

NOVEL GENETIC RISK FACTOR FOR ALZHEIMER'S DISEASE PROGRESSION

Researchers at Washington University have identified a novel genetic variant that strongly correlates with disease progression. Alison Goate and collaborators used an established biomarker for the decline of AD patients (cerebrospinal fluid tau phosphorylated at threonine 181, ptau₁₈₁) to find genetic variants that influence levels of ptau₁₈₁ in the cerebrospinal fluid. The study found a highly significant association between ptau₁₈₁ levels and the rs1868402 SNP located within a regulatory subunit of PPP3R1 (calcineurin B), a gene previously linked to AD pathogenesis. Carriers of the rs1868402 risk allele showed a 6-fold faster rate of disease progression than AD patients without the variant. In addition, individuals carrying allele rs1868402 and rs3785883, a second allele identified in the study, showed an even more pronounced rate of decline. Direct examination of brain samples from AD cases and controls revealed that rs1868402 is in fact associated with reduced PPP3R1 mRNA levels and increased tangle formation, providing biological validation for the genome-wide association study and further implicating PPP3R1 in disease pathology. rs1868402 showed no association with risk for AD or age at onset, but there was a very significant association with rate of progression of disease that is consistent in two independent series. As the first genetic variant associated with rate of AD progression to be reported, its use in clinical trial design and patient care will translate into a significant benefit to patients.

POTENTIAL AREAS OF APPLICATIONS:

- Diagnostic for individuals with rapid decline in Alzheimer's disease
- New protein pathway for drug therapies for treating Alzheimer's disease progression

PATENT STATUS: Patent pending

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