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ALZHEIMER DISEASE

The involvement of *TREM2* R47H variant in Alzheimer disease confirmed, but mechanisms remain elusive

A genetic study of over 173,000 individuals has confirmed that the *TREM2* amino-acid-substitution mutation R47H increases the risk of Alzheimer disease (AD) in people of European descent. The results, published in *Alzheimers & Dementia*, suggest the mutation contributes through tau dysfunction.

Several studies have reported the *TREM2* R47H mutation to be a risk factor for AD, but the magnitude of this mutation's role in AD and other neurodegenerative diseases has been far from clear. "The effect size estimates varied widely across datasets," says lead author Christina Lill. "We aimed to derive a realistic estimate for R47H in AD and to determine whether it is also associated with other neurodegenerative disorders."

Lill and colleagues genotyped 19,940 participants of European ancestry, including patients with neurodegenerative disorders, as well as healthy control individuals. The investigators then combined these novel data with 28 previously published data sets, yielding a total European-origin population of 24,086 individuals with AD and 149,993 controls. In this population, *TREM2* R47H mutation was associated with a substantial increase (OR = 2.71) in risk of AD.

In contrast with some previous reports, Lill and co-workers found no association between the mutation and the risk of Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), or frontotemporal lobar degeneration (FTLD). "Although our calculations and conclusions are based on the largest sample sizes analysed for each of the four diseases to date, it needs to be emphasized that the sample sizes for PD, FTLD, and ALS were substantially smaller than the data available for AD," notes Lill. "Thus, we cannot exclude the presence of much smaller effects for these diseases."

The investigators also assessed the levels of amyloid-β_{42} ($A\beta_{42}$) and total tau in the cerebrospinal fluid (CSF) of 828 individuals with AD or mild cognitive impairment. The R47H mutation was linked to an increased CSF level of total tau, but not $A\beta_{42}$. "This finding is in line with a previously published study by another group, and suggests that the role of *TREM2* in AD pathophysiology predominantly involves tau dysfunction," says Lill.

"The genetic link between AD and *TREM2* can now be considered established," contends Lars Bertram, who led the study. However, two other recent investigations suggest that the importance of *TREM2* variants as risk factors for AD depends on the population.

The study by Lill *et al.* focused exclusively on datasets with people of European descent. In a study, published in *American Journal of Alzheimer Disease and Other Dementias*, Man Huang and co-investigators evaluated the association between *TREM2* and AD in Japanese, Korean and Chinese people. Huang *et al.* conducted a meta-analysis of five studies comprising 3,962 individuals with AD and 4,403 healthy controls, and found no association between AD and the *TREM2* R47H mutation in East Asian populations.

In another study, published in *Molecular Neurodegeneration*, Sheng Chih Jin and colleagues evaluated the links between several *TREM2* variants and AD in African Americans. The investigators reported that the R47H mutation was not associated with a significant increase in risk of AD, although the authors note that the study could have been underpowered to detect such a link. Instead, Jin *et al.* found that other *TREM2* mutations were relevant to the risk of AD in the African American population. This finding is consistent with a previous study linking several *TREM2* short-nucleotide polymorphisms with AD in people of African descent.

"Most papers published to date—including ours—have only focused on the R47H variant in *TREM2*. There are, however, other nucleotide substitutions in this gene, some of which are predicted to have functional consequences," says Bertram. Future studies should assess whether these additional variants also show association with AD or other neurodegenerative diseases.

Moreover, little is known about the precise biochemical mechanisms that underlie the association between AD and *TREM2*. According to Bertram, studies on cellular and animal models are needed to shed new light on the pathophysiological processes through which *TREM2* variants confer a risk for AD.

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Original article Lill, C. M. *et al.* The role of *TREM2* R47H as a risk factor for Alzheimer's disease, frontotemporal lobar degeneration, amyotrophic lateral sclerosis, and Parkinson's disease. *Alzheimers Dement.* doi:10.1016/j.jalz.2014.12.009

Further reading Huang, M. *et al.* Lack of genetic association between *TREM2* and Alzheimer's disease in East Asian population: a systematic review and meta-analysis. *Am. J. Alzheimers Dis. Other Demen.* doi:10.1177/1533317515577128 | Jin, S. C. *et al. TREM2* is associated with increased risk for Alzheimer's disease in African Americans. *Mol. Neurodegener.* **10**, 19 (2015)