New Mutations Linked to Sporadic Schizophrenia

By Michael Smith, North American Correspondent, MedPage Today
Published: May 30, 2008
Reviewed by Dori F. Zaleznik, MD; Associate Clinical Professor of Medicine, Harvard Medical School, Boston.

NEW YORK, May 30 -- About 10% of sporadic cases of schizophrenia appear to arise from spontaneous genetic mutations not inherited from either parent, researchers here said.

So-called copy number variants were seen in 15 of 152 patients with the disease but not in their unaffected parents, according to Maria Karayiorgou, M.D., of Columbia, and colleagues.

In contrast, such uninherited variants were only seen in two of 159 unaffected controls, Dr. Karayiorgou and colleagues reported online in *Nature Genetics*.

"We now know the cause of around 10% of the cases of sporadic schizophrenia," Dr. Karayiorgou added.

The findings mean that "schizophrenia is not as much of a 'big black box' as it used to be," Dr. Karayiorgou said.

Abnormal deletions or duplications of genetic material "are increasingly being implicated in schizophrenia and autism," said Thomas Insel, M.D., director of the National Institute of Mental Health, which was one of the supporters of the research.

"Now we have a dramatic demonstration that genetic vulnerabilities for these illnesses may stem from both hereditary and non-hereditary processes," Dr. Insel said in a statement.

The research "holds promise for improved treatments -- and perhaps someday even prevention -- of developmental brain disorders," he added.

The researchers carried out a whole-genome scan of 1,077 volunteers from a genetically homogenous Afrikaner population in South Africa, including 152 patients with sporadic schizophrenia, 159 controls, 48 people with familial schizophrenia, and both biological parents in all cases.

In the first step, the researchers used microarray technologies to identify copy number variation -- either gains or losses from the parental genome -- among the sporadic cases and the controls.

They identified 19 copy number variations, including 11 gains and eight losses, among the 15 cases and two controls.

The variants were roughly eight times as common among the cases as among the unaffected controls, Dr. Karayiorgou and colleagues said, and the association with schizophrenia was significant at $P=0.00078$, using a two-tailed Fisher's exact test.

Among the 48 volunteers with familial schizophrenia, there were no spontaneous copy number variations, implying that the association is "primarily confined to the sporadic cases," the researchers said.

On the other hand, when the researchers looked at rare inherited copy number mutations among the sporadic cases and controls, they found little difference. Thirty percent of the cases carried such a mutation compared with 20% of the controls.
Dr. Karayiorgou and co-workers have previously shown that loss of genes on chromosome 22, in the region 22q11.2, is responsible for introducing sporadic cases of schizophrenia into the population.

In the current study, three of the copy number variations found among sporadic cases occurred in that region, the researchers said, and all involved loss of function.

One possibility is that the identification of the mutated genes will allow researchers to discern the brain-development pathways that are involved in disease onset, "so that in the future we can look at better ways of treating this devastating disease," she said.

The study was supported by the National Institute of Mental Health and the Lieber Center for Schizophrenia Research at Columbia University Medical Center. The microarray experiments were carried out in the Vanderbilt Microarray Shared Resource, which is supported by the Vanderbilt Ingram Cancer Center, the Vanderbilt Digestive Disease Center, and the Vanderbilt Vision Center. Dr. Karayiorgou did not report any potential conflicts.