Utility and validity of DISC1 mouse models in biological psychiatry

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Abstract

We have seen an era of explosive progress in translating neurobiology into etiological understanding of mental disorders for the past 10–15 years. The discovery of *Disrupted-in-schizophrenia 1 (DISC1)* gene was one of major driving forces that have contributed to the progress. The finding that DISC1 plays crucial roles in neurodevelopment and synapse regulation clearly underscored the utility and validity of DISC1-related biology in advancing our understanding of pathophysiological processes underlying psychiatric conditions. Despite recent genetic studies that failed to identify *DISC1* as a risk gene for sporadic cases of schizophrenia, DISC1 mutant mice, coupled with various environmental stressors, have proven successful in satisfying face validity as models of a wide range of human psychiatric conditions. Investigating mental disorders using these models is expected to further contribute to the circuit-level understanding of the pathological mechanisms, as well as to the development of novel therapeutic strategies in the future.

Introduction

The *Disrupted-in-schizophrenia 1* (*DISC1*) was initially identified as a gene disrupted by a translocation mutation co-segregating with major mental illnesses, such as schizophrenia and depression, in a Scottish pedigree (Millar et al., 2000). When this mutation was reported in 2000, the current levels of genome-wide psychiatric genetics were not available. Thus, *DISC1* was expected to be a major molecular lead to elucidate biological mechanisms underlying major mental illnesses. Has *DISC1* met this expectation?

Recent genetic studies with large cohorts for schizophrenia and bipolar disorder have failed to provide convincing evidence for the role of *DISC1* as a “genetic” contributor to sporadic cases of schizophrenia (Purcell et al., 2009; Fromer et al., 2014; Purcell et al., 2014; Kranz et al., 2015). Meta analyses also have not supported the idea that common variants of the *DISC1* gene are associated with schizophrenia (Mathieson et al., 2012). Furthermore, genome-wide association studies have failed to identify *DISC1* as a promising gene associated with schizophrenia in the current diagnostic frameworks (Ripke et al., 2013; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015).

In contrast, in the first ten years since the discovery of the gene, studies using cells and model organisms that explore biological function of *DISC1* *in vitro* and *in vivo* have been fruitful. Roles for *DISC1* in neurodevelopment and synaptic regulation have been extensively characterized (Kamiya et al., 2005; Mao et al., 2009; Hayashi-Takagi et al., 2010; Singh et al., 2010; Ishizuka et al., 2011; Singh et al., 2011). These findings have become directly relevant to our understanding of disease processes (**Fig. 1**); compelling evidence is now available that biological pathways involving *DISC1* and its protein network can play pivotal roles in the pathologies relevant to severe mental conditions, in particular those that may be shared among schizophrenia, autism, and mood disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015). This is analogous to the role for Tau in the pathology of Alzheimer’s disease (AD). The contribution of the *Tau* gene specifically to sporadic cases of AD may not be outstanding, in contrast to the *ApoE* gene (Piaceri et al., 2013). Nonetheless, the biological pathway involving the Tau protein plays a central role in AD pathology (Krüger and Mandelkow, 2015). Likewise, the potential value of the *DISC1* protein as a “biological” lead in understanding molecular mechanisms for major mental illnesses is now appreciated.

In this review article, we will summarize recent updates on *DISC1* genetically-engineered mice. Although many investigators, including our group, provided review articles on *DISC1* mouse models in the past (Brandon and Sawa, 2011; Wong and Josselyn, 2015), the present article will highlight recent findings that were not well covered in the previous reviews. Furthermore, an addition of novel *DISC1* models for the past 3–4 years has enlarged our perspectives of how we can use these models to address

biological questions in major mental illnesses in a valid manner.

DISC1 as a scaffold protein in neurodevelopment and synaptic regulation

Molecular and cell biological studies revealed multifaceted roles of DISC1 in neurodevelopment and synaptic functions. DISC1 is an intracellular scaffold protein and interacts with many other proteins that are also known to play important roles for neurodevelopment and synaptic regulation. These interacting proteins include nuclear distribution protein Nudel-like 1 (NDEL1), platelet-activating factor acetylhydrolase 1B subunit alpha (PAFAH1B1, *a.k.a.* LIS1), Bardet-Biedl syndrome 4 (BBS4), Girdin/KIAA1212, phosphodiesterase 4 (PDE4), Kalirin7, TRAF2- and NCK-interacting kinase (TNIK), and glycogen synthase kinase 3 β (GSK3 β) (Brandon and Sawa, 2011; Hikida et al., 2012). Recent studies have identified even more interactors of DISC1, such as dopamine D2 receptors (D2R) (Su et al., 2014) and mRNA for inositol-1,4,5-trisphosphate receptor type 1 (ITPR1) (Tsuboi et al., 2015). This led to the hypothesis that some, if not all, of these functions elicited by DISC1 together with its interactors likely underlie pathophysiology of major mental conditions. To test this hypothesis, a series of mouse models of *Disc1* dysfunction have been generated through genetic manipulation. Perturbation of DISC1 may elicit an alteration in brain connectivity and function during developmental trajectory, which may underlie behavioral and cognitive phenotypes relevant to the diseases. Once such a link of the clinical manifestations to underlying biological mechanisms is elucidated through DISC1 mice, the models may also be useful for developing novel therapies based on mechanistic understanding (Brandon and Sawa, 2011).

In the following section, we will overview existing genetic mouse models for *DISC1* dysfunction and discuss how each model has contributed to neurobiology and translational psychiatry.

Haploinsufficiency models

The chromosomal translocation found in the Scottish family disrupts *DISC1* gene at intron 8 on one chromosome, while keeping this gene on the other chromosome intact. The disruption of the gene may lead to loss-of-function, possibly due to nonsense-mediated mRNA decay. Thus, the overall outcome elicited by this genetic mutation may be haploinsufficiency. Three models of loss-of-function of mouse *Disc1* gene have been generated so far: (i) a model truncating exon 8 of *Disc1* with an exogenously introduced stop codon on a genetic background that carries Δ 25bp deletion in exon 6 (called Δ 25bp hereafter) (Koike et al., 2006); (ii) a model deleting exons 2/3 on a genetic background that has otherwise intact *Disc1* gene (called Δ ex2/3) (Kuroda et al., 2011); and (iii) a model deleting a large locus spanning exon 1 through exon 3 on the exon 6 Δ 25bp-carrying background (called *Disc1* locus-impairment [*Disc1*-LI]) (Shahani et al., 2015).

Although $\Delta 25\text{bp}$ mice show deficits in working memory and $\Delta \text{ex}2/3$ mice show higher impulsivity phenotype, these models have displayed no additional behavioral endophenotypes that typically occur in major mental illnesses. However, recent detailed studies revealed cellular level abnormalities in these mice. $\Delta 25\text{bp}$ mice show erroneous axonal targeting, reduced dendritic growth of hippocampal neurons, and additional deficits in proliferation and dendritic complexity in developing dentate granule cells, accompanied by changes in short-term plasticity at the mossy fiber/CA3 circuit (Kvajo et al., 2011; Lepagnol-Bestel et al., 2013; Juan et al., 2014). $\Delta \text{ex}2/3$ mice show a threshold shift in the induction of long-term potentiation (LTP) in dentate gyrus (Kuroda et al., 2011), and an exaggerated endoplasmic reticulum calcium response (Park et al., 2015), which could in part be due to defective dendritic transport of mRNA for ITPR 1, a known regulator for synaptic plasticity (Tsuboi et al., 2015). Additionally, *Disc1*-LI mice show aberrant trafficking of amyloid precursor protein (APP) in cortical neurons, which leads to aberrant C-terminal processing of APP and A-beta peptide generation (Shahani et al., 2015). These findings are in good agreement with the role of *Disc1* in neuronal development and function revealed by previous cell biological studies (Brandon and Sawa, 2011; Narayan et al., 2013).

At present, it remains an open question as to how these haploinsufficiency models could directly contribute to biological understanding of the pathologies in major mental illnesses. As will be discussed later, one caveat of these models might be that the molecular signatures and transcriptional landscape are not clear after these genetic mutations, partly due to the complex nature of *Disc1* isoform expression, and potential effects of developmental compensation of the phenotypes caused by these mutations (Brandon and Sawa, 2011; Muraki and Tanigaki, 2015). Further studies are warranted on the circuit-level disturbance and its causal link to subtle behavioral outcomes in these mice.

Point mutation models

N-nitroso-*N*-ethylurea (ENU)-mutagenesis approach in C57BL/6J mice led to the identification of two missense mutations of *Disc1*, Q31L and L100P, that led to depressive-like phenotypes and schizophrenic-like phenotypes, respectively (Clapcote et al., 2007). Additional studies on Q31L mice revealed imbalance in monoamine function, which may underlie reduced sociability and social novelty seeking activities seen in this model (Lipina et al., 2013). Cell biological studies on L100P mice revealed enhanced dopamine function (Lipina et al., 2010; Su et al., 2014), deregulated neurexin function (Brown et al., 2011), altered GSK3 α activities in synapses (Lee et al., 2011), as well as deficits in interneuron development (Lee et al., 2013). However, mice with the same mutations on a different genetic background showed phenotypes indistinguishable from the controls (Shoji et al., 2012). The data demonstrate a significant effect of genetic backgrounds on the manifestation of psychiatric phenotypes. Alternatively, subtle differences in animal handling, diet, and laboratory conditions may influence the

behavioral outcomes, suggesting that environmental factors should be taken into account when interpreting the behavioral phenotypes, as will be discussed later. In addition, biochemical underpinnings of how the two mutations lead to contrasting behavioral outcomes that also display differential therapeutic responses remain to be explained.

Transgenic models

An alternative approach to model human DISC1 breakpoint mutation has been to express putative dominant-negative (DN) isoforms of *DISC1* in mouse brains (Hikida et al., 2007; Li et al., 2007; Pletnikov et al., 2008; Shen et al., 2008). A great body of these studies agree that perturbation of Disc1 function by these transgenic approaches led to a myriad of anatomical, cell biological, and circuit-wide deficits, as well as behavioral consequences that are considered relevant to human psychiatric conditions. For example, enlarged lateral ventricles, reduction in parvalbumin-positive interneuron pools in prefrontal cortex and in hippocampus, hyperlocomotion, lowered prepulse inhibition (PPI), and social withdrawal-related behavioral phenotypes are largely common among these models (Brandon and Sawa, 2011).

Using these mouse models, several conceptual frameworks have emerged that may help understand the pathophysiology of human mental conditions. First, these models highlighted several relevant cell types that are aberrantly regulated, including astrocytes (Abazyan et al., 2014), oligodendrocytes (Katsel et al., 2011), and CA1 pyramidal neurons (Booth et al., 2014), in addition to widely studied output and interneurons in the prefrontal cortex. Thus, roles for neuron-glia interaction in the pathology of mental illness may be tested in these models.

Second, the DN-DISC1 approach revealed a developmentally critical period in which sensory experience affects cortical development and plasticity (Greenhill et al., 2015). Transient disruption of DISC1 function during a neonatal period disrupted LTP/LTD later in adulthood, providing a basis for cognitive impairment and its delayed onset in human psychiatric conditions. This study has conceptually extended a previous study in which the influence of transient knockdown of DISC1 in the developing cortex on adult behavioral deficits was reported (Niwa et al., 2010). Both studies indicate that DISC1 plays a crucial role for adult brain function and behaviors by influencing developmental trajectories in several critical periods.

Third, the DN-DISC1 transgenic approach has linked prefrontal cortex-specific elevation of oxidative stress to deficits in cognitive and motivational behavioral paradigms, as measured by tasks, such as the reversal learning and reinforcer devaluation paradigms (Johnson et al., 2013). Oxidative stress can be elicited by a combination of environmental stress and genetic insults, and thus provide a useful cell biological readout to evaluate the levels of stress caused as a result of host–environmental

interaction, as will be discussed later.

Finally, many of these studies implicated significant alterations in key neurotransmitter systems, including glutamatergic, dopaminergic, cannabinoid, or nicotinic neurotransmission (Jaaro-Peled et al., 2013; Kaminitz et al., 2014; Ballinger et al., 2015; Dawson et al., 2015; Kim et al., 2015). Taken together, these transgenic approaches, coupled with DN-DISC1 constructs, are expected to further contribute to the understanding of pathobiology associated with human psychiatric conditions (**Table 1**).

Host–environment interactions

Approximately one-third of the family members carrying the *DISC1* breakpoint mutation reportedly manifest with some aspects of mental conditions (Blackwood et al., 2001). In addition, a critical finding that emerged after generation of a series of *Disc1* mouse models was that not a single model displayed a full-blown spectrum of behavioral and cognitive deficits. These observations suggested that the host perturbation elicited by a *Disc1* locus mutation is prone to developing neurocognitive dysfunctions when an additional environmental or genetic insult occurs. A series of environmental stress paradigms have been applied to *Disc1* mouse models to test host–environment interactions possibly for mental conditions. These stress paradigms include maternal immune activation by polyI:C injection at embryonic day 9 (Abazyan et al., 2010; Lipina et al., 2013), neonatal immune activation by polyI:C injection at postnatal days 2–6, which corresponds to the second trimester of human brain development (Ibi et al., 2010; Nagai et al., 2011), chronic social defeat (Haque et al., 2012), and adolescent social isolation stress (Niwa et al., 2013), as previously reviewed (Cash-Padgett and Jaaro-Peled, 2013).

In addition, recent reports addressed an effect of exposure to lead (Abazyan et al., 2013), as well as to cannabis (Ballinger et al., 2015), in DN-DISC1 mouse models. When mice were exposed to lead in diet from conception throughout life, the volume of the lateral ventricle was significantly increased only in female DN-DISC1 mice, but not in males or the wild-type controls (Abazyan et al., 2013). Lead exposure in DN-DISC1 male mice increased the peripheral activity in the open field box, while decreasing it in control males. DN-DISC1 mice also showed a greater response to the psychostimulant MK-801 than control mice. Furthermore, DN-DISC1 female mice had a PPI deficit when exposed to lead, whereas the control mice and DN-DISC1 male mice did not. These observations present a sex-dependent, and a task-dependent example of interaction between *Disc1* dysfunction and the environmental toxin.

Cannabis use, especially in adolescence, is known to increase the risk of psychosis, but the underlying mechanisms remain elusive (Andreasson et al., 1987; Arseneault et al., 2002; Henquet et al., 2005; van Os et al., 2002). Mice injected with a cannabinoid Δ^9 -THC from four through seven weeks of age had lower levels of synaptosomal cannabinoid receptor 1 expression, comparable to that in DN-

DISC1 mice (Ballinger et al., 2015). In a cued fear conditioning test, exposure to Δ^9 -THC produced a deficit only in DN-DISC1, but not in wild-type mice. Accordingly, DN-DISC1 mice exposed to Δ^9 -THC showed a smaller increase in c-Fos immunostaining than wild-type, suggesting a lower neuronal activation in DN-DISC1 mice in response to the cue. The finding suggests a role of DISC1 in the development of cannabis-mediated psychosis.

Taken together, DISC1 mouse models have provided valuable opportunities to test various aspects of host–environment interaction underlying mental illnesses.

Enigma

It remains an enigma as to why the phenotypes observed in *Disc1* haploinsufficiency models are generally smaller than those seen for *Disc1* point mutation or DN models. One plausible reason is that the phenotypes resulting from depletion of some *Disc1* isoforms, including major full-length isoforms, could be masked due to developmental compensation mechanisms. For example, defects in neuronal proliferation during cortical development can be overcome in part by compensatory adjustments by surrounding cell populations other than neurons. Delay in neuronal migration could also be compensated by prolonged migration over time.

Alternatively, complexity in the expression of multiple DISC1 isoforms, as well as functional heterogeneity of DISC1 proteins may provide a key to understand this enigma. Although a number of DISC1 isoforms have been identified at the transcript level (Nakata et al., 2009), we do not yet know the full spectrum of transcriptional landscape of the DISC1 gene, as well as the functional properties of each isoform. For instance, exons 2/3 were deleted in Δ ex2/3 model as initially designed, but the downstream exons 7 through 11 are still expressed in this model (Kuroda et al., 2011). Given that an intergenic splicing event has been reported for *DISC1* and the upstream neighboring gene *TSNAX* (Millar et al., 2000; Li et al., 2014), possible expression of chimeric proteins spanning TSNAX and DISC1 (exons 7–11) may influence mutant phenotypes in mice. Likewise, Δ 25bp mouse model is reported to express a shorter *Disc1* isoform (Kvajo et al., 2008), which resembles a C-terminally truncated DN-DISC1, and could thus function in a dominant-negative manner or may have a yet uncharacterized functional property. Although the half-life of this shorter *Disc1* isoform appears short and its expression level low, potential effects of transient expression of various *Disc1* isoforms should be taken into account in interpreting the mutant phenotypes. Transient expression of DN-DISC1 during a neonatal stage apparently impacted neuroplasticity later in adulthood (Greenhill et al., 2015), similar to transient knockdown of DISC1 that impacts neuropharmacological and behavioral characteristics in adulthood (Niwa et al., 2010).

To solve these enigmas, detailed characterization of transcriptional and translational regulation at

Disc1 locus in particular, as well as across the entire genome, will be necessary. In this regard, we propose to carry out RNA-Seq analysis of the whole transcriptome of multiple *Disc1* mouse models. Additional strategies to address these enigmas are summarized in **Table 2**.

Discussion and future perspectives

As outlined above, DISC1 mutant mice have proven useful in modeling multiple dimensions of behavioral outcomes that are relevant to human mental conditions. Contrary to the initial expectation, as reflected by its name, DISC1 should not be considered as a gene causative for schizophrenia. Recent advances in human genetic studies have made it clear that multiple diagnostic entities of mental illnesses are caused by dysfunction of overlapping sets of genes (Huang et al., 2010; Lee et al., 2012; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015). Likewise, DISC1 deregulation is linked to multiple mental conditions beyond conventional diagnostic boundaries defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Brandon and Sawa, 2011).

At least at present, we cannot look for the etiological validity of each DISC1 model by a clear-cut genetic mutation associated with single DSM-classified mental disorder. This is not so surprising given that the disruption of the gene is tightly associated with the alteration of an endophenotype (event related potential P300) that underlies multiple mental conditions beyond the DSM classification (Blackwood et al., 2001). Instead, we can stand more on the face validity of each behavioral dimension that is associated with molecular changes in the pathways involving DISC1. It is scientifically productive and valid to explore the biology that links molecular cascades to behaviors via cellular and circuitry mechanisms. This discussion is consistent with a recent proposal by the Research Domain Criteria (RDoC), in which molecular signatures are hypothesized to underlie physiological and behavioral characteristics, rather than disease entities categorized by operational diagnostic criteria, such as DSM (Insel et al., 2010; Cuthbert and Insel, 2013; Insel, 2014).

Genome-wide studies of psychiatric genetics have provided candidate loci for schizophrenia and other mental disorders, which include several promising genes (Fromer et al., 2014; Purcell et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). DISC1 is associated with some of these molecules via direct protein interactions or functional/pharmacological interactions. In addition, administration of a p21-activated kinase (PAK) inhibitor ameliorates spine deficits and behavioral abnormalities elicited by DISC1 knockdown (Hayashi-Takagi et al., 2014). Interestingly, the same inhibitor also ameliorates the behavioral deficits of mice deficient for the *Fmr1* gene (Dolan et al., 2013), recently indicated to be the most promising risk gene for schizophrenia (Fromer et al., 2014; Purcell et al., 2014).

Because DISC1 protein can be subdivided into a series of subdomains, each of which physically

interacts with specific binding partners, we could functionally dissect DISC1 into subdomains that are responsible for achieving certain behavioral or cognitive tasks. We could utilize such structure–function information (*e.g.*, DISC1-D2R interaction) in the design of novel therapeutic approaches, in which specific interference of DISC1 binding with its partners could improve functional outcomes without showing severe side effects such as catalepsy (Su et al., 2014).

Human *DISC1* breakpoint mutation has been reported to generate fusion proteins by spanning over chromosome 1 and 11, generating aggregation-prone protein species (Zhou et al., 2010; Ji et al., 2014; Ji et al., 2015). Similarly, recent studies demonstrated that DISC1 protein is prone to self-aggregation or co-aggregation with other proteins such as dysbindin (Leliveld et al., 2008; Ottis et al., 2011; Atkin et al., 2012), likely due to impairment of the protein quality control or cellular clearance systems. It remains to be studied how these aggregated species of DISC1 are generated along the developmental trajectories or in response to genetic and environmental insults. DISC1 mouse models are expected to provide mechanistic insight into these questions, as well as behavioral outcomes relevant to psychiatric conditions.

Deeper in the brain, we are likely to find more precise mechanisms underlying functional disturbances in DISC1 mouse models at the cellular level. DISC1 is expressed not only in neurons but also in glial cells (Seshadri et al., 2010). Emerging data are beginning to point to the role of glia (*e.g.*, astrocyte, oligodendrocyte, microglia), or of neuron-glia interaction in the pathophysiology of DISC1 dysfunction (Katsel et al., 2011; Abazyan et al., 2014).

Given the ample information on a series of behavioral disturbances described for these models, we could analyze in further detail mechanisms underlying defective behavioral or cognitive dimensions at the circuit level. For example, a deficit in PPI found in some of the DISC1 mice could be studied in order to understand neural circuitries responsible for sensorimotor information processing. Using modern techniques of systems neuroscience, coupled with magnetic resonance imaging and other brain imaging techniques, one could analyze circuit-level disturbances in DISC1 mouse models. We anticipate identifying key deficits in circuitry in these models, and will validate the findings by comparing with functional imaging data from patients with mental disorders. In parallel, optogenetics and *in vivo* electrophysiological recording approaches in mice will prove the link of a specific circuit to a given functional outcome, and could also be used to test the efficacy of therapeutic agents. In addition, the Human Connectome Project will help build a model useful for understanding global network disturbance in psychiatric disorders (Deco and Kringelbach, 2014). Mouse models could provide a test case for experimental validation of theoretical ideas generated through human brain imaging and genetic studies (Owen et al., 2015; Landek-Salgado et al., 2015).

Once such mechanisms (either molecular, cellular, or circuit-level) that likely underlie

pathophysiology of each behavioral dimension that constitutes human mental conditions are corroborated using these DISC1 mouse models, we could validate whether they can be used as biomarkers useful for diagnosis, or targets for therapeutic intervention. For instance, reduction in neuronal progenitor proliferation, associated with elevated GSK3 β activity, was observed in *Disc1* knockdown mice, and GSK3 β inhibition successfully ameliorated these molecular, cellular, and behavioral deficits, including hyperlocomotion (Mao et al., 2009). Subsequent work using the point mutation *Disc1* models also showed therapeutic effects of GSK3 β inhibitors (Lipina et al., 2012a), identified a potential new drug target (Lipina et al., 2012b), as well as a novel therapeutic strategy via inhibition of D2R–DISC1 interaction (Su et al., 2014). Additionally, dendritic spine deterioration, caused by elevated PAK activation, was found in *Disc1* knockdown mice, and novel PAK inhibitors were shown to ameliorate the cellular and the associated behavioral deficits (Hayashi-Takagi et al., 2014). Thus, DISC1 mouse models are expected to continue providing platform to test ideas for novel diagnostic and therapeutic avenues for combating mental illnesses.

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Legend for Figure 1.

This diagram summarizes how DISC1 elicits its functions at the molecular and cellular levels, leading to modulation of a series of neurotransmitter systems, as well as neural circuitry, which ultimately determine a range of behavioral domains, such as emotion and cognition. Deregulated DISC1 function primarily leads to impairment of neuronal development, signaling, and synaptic activities, which, coupled with various environmental insults, further affect neurotransmitter systems and neural circuitry, leading to manifestation of behavioral abnormalities.

Dimensional characterization of a range of research domains affected by DISC1 dysfunction will help understand the pathophysiological mechanisms underlying human psychiatric conditions.

Note that, in essence, DISC1 should not be synonymous with the gene disrupted in schizophrenia; it should rather be recognized as a gene disrupted in system connectivity.

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Figure 1. Disrupted in System Connectivity: how DISC1 dysfunction leads to behavioral manifestation?

		Haploinsufficiency	Point mutation	Dominant-negative
Cellular	Early developmental deficits		↓ (Lee et al., 2011)	
	Trafficking	↓ (Tsuboi et al., 2015)		
	Oxidative stress			↑ (Johnson et al., 2013)
	Ca ²⁺ signaling	↑ (Park et al., 2015)		
	Neural plasticity			↓ (Greenhill et al., 2015)
Neurotransmitter	Dopaminergic	↑ (Nakai et al., 2014)	↑ (Su et al., 2014)	↑ (Jaaro-Peled et al., 2013; Kim et al., 2015)
	Glutamatergic			↓ (Booth et al., 2014; Dawson et al., 2015; Kim et al., 2015)
	GABAergic	↓ (Nakai et al., 2014)		
	Cannabinoid			↓ (Kaminitz et al., 2014; Ballinger et al., 2015; Kim et al., 2015)
	Nicotinic			↓ (Kim et al., 2015)
Circuitry	Local circuitry (Hippocampus)	↓ (Kvajo et al., 2011)		
	Long-range circuitry (Mesocortical circuit)			↓ (Niwa et al., 2013)
Behavior	Sensitivity to psychostimulants		↑ (Clapcote et al., 2007)	↑ (Jaaro-Peled et al., 2013)
	Prepulse inhibition		↓ (Clapcote et al., 2007)	↓ (Hikida et al., 2007)
	Working memory	↓ (Koike et al., 2006)	↓ (Clapcote et al., 2007)	
	Sociability		↓ (Clapcote et al., 2007)	↓ (Johnson et al., 2013)
	Depressive like		↑ (Clapcote et al., 2007)	↑ (Hikida et al., 2007)

↑ Upregulated function
↓ Downregulated function

Table 1. Cellular, neurotransmitter, circuitry, and behavioral deficits in *Disc1* mouse models

Enigma	Strategy to address enigma
<p>Multiple Disc1 isoforms</p> <ul style="list-style-type: none"> - Complex splicing events - Interchromosomal protein fusion 	<p>Identification and functional characterization of each isoform</p> <ul style="list-style-type: none"> - Detection of splicing and fusion events - Expression profiling (cell type-specific, brain region-specific and developmental expression pattern) - Biochemical function (specific loss of binding partners, propensity to aggregation)
<p>Developmental compensation</p>	<p>Comprehensive phenotypic characterization Comparison among mouse models</p>

Table 2. Enigma of the biological roles of DISC1