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Absence of pathogenic mutations in presenilin homologue 2 in a conclusively 17-linked tau-negative dementia family

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Sirs,

Frontotemporal dementia (FTD) is the second most-common neurodegenerative dementia after Alzheimer's disease (AD), with a frequency of 12%–20% among patients with an onset of dementia below 65 years. Causal mutations leading to FTD were identified in the microtubule-associated protein tau (*MAPT*) gene located at 17q21. In several autosomal dominant tau-negative FTD families, however, mutations in *MAPT* could not be identified, despite conclusive linkage to 17q21 [1, 2, 3]. We hypothesized that this subtype of FTD could result from mutations in the gene encoding presenilin (PS) homologue 2 (*PSH2*), located 50 kb upstream of *MAPT*. *PSH2* is one of five members of a novel family of proteins

showing membrane topology and putative catalytic domains similar to PS [4]. Because mutations in presenilins 1 and 2 are responsible for early onset AD [5] (<http://molgen-www.uia.ac.be/ADMutations>), mutations in PSHs might also lead to neurodegeneration. Previously, mutation analysis of *PSH2* in probands of four tau-negative FTD families failed to identify *PSH2* mutations [4], but these families were not informative for linkage to 17q21.

We described a four-generation family, 1083, ascertained in a population-based study in the Netherlands [6], which presented with a clinical phenotype similar to FTD and a mean onset age of 64.9 years (range 53–79 years) [2]. Autopsy demonstrated severe frontal atrophy and complete lack of tau neuropathology in the presence of ubiquitin-positive tau-negative inclusions. A genome-wide scan identified conclusive linkage (multipoint LOD score=5.51) in a candidate region of 4.8 cM at 17q21 comprising *MAPT*. Extensive mutation analysis of *MAPT* coding and regulatory sequences failed to identify disease-related mutations [2].

In this study, we performed mutation analysis of *PSH2* by direct sequencing of three overlapping PCR amplicons of genomic DNA between positions g.6 and g.2195 in XM_091623.4, corresponding to the only coding exon of *PSH2*, and including 67 bp upstream and 68 bp downstream regulatory sequences. In total we identified 5 novel (Table 1) and 10 known single nucleotide polymorphisms (SNPs) (see electronic supplementary Fig. 1). Segregation analysis in the family indicated that only 1 novel SNP g.1698G>A was contained in the disease haplotype leading to a silent mutation at codon S542. We used a pyrosequencing assay to analyze 89 Dutch control individuals and identified 2 controls that were homozygous and 20 heterozygous for the A allele, resulting in a minor allele frequency of 13.5%. Segregation analysis also illustrated that 4 of the 5 novel SNPs were in linkage disequilibrium with the extended *MAPT* haplotypes H1/H2, defined by polymorphic alleles in *MAPT* exons 1, 2, 3, 9, 11, and 13 [7] (see electronic supplementary Fig. 1).

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Table 1 Novel single nucleotide polymorphisms (SNPs) in the gene for presenilin homologue 2 (*PSH2*). For all SNPs nucleotide numbering is described relative to XM_091623.4

Genomic position	Amino acid change	Minor allele frequency ^a
g.1698G>A	S542	13.5%
g.2000C>G	P643R	38%
g.2019T>C	H649	38%
g.2031G>A	Q653	38%
g.2137C>A	–	38%

^a For g.1698G>A, allele frequencies were calculated in 190 unrelated control chromosomes, the others were calculated in the 3 patients and 1 control of family 1083 of whom 3 shared the same haplotype

These data confirmed that *MAPT* haplotype blocks extend to *PSH2*, as previously shown by Ponting et al. [4].

In conclusion, we excluded by direct sequencing pathogenic mutations in *PSH2* as a causative defect for 17q21-linked tau-negative FTD using mutation and segregation analysis in the most-informative family known to date. It is also unlikely that the single *PSH2* coding exon or part of it is deleted, since all patients were heterozygous for the linked SNP g.1698G>A, and since in all three PCR amplicons heterozygote SNPs were identified in at least one patient. A gene duplication of *PSH2* cannot be fully excluded by the methods we used in the mutation analysis. However, the apparent accumulation of non-synonymous SNPs within the *PSH2* coding sequence is indicative of a non-functional processed pseudogene [4] (this study). Therefore, our data suggest that another defective gene at 17q21 should also be considered for this subtype of FTD. Since 64% of all FTD patients do not display tau pathology, and since the *MAPT* mutation frequency in familial FTD is less than 50%, the genetic defect leading to tau-negative dementia might be an important factor in the etiology of FTD. Its identification will likely contribute to our understanding of this important neurodegenerative dementia.

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