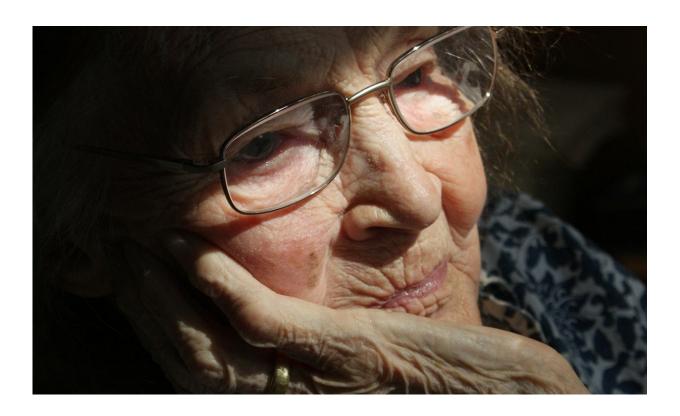


New genetic risk factors discovered for Alzheimer's disease

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A large-scale international study has discovered new genetic risk loci for Alzheimer's disease, and researchers published their work in *Nature Genetics*.

Combining genetic data on a large-scale and in a non-conventional



manner resulted in the discovery of multiple novel genetic factors and biological mechanisms that contribute to the pathogenesis of the disease. The study was led by Danielle Posthuma from the VU University in Amsterdam, Ole Andreassen from the University of Oslo, and Stephan Ripke from the Broad Institute in Boston, and was carried out as part of an initiative of the Psychiatric Genomics Consortium, which was founded by Patrick Sullivan, MD, Yeargen Distinguished Professor of Psychiatry and Genetics and Director of the Center for Psychiatric Genomics in the UNC School of Medicine. Sullivan is also lead principal investigator for the consortium.

Alzheimer's disease (AD) is the most common neurodegenerative disease. More than 30 million people are affected worldwide, and this is predicted to double every 20 years, expecting 115.4 million people to be diagnosed with Alzheimer's by 2050. To improve the current treatment, we require an improved understanding of underlying biological mechanisms that are involved in the initiation of pathological processes leading to clinical Alzheimer's, which is largely under genetic influence. And so identifying genetic risk factors will increase our insight into this devastating disease.

Genetic defects within the immune system and lipid components

The current study is the largest genetic study of Alzheimer's so far, including over 455,000 individuals. The study included clinical diagnoses to define the patient group, but also included a group of people where parental Alzheimer's status was considered. For all individuals, genetic information was available which allowed to scan the genome for possible genetic risk factors. This combined analysis yielded 29 genome-wide significant loci for the disease, including nine novel genetic loci. Results imply that genetic defects in genes involved in the



<u>immune system</u> and components associated to lipids, contribute to the Alzheimer's risk.

"Specifically, using single cell gene expression patterns, we show that genetic changes in genes that are expressed in microglia cells, are associated with increased risk for AD," Posthuma said. "Microglial cells are an important part of the immune system of the brain. This finding suggests that we should widen our focus to also include microglia models when performing functional research in AD, in addition to the conventional approach of neuronal models."

Iris Jansen, co-first author of the publication, said: "We additionally detect genetic changes in proteins that are involved in lipid components. This link has already been described for the APOE gene, the strongest genetic risk factor for AD, but our results show that other lipid proteins might also be genetically affected. This observation strengthens the hypothesis that AD pathogenesis involves an interplay between inflammation and lipids, as <u>lipid</u> changes might harm immune responses of microglia, thereby affecting the vascular health of the brain."

Indirect genetic effects on Alzheimer's through cognitive reserve

The study also tested the involvement of any indirect genetic effects on AD risk. In accordance with previous clinical research, which showed a protective effect of cognitive reserve on Alzheimer, the study reports a similar positive effect of cognitive skills on AD, yet this time supported by genetics. "This finding implies that a portion of the genetic risk factors affect cognitive reserve, which subsequently decrease the risk for AD", said Jeanne Savage, co-first author of the study.

More information: Iris E. Jansen et al. Genome-wide meta-analysis



identifies new loci and functional pathways influencing Alzheimer's disease risk, *Nature Genetics* (2019). DOI: 10.1038/s41588-018-0311-9

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