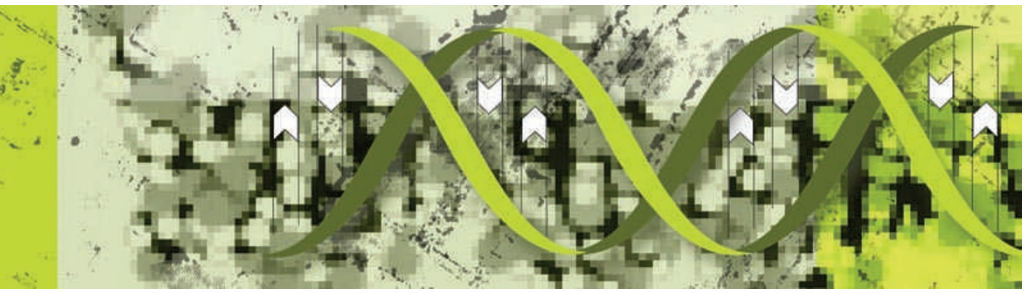
NEUROPSYCHIATRIC DISORDERS

The DISC1 pathway: a portal to understanding the genetics of mental illness?



A study of the effects of genetic variants in the Disrupted in Schizophrenia 1 (DISC1) pathway suggests that this protein controls expression of several other genes involved in mental disorders such as schizophrenia and bipolar disorder. DISC1 also seems to have an important role in the normal physiological development of the brain by regulating proliferation of neuronal progenitor cells.

"DISC1 is a remarkable protein. It acts as a scaffold that modulates the activity of many key proteins involved in neurosignaling and neurodevelopment," explains David Porteous, Head of the Medical Genetics Section at the University of Edinburgh, UK. Porteous is senior author of a study that has analyzed public domain datasets to examine how variations in the *DISC1* gene affect the expression of other genes that could be mediators of mental illness.

DISC1 was first identified in 2000 in a large Scottish family carrying a balanced translocation that directly disrupted the *DISC1* gene. "It has since been associated with many psychiatric illnesses, and is currently the best candidate gene for schizophrenia according to the ongoing meta-analysis project SchizophreniaGene," says lead author William Hennah (National Public Health Institute, Helsinki, Finland).

Hennah and Porteous' unique and inexpensive approach used data from the publicly available HapMap database and combined this with gene expression data on the same individuals from the National Center for Biotechnology Information Gene Expression Omnibus database. "This method can be applied to any disorder with a genetic component and means that large leaps in understanding can be achieved without a large research budget," notes Hennah.

One of the most notable findings was that variations in DISC1 pathway genes altered the expression levels of seven genes that are targets for existing or candidate drugs for important mental disorders. The analysis also added to the evidence that the DISC1 pathway helps regulate cytoskeletal function, synaptogenesis, neurodevelopment and sensory perception.

This observation dovetails nicely with the results of a separate study by Yingwei Mao and colleagues. "Our lab has a long track record on embryonic neurogenesis and neuronal positioning, and prior publications on DISC1 involvement in neuronal migration and in the integration of newly generated neurons during adult neurogenesis fueled our interest in this gene," explains senior author Li-Huei Tsai (Massachusetts Institute of Technology, Cambridge, MA, USA). Fascinated by the potential role of DISC1 in the etiology of psychiatric disorders, the researchers embarked on a multidisciplinary study to investigate how DISC1 affected neural progenitor cell proliferation *in vitro, in utero* and *in vivo*.

The group demonstrated that suppression of DISC1 expression reduced the proliferation of neural progenitors, causing premature cell cycle exit and differentiation. Another exciting finding from this study was that DISC1 inhibits glycogen synthase kinase 3β-mediated phosphorylation of β-catenin via a direct physical interaction. "This demonstrates that the action of DISC1 is reminiscent of lithium, the most common medication for bipolar disorder," explains Tsai. Mao *et al.* speculate that DISC1 functions to fine-tune the Wnt signaling pathway, which has important roles in multiple aspects of brain development and maturation, including neural progenitor proliferation, neurite development, synapse formation, and plasticity. Several other genes implicated in schizophrenia and/or bipolar disorder also impinge on Wnt signaling. "It is becoming clear that impairment in Wnt signaling may play a key role in the etiology of psychiatric disorders," adds Tsai.

The work of Mao *et al.* also confirms that cyclic AMP and β-catenin, like other DISC1 interactors, are transcriptional regulators, supporting the hypothesis that *DISC1* genetic variants or variants of DISC1 interactors might influence transcriptional regulation. Hennah and Porteous suggest that a network of neuronal proteins is indeed regulated by the DISC1 complex, adding a further dimension to the established roles in mediated risk of major mental illness. "We now intend to investigate if the genetic variants identified by our study can help target treatment, by testing if carriers of these variants have better or worse outcomes in clinical trials," says Hennah.

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Original articles Hennah, P. & Porteous, D. The DISC1 pathway modulates expression of neurodevelopmental, synaptogenic and sensory perception genes. *PLoS One* **4**, e4906 (2009).
Mao, Y. *et al.* Disrupted in Schizophrenia 1 regulates neuronal progenitor proliferation via modulation of GSK3β/β-catenin signaling. *Cell* **136**, 1017–1031 (2009).