# ABCA1 modulates CSF cholesterol levels and influences the age at onset of Alzheimer's disease

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Increased formation of the beta-amyloid peptide (Abeta) is a central event in the pathogenesis of Alzheimer's disease (AD). High cellular cholesterol load promotes Abeta formation. The ATP-binding cassette transporter A1 (ABCA1) mediates cholesterol efflux from cells. We hypothesized that genetic variability in ABCA1 may influence cholesterol metabolism in the central nervous system (CNS) and, thus, interfere with the development of AD. Healthy elderly carriers of the A allele of a non-synonymous (R219K) single nucleotide polymorphism (SNP) in the ABCA1 gene (rs2234884) had on average 33% lower total cholesterol in cerebrospinal fluid (CSF) than non-carriers. In 169 patients with late onset, sporadic AD, this allele was associated with delayed age at onset of the disease by 1.7 years on average. Rs2234884 and another non-synonymous SNP (R1587K) in ABCA1 (rs2234886) failed to show significant association with the risk for AD. We conclude that genetic variability of ABCA1 influences the development of AD, possibly by interfering with CNS cholesterol homeostasis.

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