Genetics of Alzheimer's disease: First identification of a strong recessive component

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A new study from deCODE genetics and collaborators is the first to uncover a strong recessive component in Alzheimer's disease.

deCODE genetics/Amgen, and collaborators from Iceland, U.S., UK,

Denmark, Norway, and Sweden published the study, "Homozygosity for R47H in TREM2 and the Risk of Alzheimer's Disease," in *New England Journal of Medicine*. This study marks a significant milestone by identifying a strong recessive component in the genetics of Alzheimer's disease.

In 2013, deCODE genetics and collaborators were first to associate a sequence variant, R47H, in the TREM2 gene with Alzheimer's disease. Disrupted Aβ clearance has been associated with R47H and the current study reveals an inheritance pattern deviating from the additive model with a strong recessive component, with high Alzheimer's risks in homozygotes (R47H/R47H) and compound heterozygotes (R47H/R62H).

Alzheimer's disease is a common neurodegenerative disorder with high heritability. While autosomal dominant forms of Alzheimer's exist—where specific sequence variants in APP, PSEN1, and PSEN2 genes lead to overproduction and/or aggregation of Aβ, causing plaque deposition and Alzheimer's disease with near-complete penetrance—R47H in TREM2 differs in its mechanism and inheritance pattern.

Rather than contributing to Aβ overproduction and/or aggregation, R47H disrupts Aβ clearance, resulting in the accumulation of amyloid plaques and a greatly increased risk of Alzheimer's disease in homozygotes (R47H homozygotes odds ratio, 97.1 [95% CI, 23.5 to 401.1]) and R47H-R62H compound heterozygotes (odds ratio, 10.0 [95% CI, 4.2 to 23.9]). This study is the first to uncover a strong recessive component in Alzheimer's disease.

The very high risk in R47H homozygotes underscores the necessity for early intervention if treatments such as Aβ-removing antibodies or TREM2 agonists are shown to have efficacy at the preclinical stage.

More information: Hreinn Stefansson et al, Homozygosity for R47H in TREM2 and the Risk of Alzheimer's Disease, *New England Journal of Medicine* (2024). DOI: 10.1056/NEJMc2314334

Provided by deCODE genetics

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