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

AKADEMISK AVHANDLING

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av

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Avhandlingen baseras på följande delarbeten:

I Johansson A, Hampel H, Faltraco F, Buerger K, Minthon L, Bogdanovic N, Sjogren M, Zetterberg H, Forsell L, Lilius L, Wahlund LO, Rymo L, Prince JA, and Blennow K. "Increased frequency of a new polymorphism in the cell division cycle 2 (*CDC2*) gene in patients with Alzheimer's disease and frontotemporal dementia" *Neuroscience Letters 2003 April 340 (1) 69-73.*

II Johansson A, Zetterberg H, Håkansson A, Nissbrandt H and Blennow K. "*TAU* haplotype and Saitohin Q7R gene polymorphism do not influence cerebrospinal fluid levels of tau and β-amyloid$_{1-42}$, in Alzheimer's disease and frontotemporal dementia" *Neurodegenerative Disorders 2005 2 (1) 28-35.*

III Johansson A, Zetterberg H, Hampel H, Buerger K, Prince J, Minthon L, Wahlund LO and Blennow K. "Genetic association of *CDC2* with CSF tau in Alzheimer's disease" *Dementia and Geriatric Cognitive Disorders 2005 20 (6) 367-374.*

IV Sjölander A, Andersson M, Zetterberg H, Minthon L, Bogdanovic N and Blennow K. "The *CDK5* gene and effect on CSF biomarkers and neuropathology in Alzheimer's disease" *Manuscript 2007.*

Handledare: Professor Kaj Blennow, Institutionen för neurovetenskap och fysiologi.

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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 on 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.

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