A rare variant in TREM2 increases risk for late-onset Alzheimer's disease

Late-onset Alzheimer's disease (LOAD) is the most common form of dementia and affects over 5 million Americans. This neurodegenerative disease results from a combination of genetic and environmental effects and currently has no effective cures, treatments, or preventions. The disease is characterized by the abnormal accumulation of two proteins in the brain, amyloid beta (A?) in plaques outside of neurons and hyperphosphorylated tau that create tangles within the neurons. These plaques and tangles are toxic to neurons and cause progressive loss of cognitive and executive function. In addition to the most recognizable symptom of the disease, memory loss, many LOAD patients also exhibit one or more of the following: depression, psychosis, sleep disturbances, sundowning, behavioral changes and mood swings.

While age is the biggest risk factor, changes in an individual's DNA (genetic variants) also can contribute to susceptibility to or protection from disease. Variants in over 20 genes have been identified to be associated with LOAD so far, however, the majority of these variants are common and have very small effects on overall risk. There are a few exceptions, including a variant in the gene for apolipoprotein E (APOE) that produces a form of the APOE protein referred to as APOE4. APOE is the best established and strongest risk factor for LOAD, increasing risk 4-fold for individuals with one copy of E4 and up to 15-fold for individuals harboring two copies of E4. More recently, a rare variant (minor allele frequency, MAF less than 0.01) with comparable effects to those of APOE4 has been identified in the gene for triggering receptor expressed on myeloid cells 2 (TREM2). First described in an Icelandic population, this substitution of a histidine for arginine at amino acid residue 47 (R47H) was shown to increase LOAD risk substantially**.**

The *TREM2* gene is expressed on cells in the brain called microglia. These microglia are responsible for inflammatory response in the brain and clearance of cellular debris, including the A? plaques associated with LOAD. We sought to replicate the association of the R47H variant of *TREM2* in a well-described Caucasian population of 4,567 LOAD cases and controls. We also examined the association of R47H with other indicators of LOAD in subsets of our overall group for which data was available. We did not find any association of the R47H variant with age-at-onset of the disease, psychosis in LOAD, or deposition of A? plaque in the brain. However, our results showed that individuals with the R47H variant have an increase in disease risk of over 7-fold compared to those who do not have the variant, consistent with other reports that this variant increases LOAD risk.

Although we have many observations and ideas about the causes of LOAD, including the plaques and tangles mentioned above, there are still many mysteries concerning how this disease develops that must be solved before we can produce effective treatments. Our study, in conjunction with many others, suggests that the *TREM2* plays a role in LOAD, but exactly how it does so remains to be determined. Thus, future efforts should focus on assessing how this gene affects the risk and

development of disease.

Publication

More evidence for association of a rare TREM2 mutation (R47H) with Alzheimer's disease risk.
Rosenthal SL, Bamne MN, Wang X, Berman S, Snitz BE, Klunk WE, Sweet RA, Demirci FY, Lopez OL, Kamboh MI
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