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Brain cell signal network genes linked to schizophrenia risk in families

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Gene variants that affect brain signal receptors may be one of several causes of schizophrenia symptoms, which can include terrifying hallucinations. Credit: Alice C. Gray

New genetic factors predisposing to schizophrenia have been uncovered in five families with several affected relatives. The psychiatric disorder

can disrupt thinking, feeling, and acting, and blur the border between reality and imagination.

Dr. Debby W. Tsuang, professor of psychiatry and behavioral sciences, and Dr. Marshall S. Horwitz, professor of pathology, both at the University of Washington in Seattle, led the multi-institutional study. Tsuang is also a staff physician at the Puget Sound Veterans Administration Health Care System.

The results are published in the April 3 online edition of the *JAMA Psychiatry*.

Loss of brain nerve cell integrity occurs in schizophrenia, but scientists have not worked out the details of when and how this happens. In all five families in the present study, the researchers found rare variants in genes tied to the networking of certain signal receptors on nerve cells distributed throughout the brain.

These NMDA (N-methyl-D-aspartate) receptors are widespread molecular control towers in the brain. They regulate the release of chemical messages that influence the strength of brain cell connections and the on-going remodeling of the networks.

NMDA receptors respond to glutamate, one of the most common nerve-signaling chemicals in the brain. NMDA receptors are also found on brain circuits that manage dopamine release. Dopamine is a nerve signal associated with reward-seeking, movement and emotions.

Deficits in glutamate and dopamine function have both been implicated in schizophrenia but most of the medications that have been developed to treat schizophrenia have targeted dopamine receptors.

Tsuang and her groups' discovery of gene variations that disturb NMDA

receptor networking functions supports the hypothesis that decreased NMDA receptor-mediated nerve-signal transmissions contributes to some cases of schizophrenia.

Tsuang pointed out that several hallucinogenic drugs, like ketamine and phencyclidine (PCP or angel dust) block NMDA receptors and can produce symptoms similar to schizophrenia. These are the strongest evidence implicating these receptors in schizophrenia. The drugs sometimes induce psychosis and terrifying sensory detachment. Reports of such effects in recreational drug users fingered faulty NMDA receptor networks as suspects in schizophrenia.

In all five of their study families, Tsuang's team detected rare protein-altering variants in one of three genes involved with the NMDA receptor network. One of the genes, GRM5, is directly linked with glutamate signaling. In the other two genes, the links are indirect and connected through other proteins synthesized in brain cells. One of these proteins, PPEF2, appears to affect the levels of certain brain nerve-cell signaling mediators, and the other altered protein, LRP1B, may compete with a normal protein for a binding spot on a subunit of the NMDA receptor.

These discoveries provide additional clues to the molecular disarray that might occur in the brain nerve cells of some patients with schizophrenia, and suggest new targets for therapy for certain patients. In a disease occurring in about 1 percent of the population, the picture of how and why schizophrenia arises in all these people is far from complete.

"Disorders like schizophrenia are likely to have many underlying causes," Tsuang noted. She added that it might eventually make sense to divide schizophrenia into categories based, for example, on which biochemical pathways in the brain are disrupted. Treatments might be developed to correct the exact malfunctioning mechanisms underlying various forms of the disease.

Tsuang gave an example: Agents that stimulate NMDA receptor-mediated nerve-signal transmissions include glycine-site blockers and glycine-transport inhibitors have shown some encouraging results in pre-clinical drug trials, but mostly in adjunctive treatment in addition to standard antipsychotic therapy.

"But perhaps the data we have generated will help pharmaceutical companies target specific subunits of the NMDA receptors and pathways," Tsuang said. She added, however, that effective treatments may lag by many years after these kinds of discoveries. Someday it may make sense to initiate such treatments in people at high genetic risk when early symptoms, such as apathy and lack of motivation, appear, and before brain dysfunction is severe.

Also, possessing the newly discovered gene mutations does not always mean that a person will become schizophrenic. In the recent family study, three of the five families had relatives with the protein-altering variants who did not have schizophrenia.

"This isn't surprising," Tsuang observed, "Given that schizophrenia is such a complex disorder, we would expect that not everyone who carries the variants would develop the disease." In the future, researchers will be seeking what triggers the gene variants into causing problems, other mutations within affected individuals' genetic profile that might promote or protect against disease, as well as non-genetic factors in the onset of the illness in genetically susceptible people.

The researchers also utilized a strategy and selected more distant relatives of affected individuals for genetic sequencing. Distant kin share, a smaller proportion of genes compared to closely related family members. For example, siblings typically on the average share about 50 percent of their genes whereas cousins on the average share 12.5 percent of their genes. The researchers also hypothesized that the causative

mutation within each family would be the same variant.

This strategy helped the researchers decrease the number of genetic variants that were detected by sequencing and thereby concentrate only on the remaining strongest candidates. They also filtered their results against the many publicly available sequencing databases to pick out genetic variants not found in people who don't have psychiatric illness.

According to Tsuang, the research team was excited by recent advances in technology enabled them to uncover unknown, rare genetic variants not previously found in large populations without psychiatric condition. The ability to rapidly sequence only those portions of the genome that code for proteins made this experiment possible.

The next step for the researchers will be to screen for the newly discovered genetic variants in a large sample of unrelated cases of schizophrenia compared to controls. They want to determine if the variants are statistically associated with the disease.

Provided by University of Washington

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