# 'Landmark' Study Identifies Genetic Link to Schizophrenia

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In what some are calling the strongest evidence to date of a genetic link to the development of schizophrenia, researchers have identified a gene that shows a significant association with the mental disorder that may explain its characteristic brain volume reductions and onset during adolescence.

After an exhaustive genome analysis involving 28,799 schizophrenia patients, 35,986 control persons, approximately 700 postmortem brains, and genetically engineered mice models, Steven McCarroll, PhD, and colleagues at the Broad Institute and Harvard Medical School, Boston, Massachusetts, say they found that complement component 4 (*C4*), an immune system gene, towers above all other possible candidates on the genomic "skyline" of more than 100 chromosomal sites linked to schizophrenia.

Although previous investigations of the human genome's influence on the risk for schizophrenia focused on the major histocompatibility complex (MHC) region, which has hundreds of immune-system genes, the identification of a specific gene remained elusive, Dr McCarroll told *Medscape Medical News*.

"It was very hard to tell which gene [was most influential], with much speculation centering on the idea of an immunologic cause, such as a virus.

"In this work, we found the responsible gene, *C4*, and the specific variants that explain this," he said. "Although *C4* had long been known for its role in the immune system, we found that it was also instructing this process of synaptic pruning."

The study was published online January 27, 2016 in *Nature*.

**Excessive Pruning**

The complement system, where *C4* resides, is known to play a key role in synaptic pruning in the brain, which occurs with normal aging. The *C4* gene may corrupt the regulation of that process, allowing the pruning to go into unregulated overdrive.

Such excessive pruning may explain the greater loss of gray matter and increased reductions in synaptic structures on neurons that have been repeatedly observed in cases of schizophrenia.

"Diverse synaptic abnormalities could in principle interact with the complement system and other pathways to cause excessive stimulation of microglia and elimination of synapses during adolescence and early adulthood," the authors write.

With treatments for schizophrenia currently capable of addressing only symptoms, the findings raise hopes of getting closer to a mechanism of the illness that could be more effectively targeted. But Dr McCarroll recommended against screening for the gene.

"We do not recommend testing for this gene," he emphasized. "The value of this is that the gene enabled this insight about biology underlying schizophrenia, which we hope could, with time, lead to entirely new medical approaches that treat the underlying disease mechanism," Dr McCarroll said.

As the research moves forward, the investigators are keeping their eyes on developments surrounding synapse loss in other diseases, which may provide further clues.

"There are signs of synapse loss in neurodegenerative disease, and there is important, ongoing research about whether pruning is a driver or not," Dr McCarroll said.

"These are really big questions that will hopefully be resolved in the coming year or two."

Jeffrey A. Lieberman, MD, the Lawrence C. Kolb Professor and chairman of the Department of Psychiatry at Columbia University College of Physicians and Surgeons, in New York City, agreed that the study's implications are important and may help guide treatment as well as diagnosis in schizophrenia.

"If we have a suspicion of schizophrenia, we could examine through imaging or another means the trajectory of their brain's change or growth, so it offers an opportunity to help with diagnostic assessment," he said.

"It could also help guide how we treat the disease. For instance, instead of looking downstream, trying to block dopamine, we can look to factors that preserve or slow synaptic elimination.

"Ultimately, this may be a method that modifies the expression of these genes or basically augments the resulting deficiency.

"This represents a landmark study which certifies more definitively than in previous studies the specific genetic contribution that causes schizophrenia," commented Dr Lieberman.

"[The research] yields a strong and unambiguous finding in an area that is biologically plausible," he said.

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