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ALZHEIMER DISEASE

TREM2 linked to late-onset AD

Rare variants in the *TREM2* (triggering receptor expressed on myeloid cells 2) gene are associated with an increased risk of late-onset Alzheimer disease (AD), report two independent groups of researchers in *The New England Journal of Medicine*. "[This discovery] points very specifically to a potential metabolic pathway that you could intervene in to change the course of Alzheimer's disease," says William Thies, chief medical and scientific officer of the Alzheimer's Association (*New York Times*, 14 Nov 2012).

As part of a large international collaboration, a team led by John Hardy focused in on the *TREM2* gene, following their earlier discovery that homozygous loss-of-function mutations in *TREM2* were associated with an unusual early-onset form of dementia in Turkish patients. "We had found the same mutations in some of our Alzheimer's cases, only heterozygous rather than homozygous," Hardy explains. As part of the deCODE project, Kari Stefansson and colleagues took a different approach, channelling their efforts into analysing whole-genome sequences in the genetically homogeneous Icelandic population.

Hardy's team reported an increase in genetic diversity across exon 2 of *TREM2* in patients with AD compared with unaffected individuals, with the Arg47His substitution (also known as rs75932628) showing the strongest association with AD. In agreement with this finding, Stefansson and co-workers reported that besides the amyloid precursor protein and apolipoprotein alleles that have previously been linked to AD, only one other marker out of 191,777 genome-wide variants showed an association with AD in their cohort—namely, the Arg47His substitution. Both sets of investigators were able to replicate this association across larger cohorts from different geographic regions, using direct genotyping techniques and imputation, with the variant allele consistently conferring an elevated risk of late-onset disease.

TREM2 codes for a membrane protein that forms part of a receptor-signalling complex, which triggers the activation of immune responses in macrophages and dendritic cells. The gene is expressed throughout the CNS; analysis of human control brains by Hardy's team confirmed that *TREM2* is expressed in high levels in the white matter, hippocampus and neocortex but at low levels in the cerebellum, consistent with the pathological features reported in AD. Furthermore, examination of five brains with possibly pathogenic variants (Gln33Xaa, Arg47His and Asp87Asn) revealed that all displayed the typical findings of fully developed AD.

TREM2 is reported to have an anti-inflammatory role in the brain. Impaired function of the TREM2 protein, therefore, probably affects inflammatory processes, and may lead to a decline in cognitive function through the inability of the brain to clear amyloid plaques. "I suspect that those people with only one working copy of this gene overreact to amyloid and they get a runaway inflammatory response; from a therapeutic point of view we should be looking for drugs that increase the activity of TREM2," says Hardy.

Interestingly, these data add to a collection of disease associations whereby homozygous and heterozygous loss-of-function mutations correspond to early-onset and late-onset diseases, respectively. "With two copies of a mutation you get an early-onset nasty disease, and if you have one copy of the same mutation, you have an increased incidence of a late-onset disease," concludes Hardy. "That's a general principle that I think will be interesting for genetics over the next few years, and I think we will find many other examples."

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Original articles Guerreiro, R. *et al. TREM2* variants in Alzheimer's disease. *N. Engl. J. Med.* doi:10.1056/NEJMoa1211851 | Jonsson, T. *et al.* Variant of *TREM2* associated with the risk of Alzheimer's disease. *N. Engl. J. Med.* doi:10.1056/NEJMoa1211103

Further reading Guerreiro, R. J. *et al.* Using exome sequencing to reveal mutations in *TREM2* presenting as a frontotemporal dementia–like syndrome without bone involvement. *Arch. Neurol.* doi:10.1001/archneurol.2013.579