CYP46: New Insight into the Genetic Risk for Alzheimer Disease

Previously, apolipoprotein E (ApoE) was the only gene unequivocally linked to a propensity for late-onset Alzheimer disease (LOAD) development, but a step was recently made towards further elucidation of the genetics involved in the disease.

24S-hydroxylase, the neuronal protein encoded by the gene CYP46, catalyses the conversion of brain cholesterol to 24-hydroxycholesterol, thereby facilitating the export of cholesterol from brain tissue via the blood-brain barrier. Brain cholesterol accumulation has been tentatively linked to the generation of beta-amyloids (Aβ), the peptides implicated in Alzheimer disease (AD) pathogenesis. It is therefore reasonable to propose that defects in the CYP46 gene may contribute to an increased genetic risk of disease development.

To further assess the contribution of 24S-hydroxylase to effective brain cholesterol metabolism and to LOAD risk, European researchers screened the CYP46 genomic region for single nucleotide polymorphisms (SNPs). rs754203, a TT polymorphism located between exons 2 and 3 on chromosome 14q, was polymorphic in 100 chromosomes and was thus deemed a candidate for genotyping. ApoE genotyping was also performed.

To determine genetic associations, studies were conducted on a hypothesis testing sample of 76 control subjects and 107 AD patients, followed by a confirming sample of 172 controls and 94 demented patients. In the two samples, CYP46*TT frequency was higher in AD subjects than in the controls (60.7% vs. 46.1%; 58.5% vs. 43.0%, respectively). Importantly, the odds ratio (OR) for the risk of AD in carriers of CYP46*TT and ApoE4 was 9.63 compared to an OR of 2.03 for carriers of only the former and an OR of 4.06 for carriers of only the latter. These results suggest a synergistic mechanism between CYP46 and ApoE on AD risk.

The relationship between CYP46 and ApoE polymorphisms and Aβ and 24S-hydroxycholesterol levels was examined by analysing brain tissue and cerebrospinal fluid (CSF) samples. Brain Aβ load was significantly higher in CYP46*TT-positive subjects than in CYP46*TT-negative subjects, and was highest in carriers of both the CYP46*TT genotype and the ApoE4 allele. The same trend was noted in CSF samples. However, while CSF levels of 24S-hydroxycholesterol were higher in AD patients than in controls, no difference in CSF 24S-hydroxycholesterol levels was noted between CYP46*TT-positive and -negative subjects. This suggests a possible alternate pathway by which the CYP46*TT genotype is contributing to Aβ accumulation.

The study was conducted on a small scale, but produced results sufficiently significant to warrant further, larger tests and to extend the hypothesis to encompass other CYP46 polymorphisms. The study supports a model of LOAD whereby CYP46 loss of function increases brain cholesterol, causing Aβ aggregation and ultimately leading to neurodegeneration. However, the data gathered to date do not rule out the possibility that the CYP46*TT genotype increases rather than decreases CYP46 activity, thus contributing to LOAD by way of an alternate mechanism. A more detailed understanding of the manner in which 24S-hydroxycholesterol is exported from the brain may indicate that other loci are involved in influencing AD susceptibility. ◆

Source

1. Papassotiropoulos A, Streffer JR, Tsolaki M, et al. Increased brain β-amyloid load, phosphorylated tau, and risk of Alzheimer disease associated with an intronic CYP46 polymorphism. Arch Neurol 2003;60:29-35.