Genes tied to schizophrenia found

Scientists looking for an inherited link in schizophrenia have hit on two genes tied to the brain disease.

A team of researchers in the United States and South Africa has pegged both of the genes, which have different and only vaguely understood functions, to chromosome 22, a bundle of genes that had previously been implicated in schizophrenia.

"There is a very significant genetic component to the predisposition to schizophrenia, and it's equally clear that there is a significant environmental, non-genetic component" to the disease, said David Housman, an M.I.T. biologist who specializes in the brain disorder.

Housman said the latest study should give researchers some "very important clues" in their search for the genes involved in schizophrenia.

"But in any study of this type, the biology is the critical element in coming to some understanding" about the interplay of genes and the disease, he added.

The study, which appears in the latest issue of the Proceedings of the National Academy of Sciences, was led by Dr. Maria Karayiorgou, a physician specializing in the genetics of psychiatric illness at Rockefeller University in New York City.

What is schizophrenia?

Schizophrenia affects roughly 1 percent of Americans, with symptoms, including psychosis, typically appearing in early adulthood.

Earlier studies have shown that between 25 percent and 30 percent of people with certain errors on a narrow region of chromosome 22 develop schizophrenia in adolescence or adulthood. The flaws, called "microdeletions," are also rampant in the rare cases of children who develop the disease.

The microdeletion area is important, but it's not the whole story, Karayiorgou said. The glitches account for only about 2 percent to 3 percent of schizophrenia cases. So the bulk of patients with inherited forms of the condition must have other gene mutations causing their illness.

More common in people with schizophrenia

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Karayiorgou's group trolled the chromosome 22 region prone to, but not containing, microdeletions in 107 adults and 27 children with schizophrenia. They found variants of two genes, PRODH2 and DGCR6, that showed up far more commonly in the chromosomes of schizophrenics than in those of people without psychosis, suggesting they may have helped trigger the disease.

PRODH2 encodes for a brain enzyme called proline dehydrogenase, which is involved in neuron signal transmission as well as cell death. The molecule, which breaks down into proline, also appears to help regulate the production of two important signaling molecules in the brain, glutamate and GABA.

In earlier work, Karayiorgou and her colleagues found that mice with mutant proline suffer severe behavioural problems and scrambled brain chemistry. DGCR6, on the other hand, is more mysterious, but may help the nervous system develop. Karayiorgou said she and her colleagues "favour proline as the culprit" for schizophrenia, because they've identified other variations of the gene in schizophrenics.

**Pseudogene**
The researchers also found that some mutations of PRODH2 resemble the genetic sequence of a so-called pseudogene -- a gene-like stretch of DNA with no function. These errors may prevent PRODH2 from properly producing its enzyme.

Karayiorgou said it may be possible in the future to overcome the proline defects by administering the protein to people with the gene variations. Whether that would prevent schizophrenia or reduce its symptoms hasn't been shown.

In an unrelated findings also appearing the journal, a team of scientists from Europe, New Zealand and Japan found that brain tissue collected in autopsies of people with schizophrenia show elevated activity of three cholesterol genes. These genes, called apolipoprotein L (apo L), reside on chromosome 22.

Apo L proteins help move cholesterol around the brain, and previous research has pointed to a role for abnormal cholesterol in schizophrenia.

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