# Four Alzheimer's Susceptibility Genes Discovered

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The first family-based genome-wide association study for Alzheimer's disease has identified four new genes that may significantly affect the risk of developing the disease.

The gene with the strongest association lies on chromosome 14, not far from the early-onset familial Alzheimer's gene presenilin-1, Dr. Rudolph Tanzi said in an interview. "What we don't know yet, is whether this is a coincidence or whether there is some interaction going on with that gene."

Dr. Tanzi, director of the Massachusetts General Hospital's genetics and aging research unit in Boston, and his coinvestigators published the results of their study in the November issue of the American Journal of Human Genetics (doi:10.1016/ j.ajhg.2008.10.008).

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The initial portion of the study included a genome-wide screen of more than 1,400 DNA samples taken from 410 families with at least three Alzheimer's-affected members. This analysis revealed five candidate genes: one closely linked to the apolipoprotein E gene, variations of which are associated with late-onset Alzheimer's, and four previously unknown single nucleotide polymorphisms (SNPs), said Dr. Tanzi.

"We took these top hits and screened another 900 families for them, and after correcting for all the possible variables, we still had overall genome-wide significance with all of them, with the best hit in the novel chromosome 14 gene."

The second-best–associated gene is involved in innate immune response. "This was quite a surprise, to see a gene involved with response to bacterial and viral infection implicated in Alzheimer's," Dr. Tanzi said. "This now has us thinking more about the possible role of infection in Alzheimer's etiology."

The third novel SNP resides in the gene that causes spinocerebellar ataxia, a neurodegenerative movement disorder. "Although none of our Alzheimer's samples had spinocerebellar ataxia, the location of this gene near the cause of another neurodegenerative disease is interesting. Perhaps a different mutation in this gene might cause Alzheimer's," Dr. Tanzi said.

The final SNP is located in a gene that produces a synaptic protein—a logical association given the role of synaptic dysfunction in Alzheimer's.

At this point, it's impossible to predict the extent of influence these genetic variants may confer on Alzheimer's risk, Dr. Tanzi said. "We refrain from making a big deal about odds ratios in family studies, because those numbers are only specific to those families—the odds ratio in the population at large could be less impressive. But if I had to guess, for our best hit I'd say it might end up to be a doubling of risk in the general population."

The study opens a new door in genetic research, Dr. Tanzi said. New genome chips capable of scanning almost the entire code at once are taking some of the guesswork out of genetic studies. "Much of what we have done in the past is look for variants in a gene that we picked based on a favorite hypothesis. This adds an element of bias to your results. The beauty of this is that these results are totally unbiased. With the gene chip, you just see what falls out as significant and wait to be surprised."

Dr. Tanzi's lab has been involved in genetic analysis of Alzheimer's since the 1980s, codiscovering all three early-onset genes out of the four total genes known for the disease. "We also learned that the four genes only account for 30% of the genetics of Alzheimer's disease," while twin studies suggest that at least 80% of cases involve some inherited factor.

"Look at how much we've learned with only 30% of the genetics solved and imagine what we could learn if we knew the other 70%." ■