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Negative results

Microtubule-associated protein tau genetic variations are uncommon cause of frontotemporal dementia in south India

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ABSTRACT

Microtubule-associated protein tau (MAPT) positive neuropathology is the characteristic feature of majority of frontotemporal dementia (FTD) cases, which is due to the mutations or haplotypic variations in the gene encoding MAPT (*MAPT*). The present study was aimed at determining the frequency of genetic variations in *MAPT* in a south Indian FTD cohort. The frequency of mutations were determined in 116 FTD, 8 progressive supranuclear palsy (PSP) and 3 corticobasal syndrome (CBS) patients and haplotype diversity were analyzed in a study cohort comprising 116 FTD, 8 PSP, 3 CBS, 194 other dementia groups, 78 mild cognitive impairment (MCI) and 130 cognitively normal individuals and report no pathogenic mutations in FTD/PSP/CBS or haplotypic association with disease risk in FTD or other dementia patients. These findings suggest that there may be other genetic or epigenetic factors contributing to the pathogenesis of FTD in the south Indian population.

1. Introduction

Frontotemporal dementia (FTD) is the second most common cause of presenile dementia, and presents with 3 clinical phenotypes: behavioral variant FTD (bvFTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD). Studies from western populations showed that up to 50% of FTD cases are familial and approximately 10% to 15% among the individuals affected harbor mutations in microtubule-associated protein tau gene (*MAPT*) (Hutton et al., 1998; Neary et al., 1998). The frequency of pathogenic *MAPT* mutations were found to vary between populations across the world (Kaivorinne et al., 2008). Moreover, *MAPT* is harbored within 2 distinct haplotypes, H1 and H2. The H1 haplotype has been associated with increased risk for developing sporadic tauopathies such as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) (Baker et al., 1999; Conrad et al., 1997). However, the association between H1 haplotype and FTD lacks consensus (Hughes et al., 2003; Verpillat et al., 2002). The present study evaluated the genetic contribution of *MAPT* variations to the pathogenesis of FTD using mutation analysis, and determined the frequency distribution of *MAPT* haplotypes in FTD, other dementia groups, and control subjects using association analysis.

2. Methods

Study participants were recruited from patients attending the Memory and Neurobehavioral Clinic at the Sree Chita Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala, India, after obtaining approval from the Institutional Ethical Committee of SCTIMST and written informed consent from all of the participants or their caregivers.

The study cohort comprised patients with FTD (n = 116), PSP (n = 8), CBS (n = 3), other dementia groups comprising AD (n = 132), VAD (n = 36), DLBD and mixed dementias (n = 26), mild cognitive impairment (MCI) (n = 78), and cognitively unimpaired control subjects (n = 130) who were matched with the patients for age and ethnicity. Clinical assessment was done by a neurologist and the standard criteria used are given in the Supplementary data. Demographic data of FTD patients is summarized in Supplementary data, Table 1. Mutation analysis was performed

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through direct DNA sequencing (Supplementary data, Table 2). *MAPT* haplotypes were assessed through genotyping the deletion polymorphism in intron 9. Genotypic and allelic frequencies were calculated and checked for deviation from Hardy–Weinberg equilibrium (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Statistical analyses were performed using GraphPad Prism software 5.01 (San Diego, CA).

3. Results

A positive family history was noticed in 17 FTD cases (15%), but the sequence analysis revealed no pathogenic mutations in either familial or sporadic FTD/PSP/CBS patients. Several non-pathogenic single nucleotide polymorphisms (SNPs) were detected (Supplementary data, Table 3). IVS9-48 is a novel intronic variation detected in this study. *MAPT* genotype frequencies did not vary significantly from Hardy–Weinberg equilibrium. The genotypic or haplotypic frequency did not show statistically significant differences, when the whole FTD group or its clinical subtypes or other dementia groups were compared with controls (except SD, $p = 0.01$) (Supplementary data, Table 4). The H2 haplotype did not show a significant association with age at onset or familial occurrence of the disease (Supplementary data, Tables 5 and 6).

4. Discussion

We herein report the absence of pathogenic mutations in *MAPT*, in a south Indian FTD cohort. To date, no genetic studies on FTD have been reported from south India and this is the first attempt to screen for mutations and haplotype distribution of *MAPT* locus in this population. 15% of FTD patients had a positive family history of similar illness but did not bear any pathogenic mutations in *MAPT*. The apparent absence of *MAPT* mutations even in familial cases may be explained by the difference in the geographical distribution pattern of *MAPT* mutations, as higher *MAPT* mutation frequencies have been reported from European countries due to founder effect and lower frequencies in Sweden, Poland, and Finland (Kaivorinne et al., 2008). There are very few reports on *MAPT* mutation analysis from Asian populations; Japanese patients show a higher frequency in familial FTD, whereas Korean patients show a lower frequency (Kim et al., 2010; Ogaki et al., 2013). This implies that difference in ethnicity may result in different etiological (genetic and environmental) factors contributing to the heterogeneity in complex diseases such as FTD. The genetic association study failed to find an association between *MAPT* haplotypes and the risk for developing FTD or other dementia groups. A significant over-representation of H2H2 genotype was found in SD patients ($p = 0.01$) but not in any of the other disease groups. However, the study is limited by the relatively small sample size (SD, n = 7). Unlike previous reports, H2 haplotype was not significantly associated with lowering of age at onset or familial FTD cases (Borroni et al., 2005; Ghidoni et al., 2006). Based on these findings, we conclude that known genetic variations in *MAPT* are an uncommon cause of FTD in a southern Indian population. More comprehensive screening studies are needed to establish the genetic linkage of other putative loci with FTD in the study population, which will definitely lead to improved early clinical diagnosis.

Disclosure statement

None of the authors have potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2013.08.010.

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