The associations between the \textit{MAPT} polymorphisms and Alzheimer’s disease risk: a meta-analysis

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ABSTRACT

Published studies revealed that the microtubule-associated protein tau (\textit{MAPT}) gene polymorphisms increased Alzheimer’s disease (AD) risk; the associations of 4 single nucleotide polymorphisms (SNPs, rs242557G/A, rs2471738C/T, rs3785883G/A and rs1467967A/G) of the \textit{MAPT} gene with AD risk, however, remain inconclusive. Here, we conducted a meta-analysis to investigate the relationship between the \textit{MAPT} SNPs and AD risk. A significant association of SNP rs242557 with AD risk was found in a dominant [odds ratio (OR) = 1.05, 95\% confidence interval (CI) = 1.01, 1.10, $P = 0.025$] genetic model, and a suggestive association in an allelic (OR = 1.03, 95\% CI = 1.00, 1.06, $P = 0.078$). When \textit{APOE} epsilon 4 carrier status was included in stratified analysis, this association was even stronger (allelic model for the \textit{APOE} epsilon 4 positive individuals: OR = 1.24, 95\% CI = 1.08, 1.43, $P = 0.003$). Furthermore, a significant association of SNP rs2471738 with AD risk was found under all the four models (allelic: OR = 1.11, 95\% CI = 1.01, 1.20, $P = 0.021$; dominant: OR = 1.10, 95\% CI = 1.00, 1.21, $P = 0.046$; recessive: OR = 1.18, 95\% CI = 1.05, 1.32, $P = 0.004$; additive: OR = 1.20, 95\% CI = 1.07, 1.34, $P = 0.002$) models. However, pooled results suggest that the neither rs3785883 nor rs1467967 is associated with AD risk under all the four genetic models. In summary, our study provides further evidence of the associations of the \textit{MAPT} SNPs with AD risk.

INTRODUCTION

One of the neuropathological hallmarks of Alzheimer’s Disease (AD) is the neurofibrillary tangle, which contains paired helical filaments (PHFs) composed of hyperphosphorylated forms of the microtubule-associated protein tau (MAPT) by mechanism which is not illustrated [1]. Increasing attention has been paid to endogenous and exogenous factors, as well as genetic risk factors contributing to the incidence of AD [2], stimulating the disease progression of AD [3]. It was believed that the identification of key genetic determinants for AD might help further understand its underlying mechanism.

Human MAPT gene is located on chromosome 17q21. There have been conflicting results showing positive or negative findings on the association between the \textit{MAPT} SNPs and AD risk. Some studies were showed that SNPs rs242557 [4, 5], rs3785883 [6] in US series, rs2471738 [6, 7] and rs1467967 [8] of the \textit{MAPT} gene might been associated with increased AD risk. Some studies were, however, reported that rs242557 [8-10], rs3785883 [11-14], rs2471738 [11, 14, 15] and rs1467967 [7, 16] might not be associated with AD risk [10, 11, 13, 16, 17].

There are many factors leading to these different results about the association between the \textit{MAPT} SNPs and AD risk. One of primary reasons is low statistical power and the limited sample size in each study. Therefore, we performed a meta-analysis on the association between the \textit{MAPT} SNPs and AD risk by pooling all available published data. In this study, we evaluated the genetic heterogeneity of the studies included and then carried out
a meta-analysis on the association between the MAPT SNPs (rs242557, rs2471738, rs3785883 and rs1467967) with AD risk to make a more accurate assessment of the relationship for greater power in detecting the disease associations.

RESULTS

Characteristic of eligible studies

The literature search was done on studies up to January 2017 and availability of an English-language abstract or paper for review; this yielded 208 hits (PubMed: 14, Google scholar: 194). 194 of these were excluded, including 16 duplicates, 67 non-AD case reports, 34 reviews, 34 irrelevant studies, 25 data not available, 10 abstracts, 5 non-English language papers (also non-Chinese) and 3 case reports. In total, 64 independent studies from 14 articles published from 2005 to 2016 providing data of the MAPT genotype, were included in the current meta-analysis (16 for rs242557, 14 for rs2471738, 14 for rs3785883 and 15 for rs1467967; Figure 1). We found that in all the studies included SNPs neither rs75721 (within exon 14) nor rs9468 (within exon 13) was significantly associated with increased AD risk (results not shown). So, we analyzed the associations between these SNPs (rs242557, rs2471738, rs3785883 and rs1467967) of the MAPT gene and AD risk involved in 14666/17532, 13812/17201, 14607/17883 and 15064/17687 cases/controls, respectively. The NOS results indicated that the methodological quality of these selected studies was generally good. The study characteristics were listed in Table 1.

Heterogeneity test

The strength of the association was estimated in the allelic, dominant, recessive and additive models. The heterogeneity among studies was tested with Q statistic and further quantified by \( I^2 \) statistic. As measured by the \( I^2 \) (Table 2), in this meta-analysis no significant heterogeneity existed between studies under all the genetic models tested for rs242557 (the range of \( I^2 \) values from 0 to 33.1%), rs3785883 (the range of \( I^2 \) values from 0 to 29.1%), and rs1467967 (the range of \( I^2 \) values from 0 to 17.5%). Therefore, the fixed-effect model (Mantel-Haenszel method) was used to calculate the pooled ORs. However, for rs2471738 there was significant heterogeneity observed between studies under the allelic and dominant models (\( F = 62.0 \) and 57.1 for the allelic and dominant genetic models, respectively). Therefore, the random-effect model (Inverse Variance method) was used to calculate the pooled ORs under allelic and dominant
Table 1: Main characteristics of the studies included in this meta-analysis of the associations between these SNPs of the MAPT gene and AD risk.

| SNP loci | Allele | Ref. no. | First author | Year | Country | Case (n) | CTR (n) | Case genotype | Control genotype | HWE<sub>c</sub> | NOS |
|----------|--------|----------|--------------|------|---------|----------|---------|---------------|-----------------|------------|-----|
| rs245257 | G>A    |          |              |      |         |          |         |               |                 |            |     |
| r2471738 | C>T    |          |              |      |         |          |         |               |                 |            |     |
| rs3585883 | G>A    |          |              |      |         |          |         |               |                 |            |     |
| rs1467967 | A>G    |          |              |      |         |          |         |               |                 |            |     |

Abbreviations: Ref no: reference number; NOS, the Newcastle-Ottawa Scale; CTR, control; HWE<sub>c</sub>, Hardy-Weinberg Equilibrium in controls;

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models (fixed-effect model for the recessive and additive genetic models).

**Meta-analysis results of the association between SNP rs242557 and AD risk**

For rs242557 when the 16 studies were pooled into the meta-analysis using the fixed-effect model, a significant association was observed under the dominant (OR = 1.05, 95% CI = 1.01, 1.10, $P = 0.025$, Figure 3) model, and there was a trend under the allelic (OR = 1.03, 95% CI = 1.00, 1.06, $P = 0.078$, Figure 2) model. However, no significant association was found under the recessive (OR = 1.06, 95% CI = 0.95, 1.08, $P = 0.766$) and additive models (OR = 1.04, 95% CI = 0.97, 1.12, $P = 0.223$).

When stratified by APOE $\varepsilon 4$ carrier status, the association between the rs242557 SNP and AD risk was observed to be stronger in the individuals with APOE $\varepsilon 4$-positive genotype (with no heterogeneity, $F = 0$, OR = 1.24, 95% CI = 1.08, 1.43, $P = 0.003$) than without stratification (OR = 1.03, 95% CI = 1.00, 1.06, $P = 0.078$) under the allelic model. But for the individuals with APOE $\varepsilon 4$-negative genotype (APOE $\varepsilon 4$-), there was large heterogeneity ($F = 81.5$, Table 2) under the allelic model, and no significant association between the rs242557 SNP with AD risk (OR = 1.29, 95% CI = 0.93, 1.80, $P = 0.132$, Table 3, Figure 4).

**Meta-analysis results of the association between SNP rs2471738 and AD risk**

A significant association between SNP rs2471738 and AD risk was identified under the allelic (random-effect, OR = 1.11, 95% CI = 1.01, 1.20, $P = 0.021$, Figure 5 and Table 3) and dominant (OR = 1.10, 95% CI = 1.00, 1.21, $P = 0.046$, Figure 6 and Table 3) models. A significant association between SNP rs2471738 and AD risk was also identified under the recessive (fixed-effect, OR = 1.18, 95% CI = 1.05, 1.32, $P = 0.004$, Figure 7 and Table 3) and additive (OR = 1.20, 95% CI = 1.07, 1.34, $P = 0.002$, Figure 8 and Table 3) models.

**Meta-analysis results of the associations between SNPs rs3785883 and rs1467967 and AD risk**

Using fixed-effect model, no significant association between SNP rs3785883 and AD risk was observed under all the four models (allelic: OR = 1.03, 95% CI = 0.99,
Similarly, no significant association between SNP rs1467967 and AD risk was found under all the four models (fixed-effect, allelic: OR = 1.01, 95% CI = 0.98, 1.05, P = 0.449, Figure 10; dominant: OR = 1.01, 95% CI = 0.96, 1.05, P = 0.737; recessive: OR = 1.04, 95% CI = 0.97, 1.12, P = 0.026; additive: OR = 1.04, 95% CI = 0.97, 1.12, P = 0.301, Table 3).

Sensitivity analysis and evaluation of publication bias

Due to large heterogeneity between studies for rs2471738, we performed a sensitivity analysis by excluding a study [Allen, M. (JS), 2014; see Table 1] with departure from Hardy-Weinberg Equilibrium (HWE) in controls, we did not observe increased homogeneity across the rest studies (data not shown), suggesting that HWE deviation was not a source of between-study heterogeneity. The sensitivity analysis showed that for rs2471738 and rs1467967 none of the studies included significantly changed the results under the allelic model (Figure 11A and 11B, respectively). Begg’s and Egger’s test were used to estimate the severity of publication bias with a P-value < 0.05 being considered statistically significant. No evidence of publication bias was found in any genetic model (Tables 3).

DISCUSSION

Tau protein is specifically expressed in neurons, directly interacts with tubulin and mediates its assembly [18]. It was found that the MAPT rs242557 (within exon 1) SNP was significantly associated with late-onset AD in 1592 Han Chinese subjects [4], in the German population [5] and in the US series [7]. However, it was reported that this SNP was not significantly associated with AD risk [10, 11] in the UK series [7]. For the rs2471738 (within intron 9) SNP, study findings revealed that there was significant association in the US series [6, 7] and US/UK series [6], or no [19] in 293 AD patients and 396 healthy controls [15], in 361 AD patients and 358 controls [16]. For the rs3785883 (within intron 3) SNP, it was found that there was significant association [13], or no [5, 14, 20]. For the rs1467967 (within exon 1) SNP, it was showed that there was significant association [5], or no [7, 11, 21]. There were consistent results on the association between the rs7521 [6, 7, 11, 22] and rs9468 [11] (too little data) SNPs and AD risk. Thus, these four SNPs of the MAPT gene were a matter of controversy.
Figure 2: Forest plot for the meta-analysis of the association of SNP rs242557 and AD risk under the allelic model (A vs. G).

Figure 3: Forest plot for the meta-analysis of the association of SNP rs242557 and AD risk under the dominant model (AA + AG vs. GG).
Figure 4: Forest plot for the meta-analysis of the association of SNP rs242557 and AD risk stratified by APOE ε4 status.

rs242557 stratified by APOE ε4 (+)

rs242557 stratified by APOE ε4 (-)

Note: Weights are from random effects analysis.
Therefore, we conducted this meta-analysis to explore the association between the MAPT SNPs and AD risk. In summary, results from this meta-analysis suggest that of these SNPs tested, rs242557 is significantly associated with increased AD risk under the dominant genetic model, and the rs2471738 SNP is significantly associated with increased AD risk under all the four genetic model. In the stratified analysis by APOE ε4 allele status, APOE ε4 allele carriers, but not APOE ε4 allele non-carriers, were showed to be significantly associated with increased AD risk. This result indicates that there appears to be a gene-gene interaction between the APOE and the MAPT genes, which could increase susceptibility to AD. More studies should, however, be conducted to assess the interaction.

Because of the moderate heterogeneity, we conducted sensitivity analyses to evaluate the effects of each study on the combined ORs by sequential removal of each eligible study. The sensitivity analysis showed that none of these studies changed the significance of the combined ORs under the allelic model. It was showed that Allele A of rs242557 with the H1p promoter variant had 2.7-fold greater transcriptional activity than allele G with the H1p promoter variant and 4.2-fold greater than allele G with the H2p promoter variant. The H1 haplotype increases the expression of total MAPT transcript [6]; allele A (AA + AG) of rs242557 was associated with CSF total tau levels elevated levels compared to non-carriers (GG) [5], indicating that SNP rs242557 might be associated with the increased expression levels of tau protein. Trabzuni, D. et al [23], found that the H1c haplotype (tagged by rs242557) was not significantly associated with increased mRNA expression of the MAPT, suggesting that there are other things about possible consequence of this SNP on the MAPT, which is needed for further investigations. In the current meta-analysis, SNP rs3785883 was found not to be associated with AD risk under all the genetic models; in AD cases, however, there was higher levels of Total tau mRNA in those individuals who carry rs3785883 minor allele (AA or AG) than those with non-carriers (GG) with evidence of beta-amyloid deposition [24], suggesting that SNP rs3785883, which changes the expression of the marker protein of AD, but is not associated with AD risk, might be an complicated SNP of the MAPT gene.

There are some limitations to this meta-analysis. First, the total number of studies was not large enough for

![Figure 5: Forest plot for the meta-analysis of the association of SNP rs2471738 and AD risk under the allelic model (T vs. C).](image-url)
Figure 6: Forest plot for the meta-analysis of the association of SNP rs2471738 and AD risk under the dominant model (TT + TC vs. CC).

Figure 7: Forest plot for the meta-analysis of the association of SNP rs2471738 and AD risk under the recessive model (TT vs. CC + TC).
such analyses to give meaningful interpretation, and only published studies were included in the meta-analysis. To be made, however, this approach requires the authors of all of the studies to share their data. Second, there was evidence of moderate heterogeneity between studies, in particularly for rs2471738. Third, the present meta-analysis failed to consider the possibility of gene-gene or SNP-SNP interactions in which further investigations are needed. So it is quite important to have more studies and sample in the future so that more precise conclusion about the association between the SNPs of the MAPT gene and AD risk could be achieved.

Figure 8: Forest plot for the meta-analysis of the association of SNP rs2471738 and AD risk under the additive model (TT vs. CC).

Figure 9: Forest plot for the meta-analysis of the association of SNP rs3785883 and AD risk under the allelic model (A vs. G).
In conclusion, our meta-analysis confirmed the following: SNPs rs242557 and rs2471738 might be associated with increased AD risk, but rs3785883 and rs1467967 not. More well-conducted studies with larger sample size are needed to confirm our conclusion.

MATERIALS AND METHODS

Search strategies

All of the potential eligible studies were screened based on the electronic databases (PubMed and Google Scholar) up to 1st Jun. 2017. Systematic searching was performed using the combination of “Alzheimer*”, “rs242557 OR rs3785883 OR rs2471738 OR rs1467967 OR rs75721 OR rs9468”.

Inclusion and exclusion criteria

Only studies published as full-length articles in peer-reviewed journals were considered in the analysis. The eligible studies must satisfy the following inclusion criteria: i) concerning the association between the MAPT gene (including SNPs rs242557, rs3785883, rs2471738, rs1467967, rs75721 and rs9468) and AD risk; ii) case-control study design; iii) sufficient information accessible (e.g. sample size for each study, allele or genotype frequencies of these SNPs); iv) cases meeting the clinical criteria for AD. The exclusion criteria include: a duplicated publication; a review; a case report; not reported the genotype frequencies; non-AD cases, a review; an irrelevant study; datum not available; an abstract; in neither English nor Chinese; inconsistent with most studies in major allele size.

Data extraction

Data extracted from the included studies were as follows: first author, year of publication, country, sample size of cases and controls, numbers of case and control genotypes, p-value for HWE in controls and Newcastle-Ottawa Scale (NOS) Quality Assessment Scale. The inclusion/exclusion criteria were applied by 2 (ZFT and WDL) independent reviewers. We used the NOS to assess the quality of the included studies. A quality score...
Figure 11: Sensitivity analysis for rs242557 A. and rs2471738 B. under the allelic model.
Figure 12: Sensitivity analysis for rs3785883 A. and rs1467967 B. under the allelic model.
was calculated based on three major components. Each component of the criteria scored 1 if present or 0 if absent. The scores were summed and a higher score represents better methodological quality.

**Meta-analysis**

All statistical analyses were performed using Stata software (College Station, TX). The association between the MAPT SNPs and AD risk was evaluated by pooled ORs and corresponding 95% CIs. Four genetic models, including allelic (G vs. A), dominant (AA + AG vs. GG), recessive (AA vs. AG + GG) and additive (AA vs. GG), were used to estimate this association. Sensitivity analyses were performed to determine whether undue influence of a single study was present. The possibility of publication bias was assessed by Begg’s and Egger’s test (P < 0.05 was considered as representative of statistically significant publication bias).

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**CONFLICTS OF INTEREST**

The authors declare that they have no conflict of interests.

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