL1*, *PCM1*, *PDE4B*) and copy number variation (*NDE1*) implicate several DISC1-binding partners as risk factors for schizophrenia in their own right. Thus, a picture begins to emerge of DISC1 as a key hub for multiple critical developmental pathways within the brain, disruption of which can lead to a variety of psychiatric illness phenotypes.

This article is part of a Special Issue entitled 'Schizophrenia'.

1. Introduction

A key objective of genetics and genomics research into psychiatric illness is to identify perturbed biological pathways and, as a consequence, potential targets for pharmacological intervention. The genetic entrée point need not itself explain a large fraction of the liability to schizophrenia – it is sufficient that genetic abrogation *can* cause schizophrenia. DISC1 and the extended DISC1 pathway illustrate this contention par excellence. DISC1 was identified through a unique family in which a chromosomal translocation event co-segregates strongly with major mental illness (Blackwood et al., 2001; St Clair et al., 1990). This translocation event directly disrupts both a protein coding gene, *DISC1,* and an antisense RNA only gene, *DISC2* (Millar et al., 2000). In the intervening period, the *DISC* locus has been repeatedly implicated in psychiatric illness by genetic linkage, association and mutation detection (reviewed in Chubb et al., 2008, see Table 1 for references and summaries of recent studies). Some studies have also pointed to epistatic interactions between the *DISC* locus and other candidate genes (Burdick et al., 2008; Hennah et al., 2007; Nicodemus et al., 2010). Despite these many confirmatory studies, there are also negative studies (Chubb et al., 2008 and references in Table 1) and, as yet, no firm basis on which to estimate the proportion of genetic liability attributable to the *DISC* locus. The *DISC* locus has appeared as a gene-wide, but not a genome-wide finding in some (Sullivan et al., 2008) but not other (Sanders et al., 2008) studies. The critical issue is what we can learn from the identification of DISC1 regarding the specifics and generalities of the biological underpinning of schizophrenia and other major mental illness.

The DISC1 protein has no known enzymatic activity; rather it exerts its effect on multiple proteins through interaction to modulate their functional states and biological activities in time and space. Many putative interacting proteins have been identified through extensive yeast-2-hybrid screening (Brandon et al., 2004; Camargo et al., 2007; Millar et al., 2003; Morris et al., 2003; Ozeki et al., 2003) and, where these have been examined, a large proportion have been validated by downstream experimentation (reviewed in Chubb et al., 2008). These multiple interactions, combined with the widespread subcellular distribution of DISC1 (reviewed in Chubb et al., 2008), a complex pattern of protein isoforms (James et al.,

Abbreviations: APP, Amyloid precursor protein; ATF4, Activating transcription factor 4; BACE1, β-site APP-cleaving enzyme-1; BBS4, Bardet–Biedl syndrome 4; CEP290, Centrosomal protein 290 kDa; CNV, Copy number variation; CRE, cAMP response element; DBZ, DISC1-binding zinc finger; DISC1, Disrupted in schizophrenia 1; Dixdc1, Dishevelled-axin domain containing-1; FEZ1, Fasciculation and elongation protein zeta 1; GluR, Glutamate receptor; GSK3β, Glycogen synthase kinase 3β; Kal7, Kalirin-7; LEF/TCF, Lymphoid enhancer factor/T cell factor; LIS1, Lissencephaly 1; mTOR, Mammalian target of rapamycin; NDE1, Nuclear distribution factor E homologue 1 or Nuclear distribution element 1; NDEL1, NDE-like 1; NRG, Neuregulin; PACAP, Pituitary adenylate cyclase-activating polypeptide; PCM1, Pericentriolar material 1; PCNT, Pericentrin; PDE4, Phosphodiesterase 4; PI3 K, Phosphatidylinositiol 3-kinase; PSD, Post-synaptic density; Rac1, Ras-related C3 botulinum toxin substrate 1; TNIK, Traf2 and Nck interacting kinase.

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Table 1
Studies investigating genetic links between the *DISC* locus or the adjacent *TSNAX* locus and major mental illness, an endophenotype thereof or, in one study, chronic fatigue syndrome published since those reviewed by Chubb et al. (2008). SNPs bracketed together indicate haplotypes. SNPs separated by a hyphen (–) indicate significance when alleles are considered together, but not independently.

Study	Sample	Condition/phenotype	SNP, haplotype, marker or variant	Notes
Positive genetic association studies				
Palo et al. (2007)	Finnish families	Psychotic disorders	(rs1655285, rs751229)	Males only
			(rs751229, rs3738401)	Males only
			(rs751229, rs3738401, rs1538977)	Males only, principally those without bipolar spectrum disorder
			(rs1655285, rs751229, rs3738401)	Males only, principally those with bipolar spectrum disorder
		Bipolar spectrum disorders	rs1655285	
			(rs1630250, rs1615409)	Principally those without psychotic disorder
			(rs1655285, rs751229)	Females only
			(rs1000731, rs821616)	
			(rs821616, rs1411771)	
			(rs821616, rs1411771, rs980898)	
	Finnish families with bipolar disorder	General intellectual functioning	rs1615409	Significant by two measures
			rs821616	Significant by one measure
			rs980989	Significant by three measures
		Attention/working memory	rs980989	Significant by three measures
		Verbal learning	rs751229	Significant by two measures
			rs1322784	Significant by one measure
			rs1000731	Significant by one measure
			rs980989	Significant by two measures
		Executive functions	rs821616	Significant by one measure
Kilpinen et al. (2008)	Finnish families	Autism	D1S2709	
		Asperger's syndrome	rs1322784	Males only
			(rs751229, rs3738401)	
			(rs751229, rs3738401, rs1322784)	Males only
Kim et al. (2008a)	Korean	Schizophrenia with poor concentration	rs821616	
Perlis et al. (2008)	American trios	Bipolar disorder	(rs10495308, rs2793091, rs2793085)	
Saetre et al. (2008)	Danish	Schizophrenia	rs3737597	
	Norwegian	Schizophrenia	rs3737597	
	Swedish	Schizophrenia	rs3737597	
Hennah et al. (2009)	Finnish	Bipolar disorder	rs1538979	Males only
	English	Bipolar disorder	rs821577	Females only
	British/Finnish	Schizophrenia	rs821633-rs1538979	Females only.
Rastogi et al. (2009)	Canadian families	Schizophrenia	(rs11122359, rs701158)	
			(rs6675281, rs11122359)	
			(rs701158, rs821597)	
Schumacher et al. (2009)	German	Schizophrenia and early onset schizophrenia	rs1015101	Females only.
			rs999710	Females only.
			rs4333837	Females only.
		Schizophrenia	18x haplotyes	5 in males only, 11 in females only
			rs1538979	Significant in males when stratified on rs821633 allele
Tomppo et al. (2009b)	Finnish	Social anhedonia	rs821577	
			rs11122381	Females only.
			rs821592	Females only.
			rs821633	Significant when stratified on rs1538979 and rs821577 alleles
Fukuda et al. (2010)	Japanese	Chronic fatigue syndrome	rs821616	Females only.
Harris et al. (2010)	Scottish, elderly	Anxiety scores	rs821577	Lower in males, higher in females
			rs821633	Lower in males, higher in females
		Depression scores	rs821577	Females only
			rs821633	Females only
		Emotional stability scores	rs821577	Females only
			rs821633	Females only
		Neuroticism scores	rs821577	Females only
			rs821633	Females only
Lepagnol-Bestel et al. (2010)	French trios	Schizophrenia	rs6675281	
		Negative symptom scores	rs6675281	
	Algerian trios	Schizophrenia	rs821616	
		Negative symptom scores	rs6675281	
Mouaffak et al. (2010)	French	Ultra-resistant schizophrenia	rs3738401	
Nicodemus et al. (2010)	American	Schizophrenia	rs10744743-rs1411771	rs10744743 is an SNP in the *CIT* gene
Okuda et al. (2010)	Japanese	Major depressive disorder	rs766288	Females only
Schosser et al. (2010)	English	Bipolar disorder	rs2492367	
			rs7546310	
			(rs7546310, rs821597)	
			(rs766288, rs2492367)	
			(rs1000731, rs7546310)	
	British	Major depressive disorder	(rs7546310, rs821597)	

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