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Genetic evidence that vascular dementia is related to Alzheimer’s disease: genetic association between tau polymorphism and vascular dementia in the Chinese population

SIR—Vascular dementia (VaD) is widely considered to be the second leading cause of dementia after Alzheimer’s disease (AD) [1]. It develops when there is impaired blood flow, which would deprive cells of food and oxygen, in some parts of the brain [2]. MAPT (microtubule-associated protein tau) is the gene encoding tau protein. Accumulation of tau protein in the form of neurofibrillary tangles is one of the major characteristics of AD [3–5]. Therefore, MAPT has long been suspected of being related to AD, but to date there has been no authentic evidence linking MAPT to the disease [6, 7]. To investigate whether MAPT is associated with late-onset AD (LOAD, which is the majority type of AD) in Chinese population and whether it is associated with other types of dementia, we implemented two case-control studies, one of 144 LOAD patients, another of 218 VaD patients, and these two studies shared 476 healthy controls. Two single-nucleotide polymorphisms (SNPs) were chosen on MAPT: rs1467967 and rs2471738, both of which have been studied in LOAD before as members of H1c haplotype (see the Supplementary data available in Age and Ageing online).

Methods

VaD patients were diagnosed by at least two clinicians based on the CMAAN (Chinese Medical Association Academy of Neurology) criterion, which integrated the DSM-IV criterion with neuroimaging methods, and thus their disease situations were confirmed by MRI (magnetic resonance imaging) test. LOAD patients were diagnosed according to criteria of DSM-IV and NINCDS–ADRDA. All healthy controls met the Mini-Mental State Examination cutoff of >25 and were without severe psychological disorders, physical disabilities, cancer or communicable diseases. Both groups of patients and controls were all from Shanghai, China. Each participant of this study was given a standard informed consent in the protocol, which was reviewed and approved by the Shanghai Ethical Committee of Human Genetic Resources.

We assessed deviations from Hardy–Weinberg equilibrium (HWE) and compared the differences of allele and genotype frequencies between case group and control group using SHEsis [8]. All genotype groups for the two SNPs were in HWE, except for rs1467967 in the VaD case group. Rs1467967, of which Fisher’s P = 0.013734, was assessed for its association with VaD and adjusted for the sex parameter using logistic regression.

We built and tested three models on R-software. In these models, homozygotes for the risk allele (1/1) were coded as 2, heterozygotes (1/0) were coded as 1, and homozygotes for the non-risk allele (0/0) were coded as 0 in the additive model. The dominant model was defined as 1/1 + 1/0 versus 0/0 and the recessive model was as 1/1 versus 1/0 + 0/0. In addition, we calculated the statistical power of the study by using Genetic Power Calculator [9], which showed the statistical power of this study on detecting an association with VaD or LOAD for rs1467967 and rs2471738.
Results

We genotyped two SNPs of MAPT in 218 Chinese VaD cases, 144 Chinese LOAD cases and 476 controls. The mean age and the sex distribution of participants are listed in Supplementary data available in Age and Ageing online. Since commonly the majority of VaD patients have not been treated in hospital until disease deteriorated, information of VaD onset was available for only 103 patients. On account of VaD being more prevalent in men [10], we adjusted the sex parameter while analysing the data.

The allele and genotype frequency of the two SNPs in both VaD and control groups was summarised in Table 1, whereas LOAD data were summarised in Supplementary data available in Age and Ageing online. The SNP rs1467967 showed significant difference between VaD and control subjects in genotype frequency (\(P = 0.0097\)), whereas rs2471738 did not. No association was found between the two of the SNPs and LOAD (Supplementary data are available in Age and Ageing online). It is noted that after Bonferroni correction multiple testing (\(P = 0.019\)) which was necessary but overly conservative, rs1467967 nonetheless showed an association with VaD. Furthermore, we found the dominant model the most appropriate for the association between rs1467967 and VaD, and we observed a positive marker for rs1467967 (OR = 1.986, \(P = 0.0166\)) in the dominant model (Table 2).

Linkage disequilibrium (LD) between the two SNPs (rs1467967, rs2471738) in MAPT was not strong (see the Supplementary data available in Age and Ageing online). We also conducted a haplotype association analysis consisting of two MAPT SNPs and found no significant difference between patient (LOAD, VaD) and control subjects (data not shown). According to Genetic Power Calculator, the sample size we used here had power value greater than 95% and 91% to detect a moderate gene effect (OR = 1.4) at \(\leq 0.05\), with VaD or LOAD for rs1467967 and rs2471738, respectively.

Discussion

All samples in this study are strictly selected, e.g. VaD patients were not only diagnosed using strict criteria but also confirmed by MRI (see details in the Methods section). Bonferroni multiple test correction was used to exclude the false-positive results and calculating the power value of our study would evaluate the probability of the false-negative results; also we tested the genotype models of rs1467967 in VaD–control study (see details in Table 2). All together, we made every effort to ensure that our data were reliable, even with a medium sample size.

MAPT pre-mRNA undergoes sophisticated alternative splicing process, giving rise to several splice variants and these variants are differentially expressed in the nervous system. Several studies have reported that the splicing regulatory elements, including intronic splicing enhancers (ISEs) and intronic splicing silencers (ISSs), are located in introns [11, 12]. These elements, which usually comprise several nucleotides, would determine the splicing pattern of a pre-mRNA, and if any of the nucleotides changes, the regulatory function of these splicing elements may also be affected. In this study, we found rs1467967 a positive marker between VaD and control, so we proposed that rs1467967, as an intronic SNP, might be involved in some kind of unknown splicing regulatory process, which would ultimately exert an influence on the expression of MAPT variants. Also, LD prompted us to consider that rs1467967 might be indirectly involved in the pathogenesis of VaD. It is likely to be found in LD with an unidentified polymorphism that influences transcriptional regulation of MAPT.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Alleles</th>
<th>SHEsis-analysis allele results</th>
<th>SHEsis-analysis genotype P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPT</td>
<td>rs1467967</td>
<td>A/G</td>
<td>0.869 0.684–1.105</td>
<td>0.251 0.0097</td>
</tr>
<tr>
<td></td>
<td>rs2471738</td>
<td>C/T</td>
<td>0.824 0.619–1.097</td>
<td>0.185 0.422</td>
</tr>
</tbody>
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*P-values calculated by \(\chi^2\) test or Fisher’s exact test.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Risk allele</th>
<th>Genotype distribution</th>
<th>Models and OR (95% CI)</th>
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<tbody>
<tr>
<td>MAPT</td>
<td>rs1467967</td>
<td>G</td>
<td>Genotype</td>
<td>Control, n (%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Additive model*</td>
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<tr>
<td></td>
<td></td>
<td>A/A</td>
<td>75 (0.164)</td>
<td>18 (0.085)</td>
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<td></td>
<td></td>
<td>A/G</td>
<td>201 (0.440)</td>
<td>113 (0.533)</td>
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<tr>
<td></td>
<td></td>
<td>G/G</td>
<td>181 (0.396)</td>
<td>81 (0.382)</td>
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*P<sub>add</sub> (additive model) was assessed by logistic regression after adjusting for sex.

*P<sub>dom</sub> (dominant model) was assessed by logistic regression after adjusting for sex.
On the other hand, our result showed no genetic association between the two of the SNPs in H1c haplotype of MAPT and LOAD, which is consistent with several studies before [7, 13, 14]. Although studies of both Myers et al. [6] and Laws et al. [7] suggested that the H1c haplotype of MAPT is associated with AD genetically in Caucasian, studies of Mukherjee et al. [13] and Bertram et al. [15] showed contrary results as ours. Thus, more evidence is needed to make a conclusion. In spite of the discrepancy in genetic association study, the level of the cerebrospinal fluid tau protein has unanimously been proposed to be a biomarker in AD [16–19]. Considering the tau protein is encoded by MAPT, this may imply functional relationship exist between MAPT and AD.

As we know, VaD and AD are the two most common dementia diseases in the world. Although they are quite different in major genotypic and phenotypic profiles [20], they share some common traits in the risk factors. First, vascular factors play an important role in the development of both AD and VaD [21, 22]. Second, these two diseases often co-exist [23], and patients with cerebrovascular disease have a greater possibility to develop AD (up to 80% dementia in old people may be associated with cerebrovascular disease) [24]. Our study showed that MAPT was associated with VaD and since MAPT is a gene playing an important role in AD, our result gave a further proof of this close relationship between VaD and AD from a genetic perspective. Moreover, G allele of rs1467967 is the risk allele, which is the major allele in Chinese population. This result is consistent with the intriguing phenomenon that VaD is common in China who is a developing country [25].

One limitation of our study is that the two tagged SNPs we selected could not cover the whole region of the MAPT gene, which is approximately 134 kb. Therefore, additional reproducible studies of more SNPs in larger populations are needed. In conclusion, our experimental results showed association between VaD and MAPT, this suggested that VaD might have a close link with AD from genetic perspective. We think reproducible studies of more SNPs in large and different populations are needed, and functional study about tau protein in VaD is worth exploring.

**Key points**

- Tau polymorphism is associated with VaD.
- Accumulation of tau protein is one of the major characteristics of AD.
- VaD might have a close link with AD.

**Supplementary data**

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

**Conflicts of interest**

None declared.

**Funding**

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**References**

Research letters


Does place of residence influence hospital rehabilitation and assessment of falls and osteoporosis risk following admission with hip fracture?

SIR—Hip fractures account for approximately 80,000 hospital admissions per annum in the United Kingdom [1] with numbers predicted to rise steeply in the coming years [2–5]. Nursing home residents contribute to around a quarter of these, reflecting this population’s increased level of frailty [1].

The Scottish Hip Fracture Audit (SHFA) Rehabilitation Report 2007 has shown that median length of hospital stay for patients admitted from care homes was 10 days compared with 27 days for patients admitted from their own homes [6]. This difference may represent easier discharge processes for those returning to a care home compared with patients who have to wait for the arrangement of increased community social services. It may also reflect the considered opinion of the multi-disciplinary team that individual care home patients have limited rehabilitation potential and therefore merit speedy hospital discharge. However, it also raises the possibility that care home residents have less access to the normal pathways of rehabilitation post hip fracture compared with patients admitted from their own homes.

The aim of this analysis was to use the latest SHFA data to determine whether place of residence is associated with a difference in access to comprehensive rehabilitation, including falls and osteoporosis risk assessment, in patients admitted with a hip fracture. We also wanted to see if there is any difference in mobility between groups.

Methods

This was a time-limited ‘sprint audit’ using the SHFA methodology (please see Appendix 1 in the supplementary data on the journal website http://www.ageing.oupjournals.org/). All patients with a hip fracture who were admitted to 20 of the 21 Scottish mainland hip fracture operating hospitals between 1st April and 30th September 2008 were included. Information regarding patient mobility at the 120-day follow-up, was available for a subgroup, namely those admitted from April to July in 17 hospitals. A full report on the sprint audit was published in 2009 [7].