Research article

Role of \textit{MAPT} mutations and haplotype in frontotemporal lobar degeneration in Northern Finland

Anna-Lotta Kaivorinne\textsuperscript{1,2}, Johanna Krüger\textsuperscript{1,2}, Katja Kuivaniemi\textsuperscript{1}, Hannu Tuominen\textsuperscript{3}, Virpi Moilanen\textsuperscript{1}, Kari Majamaa\textsuperscript{1,2,4} and Anne M Remes\textsuperscript{*1,2}

Address: \textsuperscript{1}Department of Neurology, University of Oulu, Oulu, Finland, \textsuperscript{2}Clinical Research Center, Oulu University Hospital, Oulu, Finland, \textsuperscript{3}Department of Pathology, University of Oulu, Oulu, Finland and \textsuperscript{4}Department of Neurology, University of Turku, Turku, Finland

Email: Anna-Lotta Kaivorinne - annalott@mail.student.oulu.fi; Johanna Krüger - johanna.kruger@oulu.fi; Katja Kuivaniemi - katja.kuivaniemi@mail.suomi.net; Hannu Tuominen - hannu.tuominen@ppshp.fi; Virpi Moilanen - virpi.moilanen@ppshp.fi; Kari Majamaa - kari.majamaa@utu.fi; Anne M Remes\textsuperscript{*} - anne.remes@oulu.fi

\textsuperscript{*} Corresponding author

Abstract

\textbf{Background:} Frontotemporal lobar degeneration (FTLD) consists of a clinically and neuropathologically heterogeneous group of syndromes affecting the frontal and temporal lobes of the brain. Mutations in microtubule-associated protein tau (\textit{MAPT}), progranulin (\textit{PGRN}) and charged multi-vesicular body protein 2B (\textit{CHMP2B}) are associated with familial forms of the disease. The prevalence of these mutations varies between populations. The H1 haplotype of \textit{MAPT} has been found to be closely associated with tauopathies and with sporadic FTLD. Our aim was to investigate \textit{MAPT} mutations and haplotype frequencies in a clinical series of patients with FTLD in Northern Finland.

\textbf{Methods:} \textit{MAPT} exons 1, 2 and 9–13 were sequenced in 59 patients with FTLD, and \textit{MAPT} haplotypes were analysed in these patients, 122 patients with early onset Alzheimer’s disease (eoAD) and 198 healthy controls.

\textbf{Results:} No pathogenic mutations were found. The H2 allele frequency was 11.0\% ($p = 0.028$) in the FTLD patients, 9.8\% ($p = 0.029$) in the eoAD patients and 5.3\% in the controls. The H2 allele was especially clustered in patients with a positive family history ($p = 0.011$) but did not lower the age at onset of the disease. The ApoE4 allele frequency was significantly increased in the patients with eoAD and in those with FTLD.

\textbf{Conclusion:} We conclude that although pathogenic \textit{MAPT} mutations are rare in Northern Finland, the \textit{MAPT} H2 allele may be associated with increased risks of FTLD and eoAD in the Finnish population.

\textbf{Background} 

Frontotemporal lobar degeneration (FTLD) is a clinically and neuropathologically heterogeneous group of neurodegenerative disorders affecting the frontal and/or temporal lobes and causing changes in personal and social conduct, disinhibition and progressive changes in lan-
guage. The main clinical syndromes are frontotemporal dementia (FTD), semantic dementia (SD) and progressive non-fluent aphasia (PA).[1] FTD can be divided neuropathologically into diseases with tau-positive inclusions and diseases with tau-negative and ubiquitin-positive inclusions.[2] A positive family history is present in 30–50% of FTD cases.[3,4] Mutations in microtubule-associated protein tau (MAPT), progranulin (PGRN) and charged multi-vesicular body protein 2B (CHMP2B) are associated with the autosomal dominant form of the disease.[5-9]

Mutations in MAPT are associated with tau-positive neuropathology and occur in familial FTD in frequencies that vary in the range 5–50% between populations.[3,10-15] Several polymorphisms throughout the MAPT gene are in complete linkage disequilibrium with each other and are inherited as two separate haplotypes, H1 and H2. The predominant haplotype, H1, has been found to be associated with sporadic tauopathies, [16-18] and also to have a faint association with FTD.[19,20] However, in some studies the H2 haplotype has also been found to be associated with FTD.[15,21]

The aim of this work was to investigate the frequency of MAPT mutations in Finnish patients with FTD and to examine the association between the MAPT haplotypes and FTD. We sequenced exons 1, 2 and 9–13 of MAPT in 59 Finnish patients with FTD and analysed the MAPT haplotypes in these patients, 122 patients with early onset Alzheimer’s disease (eoAD, age at onset before 65 years) and 198 healthy middle-aged controls.

**Methods**

**Patients**

We examined 59 patients with FTD (mean age at onset 58.5 years, range 38–79, 49% men) and 122 patients with eoAD (mean age 58.2 years, range 38–64, 45% men) in the memory clinic of the Department of Neurology, Oulu University Hospital, Finland, during the years 1999–2006. Population of the Northern Ostrobothnia area served by this hospital was 380 668 (as of 31.12.2006). A clinical diagnosis of FTD was made according to the criteria of Lund and Manchester, and the NINCDS-ADRDA criteria were used to establish a diagnosis of probable AD.[22,23] The FTD group consisted of 34 (58%) patients with FTD, 19 (32%) with PA and six (10%) with SD. Six patients (10%) also suffered from symptoms of motor neuron disease. 27% of the patients in the FTD group had a positive family history of FTD, i.e. a first-degree relative suffering from dementia. PGRN gene mutations in the FTD patients were excluded by direct sequencing as described previously.[24] Most of the patients were alive during this study and neuropathological examinations were performed only on five deceased subjects.

Control samples were obtained from 198 healthy anonymous middle-aged volunteers (mean age 40.6 years, range 19–64 years) as part of blood donations at Finnish Red Cross offices in the capitals of the provinces of Northern and Central Ostrobothnia and Kainuu.

Written informed consent was obtained from all the patients or their guardians. The research protocols were approved by the Ethics Committees of the Faculty of Medicine at the University of Oulu, the Northern Ostrobothnia Hospital District and the Finnish Red Cross.

**Methods**

Total genomic DNA was extracted from the blood samples by the standard sodium dodecyl sulphate-proteinase K method. MAPT exons 1, 2 and 9–13 were amplified by polymerase chain reaction using genomic primers designed to cover the flanking intronic sequences as well. These exons were selected, because pathogenic mutations in MAPT have been associated to exons 1 and 9–13. Exon 2 was randomly selected to add data of polymorphisms between H1 and H2 haplotypes. Sequencing was carried out using the BigDye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems) and the ABI PRISM 3100 Genetic Analyzer (Applied Biosystems).

The MAPT haplotype was determined by testing for the presence of a 238 bp deletion between exons 9 and 10, which is characteristic of the H2 haplotype.[25] The haplotypes were assessed by visualizing the PCR products on a 1.5% agarose gel.

A novel exon13 +67delAAT polymorphism was screened by PCR using mismatch primers (forward 5’-GAGATCGT-GTACAAGTCGGCAAGT-3’ and reverse 5’-AGAGGGCG-GGGGCCGGGATCAAT-3’). The amplified fragments were digested with SspI restriction enzyme and then visualized using a 5% Metaphor gel. The apolipoprotein E (ApoE) genotype was determined as described previously.[26]

Statistical analyses were performed using the SPSS 16.0 software for Windows. The minimum significance level was set at \( P = 0.05 \). Differences in allele distributions were analysed using the \( \chi^2 \) test. Fisher’s exact test was used to analyse contingency tables when the expected value was less than five. Binary logistic regression analyses were performed to estimate both the marginal and partial (i.e. correcting for age, gender and ApoE4 allele) potential effects of genetic patterns.
Results

We sequenced exons 1, 2 and 9–13 of the MAPT gene in 59 Finnish patients with FTLD and analysed MAPT haplotypes in these patients, 122 patients with eoAD and 198 middle-aged healthy controls. No pathogenic MAPT mutations were found in the patients with FTLD.

We detected seven polymorphic sites which have previously been found to be associated with the H2 haplotype (Table 1), but did not find any novel polymorphisms in the H2 haplotype. The previously described Thr39Thr, P270P, Exon10 -47 and Exon11 +90, Exon11 +104 polymorphisms were found to be associated with the H1 allele (Table 2), in addition to a novel polymorphism Exon13 +67delAAT, which was found in 10 H1 alleles of patients with FTLD. One H1/H1 homozygous patient was also homozygous for the Exon13 +67delAAT polymorphism. The frequencies of Exon13 +67delAAT were 9.5% among the FTLD patients with the H1 allele, 8.5% in the whole FTLD group, 5.9% in the AD patients and 3.2% in healthy controls. Results of a neuropathological examination were available for one man with this polymorphism, who had had FTLD with ALS (amyotrophic lateralis sclerosis), for six years with onset at the age of 59 years. These results revealed tau-negative, ubiquitin-positive FTLD and motor neuron disease.

The frequencies of the H2 allele were 11.0% in the patients with FTLD and 9.8% in those with eoAD, as opposed to 5.3% in the controls (Table 3). Thus the frequencies of the H2 allele and the genotypes H1/H2 + H2/H2 were significantly increased in the FTLD patients relative to the controls (Table 3 and Table 4), and they also showed a significant increase among the patients with eoAD. The H2 allele was clustered with the familial form of FTLD, so that a positive family history was found in 58% of the FTLD cases with the H1/H2 or H2/H2 genotype (Fisher’s exact test, $P = 0.011$). The H2 allele was not associated with onset of the disease at an earlier age, the age at onset being $56.0 \pm 6.7$ years (mean $\pm$ SD) in the H1/H2 or H2/H2 carriers, and $59.2 \pm 6.5$ years in the H1/H1 carriers ($P = 0.138$).

Table 1: Polymorphisms in the H2 haplotype

| Exon  | Position Relative to Exon | Codon | Nucleotide Change |
|-------|---------------------------|-------|-------------------|
| 5' UTR| -13 from ATG              |       |                   |
| Exon 2| -93                       |       |                   |
|       | +18                       |       |                   |
| Exon 9|                           |       |                   |
| Exon 11| +34                       | A227A | GCA > GCG         |
| Exon 13| +34                       | N255N | AAT > AAC         |

Only one patient, with a negative family history of neurological disorders, had the H2/H2 genotype. In this case progressive apheric symptoms and changes in personality had started at the age of 52 years and by the end-stage of the disease he was completely apheric and had evident extrapyramidal symptoms. He died at the age of 62 years. Neuropathological evaluation revealed marked atrophy in both the frontal and temporal lobes. Tau-pathology was widespread. Tangle-like, globose and granular neuronal inclusions were present in neocortex, other than occipitally, and in the hippocampal pyramidal and fascia dentata neurones, basal ganglia, substantia nigra, locus ceruleus and cerebellar dentate. Tau-positive neuropil threads were seen in the same areas and in the subcortical white matter, and some white matter glial cells were tau-positive. Beta-amyloid and synuclein were absent.

The ApoE4 allele was found in 42.4% of the FTLD patients and 63.1% of the eoAD patients, the latter frequency being significantly increased ($P < 0.001$), but the former less so ($P = 0.049$).

Discussion

We analysed MAPT mutations and the role of the MAPT haplotype in 59 patients with FTLD in Northern Finland. A positive family history was found in 27% of these patients, but no pathogenic mutations in MAPT were detected. The relative frequency of MAPT mutations has varied previously between 0 and 50% depending on type of study, the area concerned and whether there has been a family history of the disease, [4,10,12-14,27,28] although the differences in frequency may also be explained by varying methods of case ascertainment. The frequency is obviously higher in familial forms of FTLD, however, an effect that has been attributed to the founder mutation in France and the Netherlands.[4,10,12] Interestingly, very low frequencies of MAPT mutations have been reported in Sweden and Poland.[27,28] The roots of the Finnish population reach back over 2000 years, but internal migration to Northern Ostrobothnia in the 16th century created a regional subisolate in the population of some 380000 inhabitants examined here.[29] which may explain the extremely low MAPT mutation frequency. On the other
hand, the geographical variation may reflect differences in the prevalence of MAPT mutations between populations. Our data support the findings of very low frequencies of MAPT mutations in the Baltic countries.[27,28]

We found that the H2 allele frequencies in patients with either FTLD or eoAD were two-fold compared with those in the controls, and that the frequencies of both the H2 allele and the H1/H2 + H2/H2 genotypes were significantly higher in both patient groups. The H2 allele in particular was associated with the familial form of FTLD. The H1 haplotype is the most common, having an allele frequency of about > 70% in European populations,[30] while the H2 haplotype has been associated with Cauca-sian ancestry, since Middle Eastern and European populations have frequencies of about 25%, the Finnish population about 8% and Central Asian populations about 5%, while the allele is essentially practically non-existent in other populations.[30] H1 has been associated with sporadic tauopathies, including Parkinson’s disease,[16,17] progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).[18] In particular, the H1c variant of the H1 haplotype has been linked with CBD, PSP and AD.[18,31] Recently, however, the H2 haplotype has been found to increase the risk of familial FTLD in an Italian population.[21] Two Belgian families with FTLD have been linked with the extended rare H2 haplotype and a PGRN mutation.[7,15] However, no pathogenic mutations in PGRN were found in our cohort.[24]

The H2 haplotype has also been reported to lower the age of onset of the disease,[32] but this finding could not be confirmed in the present study. Interestingly, this is the first study showing the association between the H2 haplotype and Alzheimer’s disease.

The H2 haplotype is assumed to be an ancestral one and to manifest only minor variability,[18,33] as confirmed here. A novel polymorphism Exon 13 +67 delAAT was found to be associated with the H1 allele and to have an increased frequency in patients with FTLD and eoAD, although it was also frequent in the controls, thus suggesting a non-pathogenic nature.

A significant association was found between the ApoE4 allele, the most important genetic risk factor for AD, and eoAD, and a similar association was also evident with FTLD. Increased frequency of the ApoE4 allele in patients with FTLD has also been reported previously,[32,34] and it has also been found to increase the penetrance of dementia, since valosin-containing protein (VCP) is associated with FTD,[35] and to impair long-term memory functions and reduce parahippocampal perfusion in FTLD patients.[36]

**Conclusion**

We conclude that, although pathogenic MAPT mutations are rare in Northern Finland, the frequency of the H2 allele of MAPT is significantly increased in patients with FTLD and also in patients with eoAD. Either the H2 hap-

---

**Table 2: Polymorphisms in the H1 haplotype**

| Exon | Position Relative to Exon | Codon | Nucleotide Change | Allele Frequency in Patients with FTLD |
|------|---------------------------|-------|-------------------|---------------------------------------|
| Exon 1 | T39T | ACG > ACA | 3 |
| Exon 2 | T52A | ACT > GCT | 1 |
| Exon 9 | P270P | CCG > CCA | 1 |
| Exon 10 | +47 | C > A | 2 |
| Exon 11 | +90 | G > A | 16 |
| Exon 11 | +104 | A > G | 1 |
| Exon 13 | +67 | del AAT | 10 |

**Table 3: MAPT genotypes and haplotypes in patients with FTLD and eoAD**

| Sample | N Individuals | H1/H1 N (%) | H1/H2 N (%) | H2/H2 N (%) | Genotype vs. controls<sup>b</sup> | N Alleles | H1 N (%) | H2 N (%) | Haplotypes vs. controls<sup>a</sup> |
|--------|---------------|-------------|-------------|-------------|----------------------------------|-----------|-----------|-----------|----------------------------------|
| FTLD   | 59            | 47 (79.7)   | 11 (18.6)   | 1 (1.7)     | P = 0.018<sup>a</sup>            | 118       | 105 (89.0)| 13 (11.0) | P = 0.028<sup>a</sup> |
| EoAD   | 122           | 98 (80.3)   | 24 (19.7)   | 0           | P = 0.006<sup>a</sup>            | 244       | 220 (90.2)| 24 (9.8)  | P = 0.029<sup>a</sup> |
| Controls | 198         | 180 (90.9)  | 15 (7.6)    | 3 (1.5)     |                                  | 396       | 375 (94.7)| 21 (5.3)  |                                  |

<sup>a</sup> Indicates statistical significance

<sup>b</sup> The genotypes were grouped into H1/H1 and H1/H2 + H2/H2 for statistical analysis
1. Neary D, Snowden J, Mann D: and the Päivikki and Sakari Sohlberg Foundation (AMR). We thank Ms Anja Heikkinen and Ms Pirjo Keränen for their excellent technical assistance.

Acknowledgements

This work was supported by grants from the Finnish Medical Foundation and the Paiviikki and Sakari Sohlberg Foundation (AMR). We thank Ms Anja Heikkinen and Ms Pirjo Keränen for their excellent technical assistance.

References

1. Neary D, Snowden J, Mann D: Fronto temporal dementia. Lancet Neurol 2005; 4:771-780.
2. Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, White CL, Jrd, Schneider JA, Grnberg LT, Halliday G, Duyckaerts C, Lowe JS, Holm IE, Tolnay M, Okamoto K, Yokoo H, Murayama S, Wouffe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann D: Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol 2007; 114:5-22.
3. Poirier J, Grossman P, Steinbart E, Payami H, Sadovnick A, Nochlin D, Tabira T, Trojanowski JQ, Boksa P, Saito Y, Fahn S, Dark F, Tannenberg T, Dodrick R, Hayward N, Kwojk J, Schofield PR, Andresis A, Snowden J, Craufurd D, Neary D, Owen F, Oostera BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T, Heutink P, Association of missense and splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998, 393:702-705.
4. Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghe B: Mutation in the tau gene in familial multiple system atrophy with presenile dementia. Proc Natl Acad Sci USA 1998, 95:7377-7741.
5. Cruts M, Gjesselin I, Zee J van der, Engelborghs S, Wils H, Pirici D, Rademakers R, Vandenberghe R, Lermontov A, Jll, Jvuijn D, Peeters K, Sciot R, Santens P, De Poorter T, Mathejssens M, Broeck M Van den, Cuyp J, Vennekens K, De Deyn PP, Kumar-Singh S, Van Broeckhoven C: Null mutation in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006, 442:920-924.
6. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:916-919.
7. Woulfe J, Munoz DG, Dickson DW, Ince PG, Trojanowski JQ, Mann D: Neurological and pathological classification of FTLD and AD. Lancet 2005, 366:1015-1027.
8. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006, 442:920-924.
9. Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich J, Niels J, Hodes J, Spillantini MG, Thysgaard T, Brandner S, Brun A, Rossor MN, Gade A, Johannsen P, Sorenson SA, Gyden H, Fisher EP, Collinge J: Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. Nat Genet 2005, 37:806-808.
10. Dumanich C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:916-919.
11. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006, 442:920-924.
12. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:916-919.
13. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006, 442:920-924.
14. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:916-919.
15. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006, 442:920-924.
16. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:916-919.
17. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006, 442:920-924.
18. Duyckaerts C, Camuzat A, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boehn B, Feldman H, Hutton M: Mutations in progranulin cause ubiquitin-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:916-919.
Lubke U, Broeck M Van den, Martin JJ, Cruts M, De Deyn PP, Van Broeckhoven C, Dermaut B. A Belgian ancestral haplotype harbours a highly prevalent mutation for 17q21-linked tau-negative FTD. Brain. 2006, 129:841-852.

16. Fidani L, Kalinderi K, Bostantjopoulos S, Clarimon J, Goulas A, Katsarou Z, Hardy J, Kotsis A: Association of the Tau haplotype with Parkinson's disease in the Greek population. Mov Dis 2006, 21:1036-1039.

17. Zabetian CP, Hutter CM, Factor SA, Nutt JG, Higgins DF, Griffith A, Mingers J, Benson DF: The H2 MAPT haplotype is associated with familial frontotemporal dementia. Arch Neurol 1991, 48:137-144.

18. Pittman AM, Myers AJ, Abou-Sleiman P, Fung HC, Kaleem M, Marlowe L, Duckworth J, Leung D, Williams D, Kilford L, Thomas N, Morris CM, Dickson D, Wood NW, Hardy J, Lees AJ, de Silva R: Linkage disequilibrium fine mapping and haplotype association analysis of the tau gene in progressive supranuclear palsy and corticobasal degeneration. J Med Genet 2005, 42:837-846.

19. Verpillat P, Camuzat A, Hannequin D, Thomas-Anterion C, Puel M, Belliard S, Dubois B, Didic M, Michel BF, Lacombe L, Moreaud O, Selat F, Golfeer V, Campion D, Clerget-Darpoux F, Brice A: Association between the extended tau haplotype and frontotemporal dementia. Arch Neurol 2002, 59:935-939.

20. Hughes A, Mann D, Pickering-Brown S: Tau haplotype frequency in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Exp Neurol 2003, 181:12-16.

21. Ghidoni R, Signorini S, Barbiero L, Sina E, Cominelli P, Villa A, Benussi L, Barcikowska M, Binetti G: The H2 MAPT haplotype is associated with familial frontotemporal dementia. Neurobiol Dis 2006, 22:357-362.

22. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Ferman M, Gomez-Isla T, O'Brien JT, Perry EK, Trojanowski JQ, Neumann M, Bainton DF, Terry DR, Trojanowski JQ: NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s disease. Neurology 1984, 34:939-944.

23. Fullerton SM, Young JH, Page LA, Amick K, Ostrander EA, Eng C: Mutation screening of the MAPT and STH genes in Polish patients with clinically diagnosed frontotemporal dementia. Neurogenetics 2001, 2:93-101.

24. Krüger J, Kaivoriininen A-L, Udd B, Majamaa K, Remes AM: Low prevalence of progranulin mutations in Finnish patients with frontotemporal lobar degeneration. Eur J Neurol 2008, 15(1):27-30.

25. Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, Hardy J, Lynch T, Bigio E, Hutton M: Association of an extended haplotype in the tau gene with progressive supranuclear palsy. Hum Mol Genet 1999, 8:711-715.

26. Wenham PR, Price WH, Blandell G: Apolipoprotein E genotyping by one-stage PCR. Lancet 1991, 337:1158-1159.

27. Ingersoll M, Fabre SF, Lilius L, Andersen C, Vistanen M, Almkvist O, Wahnlo LO, Lannfelt L: Increased risk for frontotemporal dementia through interaction between tau polymorphism and apolipoprotein E epsilon4. Neuroreport 2001, 12:905-909.

28. Zekanowcki C, Peptotska B, Styczyska M, Gustaw K, Kuzniacki J, Barciowska M: Mutation screening of the MAPT and STH genes in Polish patients with clinically diagnosed frontotemporal dementia. Dement Geriatr Cogn Disord 2003, 16:126-131.

29. Norio R: Finnish Disease Heritage I: characteristics, causes, background. Hum genet 2003, 112:441-456.

30. Emery BV, Fung HC, Steele J, Eeola J, Tiener P, Pittman A, Silva R, Myers A, Vrieze FW, Singleton A, Hardy J: The tau H2 haplotype is almost exclusively Caucasian in origin. Neurosci Letters 2004, 361:183-185.

31. Myers AJ, Kaleem M, Marlowe L, Pittman AM, Lees AJ, Fung HC, Duckworth J, Leung D, Gibson A, Morris CM, de Silva R, Hardy J: The H1c haplotype at the MAPT locus is associated with Alzheimer’s disease. Hum Mol Genet 2005, 14:2399-2404.

32. Borroni B, Yancopoulou D, Tsutsui M, Padovani A, Sawcer SJ, Hodges JR, Spillantini MG: Association between tau H2 haplotype and age at onset in frontotemporal dementia. Arch Neurol 2005, 62:1419-1422.

33. Oliveira SA, Scott WK, Zhang F, Stajich JM, Fujiwara K, Hauser M, Scott BL, Pericak-Vance MA, Vance JH, Martin ER: Linkage disequi-