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Genetics overlap found between Alzheimer's disease and cardiovascular risk factors

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An international team of scientists, led by researchers at University of California, San Diego School of Medicine, have found genetic overlap between Alzheimer's disease (AD) and two significant cardiovascular disease risk factors: high levels of inflammatory C-reactive protein (CRP) and plasma lipids or fats. The findings, based upon genome-wide association studies involving hundreds of thousands of individuals, suggest the two cardiovascular phenotypes play a role in AD risk - and perhaps offer a new avenue for potentially delaying disease progression.

The findings are published in current online issue of *Circulation*.

"For many years we have known that high levels of cholesterol and high levels of inflammation are associated with increased risks for Alzheimer's disease," said study co-author Paul M Ridker, MD, MPH, the Eugene Braunwald Professor of Medicine at Harvard Medical School and director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital. "The current work finds that specific genetic signals explain a part of these relationships. We now need to characterize the function of these genetic signals and see whether they can help us to design better trials evaluating inflammation inhibition as a possible method for Alzheimer's treatment."

The researchers used summary statistics from genome-wide association studies of more than 200,000 individuals, looking for overlap in single nucleotide polymorphisms (SNPs) associated with clinically diagnosed AD and CRP and the three components of total cholesterol: high-density

lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG). SNPs are fragments of DNA sequence that commonly vary among individuals within a population.

They found up to a 50-fold enrichment of AD SNPs for different levels of association with CRP, LDL, HDL and TG, which then lead to identification of 55 loci - specific locations on a gene, DNA sequence or chromosome - linked to increased AD risk. The researchers next conducted a meta-analysis of these 55 variants across four independent AD study cohorts, encompassing almost 145,000 persons with AD and healthy controls, revealing two genome-wide significant variants on chromosomes 4 and 10. The two identified genes - HS3ST1 and ECHDC3 - were not previously associated with AD risk.

"Our findings indicate that a subset of genes involved with elevated plasma lipid levels and inflammation may also increase the risk for developing AD. Elevated levels of plasma lipids and inflammation can be modified with treatment, which means it could be possible to identify and therapeutically target individuals at increased risk for developing cardiovascular disease who are also at risk for developing Alzheimer's disease," said Rahul S. Desikan, MD, PhD, research fellow and radiology resident at the UC San Diego School of Medicine and the study's first author.

If so, the research may have significant ramifications. Late-onset AD is the most common form of dementia, affecting an estimated 30 million persons worldwide - a number that is expected to quadruple over the next 40 years. The societal costs, from medical to lost productivity, are staggering. The 2010 World Alzheimer Report estimated total annual costs at $606 billion.

"Currently, there are no disease modifying therapies and much attention has been focused upon prevention and early diagnosis," said Ole A.

Andreassen, MD, PhD, a senior co-author and professor of biological psychiatry at the University of Oslo in Norway. "Delaying dementia onset by even just two years could potentially lower the worldwide prevalence of AD by more than 22 million cases over the next four decades, resulting in significant societal savings."

Senior author Anders M. Dale, PhD, professor of neurosciences and radiology and director of the Center for Translational Imaging and Precision Medicine at UC San Diego, said further research will be needed: "Careful and considerable effort will be required to further characterize the novel candidate genes detected in this study and to detect the functional variants responsible for the association of these loci with Alzheimer's risk. It will also be important to understand whether these genes, in combination with other known markers such as brain imaging, cerebrospinal fluid measurements and APOE E4 status, can improve the prediction of disease risk in AD."

Provided by University of California - San Diego

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