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Gene Nearly Triples Risk of Alzheimer's, Global Team Including Mayo Clinic Finds

JACKSONVILLE, Fla. — A gene so powerful it nearly triples the risk of Alzheimer's disease has been discovered by an international team including researchers from Mayo Clinic. It is the most potent genetic risk factor for Alzheimer's identified in the past 20 years. The findings were reported Wednesday in the online edition of the *New England Journal of Medicine.*

The team included researchers from 44 institutions around the world, including 10 from Mayo Clinic's campuses in Florida and Minnesota. The study was led by John Hardy, Ph.D., a researcher at the Institute of Neurology at University College London and a former professor at Mayo Clinic in Florida.

The researchers used new sequencing techniques to home in on the *TREM2* gene. Additional *TREM2* sequencing was then performed, in part, by scientist Aleksandra Wojtas in the Mayo Clinic in Florida laboratory of Rosa Rademakers, Ph.D. These studies led to identification of a set of rare variants in *TREM2* that occurred more often in 1,092 Alzheimer's disease patients than in a control group of 1,107 healthy people.

The most common variant, R47H, was then evaluated in follow-up studies of a large number of Alzheimer's disease patients and controls. Minerva Carrasquillo, Ph.D., a scientist in the Mayo Clinic in Florida laboratory of Steven Younkin, M.D., Ph.D., spearheaded the direct genotyping and analysis of R47H in DNA samples from 1,994 Alzheimer's disease patients and 4,062 "control" participants — individuals verified not to have Alzheimer's. The patients and control participants were evaluated by Mayo Clinic physicians, led by co-authors Dennis Dickson, M.D., Neill Graff-Radford, M.D., and Ronald C. Petersen, M.D., Ph.D. These follow-up studies showed unequivocally that the R47H variant of *TREM2* substantially increases the risk of Alzheimer's disease.

"The *TREM2* variant may be rare, but it is potent," Dr. Carrasquillo says. "In our series, it was present in 1.9 percent of the Alzheimer's patients and in only 0.37 percent of the controls. This strong effect rivals that of the well-established genetic variant known as *APOE* 4, and it was observed both in our study and in the independent study led by deCODE that was published with ours. R47H isn't fully penetrant — meaning that not all people who have the variant will develop Alzheimer's and in those who do, other genes and environmental factors will also play a role — but like *APOE* 4 it does substantially increase risk."

Dr. Younkin comments: “R47H is the first goldilocks variant to show strong association with Alzheimer’s disease.” Now being identified using the new sequencing technologies, goldilocks variants are an important type of rare variant so named because they are just right, not too rare and strong enough to show highly significant association in well-powered follow-up genotypic studies like the one performed at Mayo.

“There is a broad consensus that prevention will be the best way to manage Alzheimer’s disease,” Dr. Younkin says. “In my view, common variants like *APOE* 4 and goldilocks variants like *TREM2* R47H are important because they could be used, in principal, to identify many healthy people at high risk of Alzheimer’s disease who would be suitable for prevention trials. Patients whose Alzheimer’s disease is driven by high risk genetic variants will frequently transmit these variants to their children. We now know that it takes a long time for the pathology of Alzheimer’s disease to produce symptoms, so prevention in children who receive these variants would ideally begin when their elderly parents are diagnosed.”

“The variant found in our study identifies a fascinating new Alzheimer’s disease gene, *TREM2*, which is involved in the immune system,” Dr. Rademakers says. “This fits well with other evidence linking the immune system to Alzheimer’s disease, but additional studies are needed to establish that R47H does, in fact, act by altering immune function. Fortunately, this variant changes an amino acid in *TREM2* and that will greatly facilitate the biological studies that follow.”

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