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GENETICS

ALZHEIMER DISEASE AND DYSLIPIDAEMIA

Inflammation and dyslipidaemia have been associated with risk of developing Alzheimer disease (AD) and dementia, but the reasons for this link are not well understood. In a new analysis of existing AD genome-wide association studies (GWAS), Desikan *et al.* identified genetic polymorphisms associated with increased levels of C-reactive protein (CRP) and plasma lipids that were also associated with increased risk of AD.

"Recent GWAS of late-onset AD implicate multiple genes involved [in] cholesterol metabolism and neuroinflammation," says Rahul Desikan, the first author of the study report. In their new study, summary statistical data from GWAS of >200,000 individuals were searched for single nucleotide polymorphisms (SNPs) associated both with clinically-diagnosed AD and with serum levels of CRP and plasma lipid levels (triglycerides, HDL, and LDL).

After applying progressively stringent *P*-value thresholds for AD SNPs, researchers found a >50-fold enrichment for CRP SNPs, a 30-fold enrichment for triglycerides SNPs, 20-fold for HDL SNPs, and 40-fold for LDL SNPs. Ranking SNPs from a discovery cohort of patients with AD and controls according to their genetic association with CRP and lipid levels yielded 55 susceptibility loci (conditional false discovery rate <0.05). These 55 loci were then studied in a meta-analysis of four independent AD cohorts, resulting in the identification of two novel genome-wide significant loci (rs13113697, OR = 1.07, 95% CI 1.05–1.11, $P = 2.86 \times 10^{-8}$; and rs7920721, OR = 1.07, 95% CI 1.04–1.11, $P = 3.38 \times 10^{-8}$). Gene expression of *HS3ST1* and *ECHDC3*, the two genes closest to each of the two variants identified, was different between brains from patients with AD and controls.

"Our findings indicate abundant genetic pleiotropy between AD, CRP, and plasma lipids," says Desikan. "Many cardiovascular disease traits, such as dyslipidaemia and inflammation, are modifiable and can serve as therapeutic targets for AD." Whether the polymorphisms detected in this and other studies associate with known biomarkers of AD, such as longitudinal brain atrophy or neurofibrillary tangles and amyloid plaques, remains to be determined.

João H. Duarte

Original article Desikan, R. S. *et al*. Polygenic overlap between C-reactive protein, plasma lipids and Alzheimer's disease. *Circulation* doi:10.1161/circulationaha.115.015489