Using new approach, researchers find level of gene alters risk of Alzheimer's disease

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Using sophisticated techniques that scan the genomes of patients, researchers at the Mayo Clinic campus in Florida have found that a gene appears to either help protect against development of Alzheimer's disease, or promote the disorder depending on the level of gene in the brain.

In two research studies published almost simultaneously in the journals *Neurology* and *PLoS ONE*, the scientists found strong evidence for the role of the gene, insulin-degrading enzyme (IDE), in influencing risk of Alzheimer's disease. The Mayo researchers were one of the groups that first found an association between IDE and Alzheimer's several years ago, but these new findings now offer a novel theory about how the gene could be involved in the disease process.

"We found a new mechanism of action for this Alzheimer's disease susceptibility gene, that acts by altering gene expression levels," says neuroscientist and neurologist Nilufer Ertekin-Taner, M.D., Ph.D., the lead investigator on the *Neurology* study and contributor to the *PLoS ONE* research.

Fanggeng Zou, Ph.D., and Minerva Carrasquillo, Ph.D., are the joint first authors of the *Neurology* study. Drs. Carrasquillo and Zou, Olivia Belbin, Ph.D., and Ph.D. candidate Mariet Allen are the joint first authors of the *PLoS ONE* study. Both studies were published online in early 2010.

IDE is known to break apart amyloid beta, the protein that clumps together in the brains of Alzheimer's patients. The Mayo researchers say their findings suggest that too little expression of IDE may promote development of the disease, while increased expression appears to protect against the disorder.

"It is an issue of the level of the normal gene, not whether a gene is in a mutant form that is not acting properly," says Dr. Ertekin-Taner. "We believe this is a novel and potentially powerful approach to understanding the complex biology behind development of Alzheimer's disease."

Until these studies, scientists have searched for Alzheimer's disease genes by looking to see if patients had different variations in genes from non-patients - variations that increased the risk for disease development. Apolipoprotein E-4 (APOE-4) — the only major Alzheimer's disease susceptibility gene discovered to date — also was found that way. Humans can inherit three different forms of APOE, and researchers found that people who had one or two copies of APOE-4 have a substantially increased risk of developing Alzheimer's.

The Mayo researchers took a different tack in this research. In the *Neurology* study, spearheaded by Dr. Zou, they measured messenger RNA (mRNA) expression levels of 12 genes in an unaffected area of the brain in 200 people with Alzheimer's disease. These 12 genes were previously identified as potential risk genes for Alzheimer's by this group and others in the literature. They then identified genetic variations within and around these 12 genes, from among the hundreds of thousands of variations measured as part of the whole genome screen for Alzheimer's disease. That work was spearheaded by Dr. Carrasquillo in the laboratory of Steven Younkin, M.D., Ph.D., George M. Eisenberg Professor of Neuroscience at the College of Medicine, Mayo Clinic.

Measuring mRNA is a way to quantify gene expression. Genes that are activated produce more mRNA in order to make protein.

The comparison of the different gene variations and gene mRNA levels led to identification of 3 SNPs — a form of genetic variation - that seemed to be linked to IDE expression levels. One of these SNPs was significantly associated with both increased expression levels of IDE and reduced risk of Alzheimer's, but the researchers did not know whether these SNPs were the functional IDE variations or whether they were marking a functional, nearby IDE variant.

Drs. Younkin and Carrasquillo and their colleagues worked on that piece of the puzzle - results of which are detailed in the PLoS One study. They identified variants in IDE in areas that are identical among humans, mice and rats. They postulated that these variants should be important in altering the function of the gene (or functional variants), because the variants reside in potentially important functional areas of the gene that are conserved between different species. When they tested these IDE variants for their effects on gene expression, they found one genetic variation that had the strongest effect on brain IDE levels and also influenced Alzheimer's disease risk. Dr. Younkin's group then tested the IDE gene with this variant in laboratory cells and showed that it led to different levels of expression of the IDE gene.

The investigators determined that the IDE variant identified in the Neurology study was a proxy (or marker) for the functional IDE variant in the PLoS ONE study. Their results suggest that genetic variation in IDE can influence levels of this gene in the brain, thereby modulating development of Alzheimer's by modifying its efficiency in breaking apart amyloid beta.

Both methods of investigations — testing genes for their effects on disease risk and gene expression levels — should be used in the future to

look for Alzheimer's disease susceptibility genes, Dr. Ertekin-Taner says.

"We show that measuring gene expression leads us to disease susceptibility genes in a way that is more powerful than just looking for genetic variations that influence disease risk," says Dr. Ertekin-Taner. "There is no way we would have found this IDE variant if we only looked for its effect on disease risk and not gene expression."

Provided by Mayo Clinic