PSYCHIATRIC DISORDERS

Multiple pathways to DISC1-related disease?

The scaffolding protein disrupted in schizophrenia 1 (DISC1) has multiple roles in neurodevelopment. Both rare and common variants of this protein may influence psychiatric phenotypes, although it remains unclear how DISC1 is mechanistically linked to disease. Now, two studies provide evidence for possible DISC1-mediated pathophysiological pathways.

Tsai and colleagues examined the functional significance of three common DISC1 variants (R264Q, L607F and S704C DISC1) and one rare variant (A83V DISC1), which they identified from a group of healthy individuals and patients with psychiatric disorders.

DISC1 can bind glycogen synthase kinase 3β (GSK3β), activating canonical WNT signalling. Using *in vitro* assays, the authors showed that A83V, R264Q and L607F DISC1, unlike wild-type and S704C DISC1, were unable to stimulate WNT-induced transcription and proliferation (a process regulated by WNT signalling) in murine neuroblastoma cells, and that the absence of such effects was due to a reduction in the variant's GSK3β-binding capacity. They also showed that expression of S704C DISC1 but not the other variants rescued neural progenitor proliferation defects in embryonic mouse brain following knockdown of DISC1 and that transcription assays involving human-derived lymphoblast cell-lines yielded results that were in line with the previous data.

Thus, the R264Q, L607F and A83V DISC1 variants may increase the risk of psychiatric disease through impairment of canonical WNT signalling and neurodevelopment. Interestingly, S704C DISC1 may impair neurodevelopment through a different pathway, as the authors found that this variant — unlike R264Q, L607F and A83V DISC1 — was unable to rescue WNT-independent neuronal migration deficits in mouse embryonic cortex following knockdown of DISC1 expression.

In the second study, Ming and colleagues examined the role of DISC1 in the development of adult-born neurons, focusing their attention on the previously reported interactions of DISC1 with two proteins implicated in neural developmental processes: nuclear distribution protein nudE-like 1 (NDEL1) and fasciculation and elongation protein-ζ1 (FEZ1). They found that knockdown of FEZ1 expression in the dentate gyrus accelerated dendritic growth and caused an increase in soma size in newly born neurons. Moreover, simultaneous knockdown of DISC1 and FEZ1 further accelerated dendritic growth, suggesting that in adult-born neurons, both proteins regulate dendrite development.

In contrast to the phenotypes observed with FEZ1 knockdown, knockdown of NDEL1 expression caused the formation of ectopic dendrites in adult-born dentate granule cells and the abnormal positioning of these cells in granule cell layers. Such phenotypes are also observed following knockdown of DISC1 expression, suggesting that FEZ1 and NDEL1 regulate adult-born neuron development through parallel pathways involving DISC1. Supporting this assertion, the simultaneous knockdown of NDEL1 and FEZ1 did not elicit any synergistic effects on newly born neurons, and a series of immunoprecipitation experiments showed that NDEL1 and FEZ1 did not directly interact; rather, they both bound DISC1.

Alongside their studies in mice, Ming and colleagues undertook a genetic association study of *FEZ1* with schizophrenia, from which they uncovered an epistatic interaction between a *FEZ1* polymorphism and the allele encoding S704C DISC1. This finding is consistent with the synergistic effect of knocking down the expression of FEZ1 and DISC1 in newly born neurons and shows how polymorphisms in *DISC1* and associated genes may combine to increase the risk of disease.

Taken together, these studies suggest pathways whereby DISC1 variants impair neurodevelopment and increase susceptibility to schizophrenia. Moreover, they highlight how mechanistic insights into psychiatric disease may be garnered from complex genetic findings.

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ORIGINAL RESEARCH PAPERS Singh, K. K. *et al.* Common DISC1 polymorphisms disrupt Wnt/GSK3β signaling and brain development. *Neuron* **72**, 545–558 (2011) | Kang, E. *et al.* Interaction between FEZ1 and DISC1 in regulation of neuronal development and risk for schizophrenia. *Neuron* **72**, 559–571 (2011)
FURTHER READING Brandon, N. J. & Sawa, A. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. *Nature Rev. Neurosci.* **12**, 707–722 (2011)