Evidence Linking DISC1 Gene to Mental Illness Builds

Animal studies add weight to the view that an important gene for brain development plays a role in diseases such as schizophrenia and depression.

Every clan has its misfits, but an extended family in northern Scotland is extraordinary. More than half have suffered from schizophrenia or some other form of mental illness. A group of Scottish researchers reported in 1990 that the affected people all carried the same genetic anomaly—a translocation, or swap, of two stretches of DNA on the long arms of chromosomes 1 and 11. With modesty, the investigators wrote that this “may be a promising area to examine” for genes that predispose people to mental illness.

The area turned out to be very promising indeed. By the year 2000, it had led researchers to a gene called DISC1, which may be a key player in the chain of events leading to mental illness. The circumstantial evidence for assigning a major role to DISC1 (Disrupted-in-Schizophrenia 1) is strong. Several studies have linked the gene to schizophrenia, major depression, bipolar disorder, and autism; recent findings on DISC1’s biological function appear to support the hypothesis.

Animal studies have shown that the gene is needed for normal brain development both in the embryo and later in life and that blocking its function produces subtle abnormalities in brain structure resembling those seen in patients with schizophrenia. The protein encoded by the gene also turns out to be part of a nerve cell signaling pathway involved in learning, memory, and mood. “I think this gene is really the first big breakthrough in schizophrenia … and other mental diseases,” says Christopher Ross of Johns Hopkins University School of Medicine in Baltimore, Maryland.

After decades of following false leads, researchers are cautiously optimistic that they are on the right track with DISC1. But the evidence isn’t airtight. Except in the Scottish family, researchers haven’t consistently linked any particular DISC1 variant to a mental disease. “There’s no smoking gun,” cautions psychiatrist Daniel Weinberger of the National Institute of Mental Health in Bethesda, Maryland. But if the connection between DISC1 and mental disorders holds up, it might lead to better therapies for treating the conditions—especially schizophrenia, a devastating disease that is now poorly controlled at best.

The hunt begins

Gene hunters have had a hard time pinning down the genes involved in mental disorders mainly because the diseases are complex, meaning that several genes, as well as environmental factors, contribute to their development. That’s why the Scottish family proved to be such a boon. The 1990 study, which was conducted by a team including David St. Clair, Douglas Blackwood, and Walter Muir of the University of Edinburgh, U.K., suggested that the region disrupted by the translocation seen in affected members of the Scottish family held one or more genes involved in the disorders.

The gene search went slowly at first, but in 2000, a team led by David Porteous and Kirsty Millar, also at Edinburgh, identified two previously unknown genes on chromosome 1 that were interrupted by the genetic anomaly. Attention has focused on the first, DISC1, which normally produces a large protein the structure of which suggests that it interacts with other proteins.

Shortly after identification of DISC1, a follow-up study by the Edinburgh workers buttressed a causative role for the gene in the mental disorders of the Scottish family; that linkage analysis had a high degree of statistical validity—a LOD score of 7 when 3 is considered good. In this family, “we’re as close to causality as you could get,” Porteous says. Even so, environmental influences may still be important, as a few members carry the translocation but remain unaffected.

The Scottish family is unusual because so many members develop bipolar disorder and depression, as well as schizophrenia, and no one has detected a similar DISC1 abnormality in other families. In 2003, however, Leena Peltonen of the National Public Health Institute in Helsinki, Finland, and her colleagues reported a link between a particular set of three single-nucleotide variants (single-nucleotide polymorphisms) in DISC1 and schizophrenia in a group of 458 Finnish families. “This is the first genetic evidence that DISC1 has something to do with the more common garden variety of schizophrenia,” Peltonen says.

Other workers have picked up linkages between DISC1 variants and schizophrenia in a few U.S. and European families. And this year, the Peltonen team linked the gene to bipolar disorder and to autism in their Finnish population.
Research on DISC1’s normal function has strengthened the case that it is involved in mental disease. For starters, the gene is expressed in many tissues, but particularly in brain areas such as the hippocampus and cerebrocortical cortex. That puts the gene’s protein product in the right locations to influence the development of the mental disease.

In addition, as predicted from DISC1’s structure, researchers have unmasked numerous binding partners for the protein. The current count stands at about 50, Porteous says, including “10 or 12 where the interaction influences function.” Several of these partners suggest a role for DISC1 in brain development and cognition.

For example, about 5 years ago, three independent groups, those of Porteous, Akira Sawa of Johns Hopkins University School of Medicine, and Christopher Austin at Merck Research Laboratory in West Point, Pennsylvania, found that DISC1 binds to a protein called NUDEL (for NudE-like) that is needed for the neuronal migrations that occur during brain development. Several other partners of DISC1, including FEZ1, LIS1, dynein, and tubulin, are also involved in nerve-cell migrations.

That suggests that brain development might go awry if DISC1’s function is altered or missing. Evidence supporting that idea includes the demonstration about 3 years ago by the Sawa team that inhibiting DISC1 synthesis in mouse embryos with small interfering RNAs causes abnormal migration of neurons to the cerebral cortex.

More evidence comes from animal models developed in the past year. This fall, two Johns Hopkins groups, one led by Sawa and the other by Mikhail Pletnikov, published reports on two similar mouse models produced by introducing a truncated version of the DISC1 gene into mice. Both lines showed similar changes. “The brain is superficially normal but isn’t wired correctly,” says Ross, a member of the Pletnikov team.

Outgrowth of neuronal projections called neurites, which help guide neuronal migrations, was reduced. In addition, interior brain spaces called ventricles were larger than normal—an alteration also seen in people with schizophrenia. And although it’s not possible to diagnose mice as “schizophrenic,” the animals showed certain behavioral changes seen in human patients, such as hyperactivity and social and cognitive impairment. (The Sawa team’s results were published online 3 August in the Proceedings of the National Academy of Sciences; those of the Pletnikov team appeared online in Molecular Psychiatry on 11 September.)

In these mice, the mutant DISC1 protein exerted its effects in the embryos. Another Johns Hopkins group led by Hongjun Song has traced the gene’s effects in the brains of adult mice. In these experiments, described in the 21 September issue of Cell, the researchers showed that inhibiting DISC1 expression in newly formed adult brain neurons produces effects opposite to those seen in the other mouse models. Neurite outgrowth increased rather than decreased, and neurons migrated farther than normal. “If you disrupt DISC1 function, everything goes faster,” Song says.

Sawa notes that there are precedents for the same molecule having opposite effects depending on its context. Indeed, he is now working with Song and Pletnikov to identify the molecular change that can switch DISC1’s activity from inhibiting to stimulating neuronal migration. But whatever the outcome, researchers have long thought that schizophrenia is the result of aberrant brain development, and the results with these models buttress the case that irregularities in DISC1 function contribute to that.

A cAMP connection

Although it may not be possible to help patients by correcting abnormalities in brain development, work by Porteous and Millar, in collaboration with Miles Houslay of the University of Glasgow, U.K., suggests another tack to take. Two years ago, this group identified an enzyme called phosphodiesterase 4B (PDE4B) as one of DISC1’s many binding partners. This enzyme is a key regulator of cyclic adenosine monophosphate (cAMP), which transmits nerve signals into cellular responses, including those needed for memory formation.

The PDE4B enzyme breaks down cAMP after it has done its job in the cell, and further work by the Edinburgh group indicates that DISC1 inhibits this activity until rising cAMP concentrations cause it to drop off the PDE4B molecule. Alterations in DISC1 structure that disrupt the normal DISC1-PDE4B interaction might therefore interfere with learning and memory, among other things. “This is very important work,” Sawa says. “Memory and cognition are both disturbed in schizophrenia and bipolar disease.”

Additional evidence that disrupting the DISC1-PDE4B interaction can affect mental states comes from work on mouse models developed by Steven Clapcote and John Roder of Mount Sinai Hospital in Toronto, Canada, and their colleagues in collaboration with the Porteous team. (The results appeared on 3 May in Neuron.) By screening a library of mutant mice at the RIKEN research institute in Japan, the researchers identified two lines of mice, each with a different DISC1 mutation that reduces DISC1 binding to PDE4B.

Behavioral studies further showed that mice with one mutation display symptoms construed as schizophrenia-like, including hyperactivity and impaired learning and memory. Those symptoms were reduced by treatment with the drug rolipram, a PDE4B inhibitor, and also by treatment with two drugs used to treat human schizophrenia. The other mouse strain, Porteous says, had more depression-like symptoms. For example, when placed in water, the animals quickly gave up trying to escape and simply floated. These animals responded to treatment with antidepressant drugs. Developing drugs to regulate an enzyme such as PDE4B might lead to better ways of treating schizophrenia and other mental disorders.

The fact that DISC1 associates with so many different proteins might help explain the diversity of conditions to which it has been linked. “It seems that DISC1 acts as a scaffold around which other proteins cluster,” Porteous says. Thus, the symptoms that develop in a given individual might depend on which interaction is altered by a genetic variation in DISC1. And conversely, variations in any of DISC1’s partners could also lead to abnormal brain development or function. Geneticists have begun hunting for linkages between these other proteins and various mental disorders.

Neurobiologists are heartened by what they’ve learned so far about DISC1. At the very least, the work has tapped into what could be a very important pathway for regulating brain neuron activities. As Ross puts it, “the findings support the idea that schizophrenia is a brain disease and can be studied the same way as degenerative diseases.”

—JEAN MARX