Genetic Discovery May Determine Alzheimer's Disease Risk and Age of Disease Onset

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A newly identified gene appears to be highly predictive of not only the risk of developing Alzheimer's disease, but also the approximate age at which the disease will begin to manifest itself, according to researchers at Duke University Medical Center.

This new gene may be the most highly predictive gene discovered to date in Alzheimer's disease.

In findings presented today at the International Conference on Alzheimer's Disease, the gene TOMM40 was found to predict the age of Alzheimer's disease development within a five- to seven-year window among people over age 60.

"If borne out through additional research, a doctor could evaluate a patient based on age, especially among those over age 60, their APOE genotype and their TOMM40 status, to calculate an estimated disease risk and age of onset," said Allen Roses, MD, director of the recently established Deane Drug Discovery Institute and the study's lead author.

Roses earlier uncovered the association of apolipoprotein E (APOE) genotypes, particularly APOE4, with the risk and lower age of onset for Alzheimer's disease. This discovery remains one of the most confirmed genetic associations for any complex disease.

"It now looks fairly clear that there are two major genes -- APOE4 and TOMM40 -- and together they account an estimated 85-90 percent of the genetic effect," Roses said.

APOE4 accounts genetically for 50 percent of late onset cases of Alzheimer's disease but the other half remained a mystery. Genome-wide screening and other new techniques have been used repeatedly without success. Roses' team employed a different approach.

The APOE gene is present in all people and is characterized by three variants numbered two through four. The Duke researchers found that a variant of TOMM40 apparently evolved independently when attached to the APOE3 version of the gene than it did when attached to the APOE4 version.

Roses said the genetic association with Alzheimer's disease age of onset now goes beyond just APOE4. The researchers found that TOMM40 linked to APOE3 had either short or long repeated sequences, while all APOE4-linked repeat sequences were long. The study concluded that a longer version of TOMM40 attached to both APOE3 and APOE4 are significantly associated with an earlier disease onset, while the short repeat sequences were associated with a later onset of disease.

"Genome-wide screening detects big blocks of DNA inherited together, but it doesn't tell us all the differences within that block," Roses said. "We conducted a phylogenetic analysis to explore the evolution of the DNA and to see what changes take place on the backbone of other changes."

The technology has not been widely used in human genetics, Roses explained. "From all the genome-wide scans that were performed over the past four years, it was apparent that the variance within APOE could not account for the extremely high statistical significance which

characterized this small block of genes, including APOE and TOMM40, which were inherited in a block."

"If someone gets APOE4 from their mother and APOE3 from their father, they also get TOMM40 as a linked caboose," Roses said. "If the TOMM40 is a short version of the gene attached to APOE3, then that person has a better chance of getting Alzheimer's disease very late, after age 80. But if it's a long TOMM40 they have a better chance of getting the disease before age 80."

The Duke team now plans to validate the association of the APOE genotypes and TOMM40 with age of disease onset and to determine how well these genes predict age of onset. They are planning a prospective, five-year study combined with a drug trial aimed at prevention or delay of disease onset.

The prevalence of Alzheimer's disease is predicted to quadruple world-wide by 2050 to more than 107 million cases, meaning that 1 in 85 persons will be living with the disease. It has been estimated that delaying disease onset by one or two years will decrease the disease burden in 2050 by 9.5 million or 23 million cases, respectively.

The research team also plans to use this type of phylogenetic analysis to uncover genetic associations in other diseases, including autism, diabetes and chronic obstructive pulmonary disease (COPD).

Provided by Duke University (news : web)