Neurogenetics (2004) 5:79–80
DOI 10.1007/s10048-003-0162-z

LETTER TO THE EDITORS

R. Rademakers · M. Van den Broeck · K. Sleegers · C. van Duijn · C. Van Broeckhoven · M. Cruts

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

Published online: 8 October 2003

Keywords Tau-negative dementia · Presenilin homologue 2 · Lack of pathogenic mutations

Electronic Supplementary Material Supplementary material is available for this article if you access the article at http://dx.doi.org/10.1007/s10048-003-0162-z. A link in the frame on the left on that page takes you directly to the supplementary material.

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).

R. Rademakers · M. Van den Broeck · C. van Duijn · C. Van Broeckhoven · M. Cruts
Department of Molecular Genetics,
Flanders Interuniversity Institute for Biotechnology,
University of Antwerp, Antwerpen, Belgium

K. Sleegers · C. van Duijn
Genetic Epidemiology Group,
Department of Epidemiology and Biostatistics,
Erasmus Medical Center, Rotterdam, The Netherlands

M. Cruts (✉)
Department of Molecular Genetics (VIB8), Neurogenetics Group,
University of Antwerp (Campus UIA),
Universiteitsplein 1, 2610 Antwerpen, Belgium
e-mail: marc.cruts@ua.ac.be
Tel.: +32-3-8202631
Fax: +32-3-8202541

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.

Acknowledgements We acknowledge C. Ponting and K. Davies for sharing their data on *PSH2* before publication. We acknowledge the VIB Genetic Service Facility (http://www.vibgeneticservicefacility.be/) for the genetic analyses. The research was funded by the Special Research Fund of the University of Antwerp, the Fund for Scientific Research Flanders (FWO-F), the InterUniversity Attraction Poles program P5/19 of the Federal Office of Scientific, Technical, and Cultural Affairs, the International Alzheimer Research Foundation, and The Medical Foundation Queen Elisabeth, Belgium, The Netherlands Organization for Scientific Research (NWO), and the Alzheimer Association USA. R.R. is a PhD fellow and M.C. a postdoctoral fellow of the FWO-F.

References

1. Lendon CL, Lynch T, Norton J, McKeel DW Jr, Busfield F, Craddock N, Chakraverty S, Gopalakrishnan G, Shears SD, Grimmett W, Wilhelmsen KC, Hansen L, Morris JC, Goate AM (1998) Hereditary dysphasic disinhibition dementia: a frontotemporal dementia linked to 17q21–22. Neurology 50:1546–1555
2. Rademakers R, Cruts M, Dermaut B, Sleegers K, Rosso SM, Van den BM, Backhovens H, Van Swieten J, Duijn CM van, Van Broeckhoven C (2002) Tau negative frontal lobe dementia at 17q21: significant fine mapping of the candidate region to a 4.8 cM interval. Mol Psychiatry 7:1064–1074
3. Rosso SM, Kamphorst W, Graaf B de, Willemsen R, Ravid R, Niermeijer MF, Spillantini MG, Heutink P, Swieten JC van (2001) Familial frontotemporal dementia with ubiquitin-positive inclusions is linked to chromosome 17q21–22. Brain 124:1948–1957
4. Ponting CP, Hutton M, Nyborg A, Baker M, Jansen K, Golde TE (2002) Identification of a novel family of presenilin homologues. Hum Mol Genet 11:1037–1044
5. Cruts M, Van Broeckhoven C (1998) Presenilin mutations in Alzheimer's disease. Hum Mutat 11:183–190
6. Duijn CM van, Hendriks L, Farrer LA, Backhovens H, Cruts M, Wehnert A, Hofman A, Van Broeckhoven C (1994) A population-based study of familial Alzheimer disease: linkage to chromosomes 14, 19, and 21. Am J Hum Genet 55:714–727
7. Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E, Hutton M (1999) Association of an extended haplotype in the Tau gene with progressive supranuclear palsy. Hum Mol Genet 8:711–715