Alzheimer’s Disease: effect of Tau-related genes on the pathology, neurochemistry and risk of disease

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ABSTRACT

Alzheimer’s disease (AD) is the most common form of dementia in the elderly. The predominant sporadic form of AD is a genetically complex disorder probably involving a combination of genetic factors together with environmental influences. To date, the best established genetic risk factor identified is the APOE ε4 allele. However not all AD cases have the APOE ε4 allele, thus several susceptibility genes remain to be found. One of the characteristics of AD is the intraneuronal accumulation of neurofibrillary tangles (NFTs). NFTs are composed of a hyperphosphorylated form of the tau protein. Since tau pathology is a central and an important event in AD this thesis has focused on studying genes that are directly or indirectly related to tau and examine their effect on pathology, neurochemistry and risk of disease. In the first paper, we identified a single nucleotide polymorphism (SNP) in the cell division cycle (CDC2) gene. In AD brain, cdc2 is expressed in neurons and is involved in hyperphosphorylation of tau. The SNP was tested for association with sporadic AD. A significant association between both genotype and allele frequencies and AD was found. In next paper, we examined a SNP in the Saitohin (STH) gene, a gene located in one of the introns of the human TAU gene. Numerous SNPs span the human tau gene and are in complete linkage disequilibrium (LD) with each other yielding two separate haplotypes, H1 and H2. Patients with AD, FTD and PD and controls were genotyped for the STH SNP and/or the TAU haplotype. Genotype data were tested for their association to AD biomarkers in the cerebrospinal fluid (CSF) and to neuropathological scores of senile plaques. The STH SNP and the TAU haplotype were in complete LD in all patients (AD and FTD) and controls investigated for both genes. There were no significant differences in genotype or allele distributions in AD, FTD or PD patients compared to controls. Neither TAU haplotype nor STH influenced CSF biomarkers or neuropathological scores significantly. In next study, we followed up the findings from paper I and examined possible effects of the CDC2 SNP on CSF biomarkers and neuropathological scores in AD patients. The CDC2 I allele was associated with a gene dose-dependent increase of CSF total-tau levels. In conclusion, the results from paper I suggest a link between the CDC2 gene and AD. This is further supported by the findings from paper III, where we could provide evidence for an involvement of CDC2 in the pathogenesis of AD. We found no evidence that could support a major pathogenic role of STH and TAU haplotype in AD, FTD or PD in paper II.