An exploratory study on STX6, MOBP, MAPT, and EIF2AK3 and late-onset Alzheimer's disease

Qiu-Yan Liu ¹, Jin-Tai Yu ¹, Dan Miao, Xiao-Ying Ma, Hui-Fu Wang, Wei Wang, Lan Tan*

Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao, Shandong Province 266071, China

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ABSTRACT
Both Alzheimer's disease (AD) and progressive supranuclear palsy (PSP) are a class of neurodegenerative diseases associated with the pathologic aggregation of tau protein in the human brain. They share some clinical and pathologic characteristics. A recent genome-wide association study reported several single-nucleotide polymorphisms at the STX6, MOBP, MAPT, and EIF2AK3 in association with PSP. To explore whether these single-nucleotide polymorphisms are associated with AD risk, we conducted a case-control study to investigate the PSP-associated loci in 1592 Han Chinese subjects. Rs242557 at the MAPT locus was associated with late-onset AD (LOAD) (odds ratio [OR], 1.175; p = 0.026), which appeared to be stronger for LOAD patients with apolipoprotein E (APOE) ε4 allele (OR, 1.510), and this positive association was not changed after adjusting for age, sex, and the APOE ε4-carrier status (additive model: OR, 1.163; p = 0.036; dominant model: OR, 1.315; p = 0.010). Rs1768208 in MOBP and rs7571971 in EIF2AK3 showed association only in the APOE ε4 positive subjects, and these did not appear to be independent of APOE. As for rs1411478 in STX6, we did not explore any association with LOAD. Our exploratory analysis mainly suggests an association of MAPT with LOAD, especially in APOE ε4 carriers. Genotypes at MOBP and EIF2AK3 confer risk predominantly in APOE ε4-positive subjects, with indications of an interaction between APOE and MOBP or EIF2AK3 on AD risk.

1. Introduction
Both Alzheimer's disease (AD) and progressive supranuclear palsy (PSP) are a class of neurodegenerative diseases associated with the pathologic aggregation of tau protein in the human brain (Crespo-Biel et al., 2012; Höglinger et al., 2011). These 2 conditions share some clinical and pathologic characteristics. On the 1 hand, PSP cases display tau pathology similar to late-onset AD (LOAD) (Abraham et al., 2009). Both of them involve abnormal accumulation of tau protein within neurons as neurofibrillary tangles (NFT). On the other hand, they are clinically progressive and manifest cognitive decline eventually (Waldemar et al., 2007). These connections suggest that AD and PSP might have some shared risk factors and/or common pathogenic mechanisms. However, little effort to date has been made to research potential genetic risk factors that might contribute to both diseases.

Recently, a large genome-wide association study (GWAS) has reported several novel susceptibility genetic loci for PSP, including syntaxin6 (STX6), myelin oligodendrocyte-associated basic protein (MOBP), and eukaryotic translation initiation factor 2-α kinase 3 (EIF2AK3) (Höglinger et al., 2011). Meanwhile, the tau gene (MAPT) was also confirmed in this PSP GWAS. The expression levels and functional features of these genes exclusively supported their associations with PSP (Zou et al., 2012). Therefore, we explored the relationship of LOAD with selected single-nucleotide polymorphisms (SNPs) from the PSP GWAS (rs1411478 for STX6, rs1768208 for MOBP, rs7571971 for EIF2AK3, and rs8070723 and rs242557 for MAPT) in a large LOAD case-control study.

2. Methods
2.1. Subjects
A total of 796 sporadic LOAD cases (400 male and 396 female; age ≥ 65 years; age at onset = 75.28 ± 6.57 years) and 796 healthy control subjects (408 male and 388 female; mean age = 74.81 ± 6.96 years) matched for sex and age were recruited for this study. All the subjects were Han Chinese originally. The patients were from the Department of Neurology at Qingdao Municipal Hospital,
and several other hospitals in Shang dong Province. A clinical probable AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s disease and Related Disorders Association (McKhann et al., 1984). None of the AD patients had a family history of dementia. The control subjects were selected from the Health Examination Center of the Qingdao Municipal Hospital, and they were confirmed healthy and neurologically normal by medical history, general examinations, laboratory examinations, and Mini Mental State Examination. Our study was conducted with informed consent of all individuals or legal guardians and with approval from the Institute Ethical Committee.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using standard procedures (Promega). The selected 5 SNPs in STX6, MOBP, EIF2AK3, and MAPT were genotyped with the method of polymerase chain reaction (PCR)–ligase detection reaction (LDR) on an ABI Prism 377 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) (Favis et al., 2000; Xiao et al., 2006), with technical support from the Shanghai Genesky Biotechnology Company. The primer sequences used for the PCR reaction were: rs1411478, forward: CCGTTACAGGAGCGGATCATG; reverse: GTGACACCCTGGGGACAGGC; rs242557, forward: TCTCCCAGAAAAATAGAAGCATCATACC, reverse: GACCCTTTTCTAATTTCTACA, reverse: GAGGGAGATGTTTGGCTGGTTTG; rs7571971, forward: TCTCCCAAGAAAAATGAACAGCATCATACC, reverse: GACCCTTTTGCCCATGGTAAA; rs242557 in MAPT were significantly different between different AD and control subjects (genotype: p = 0.032; allele: p = 0.026). The minor allele G significantly raised the risk of LOAD (OR, 1.175; 95% CI, 1.020–1.353). None of the SNPs rs1411478 for STX6, rs1768208 for MOBP, and rs7571971 for EIF2AK3 was related to LOAD risk. Similarly, multivariate logistic regression still revealed that only rs242557 polymorphism was associated with LOAD (additive model: OR, 1.163; 95% CI, 1.010–1.339; p = 0.036; dominant model: OR, 1.315; 95% CI, 1.068–1.619; p = 0.010) after adjusting for age, sex, and the APOE ε4-carrier status (Table 3). The G allele was associated with an increased risk of LOAD.

Furthermore, we divided these data into 2 subgroups according to the APOE ε4 status (Table 4). Interestingly, besides rs242557 in MAPT, there was a significant difference for rs1768208 in MOBP when alleles or genotypes were compared between AD and controls with APOE ε4 alleles. The G allele of rs242557 has a 1.51-fold increased risk compared with the A allele (OR, 1.51; 95% CI, 1.089–2.090; p = 0.013), and the C allele of rs1768208 has a 37.2% decreased risk compared with the T allele (OR, 0.628; 95% CI, 0.454–0.868; p = 0.005). Moreover, in subjects with APOE ε4 alleles, the genotype distribution of rs7571971 for EIF2AK3 was also significantly different between AD and control subjects (p = 0.009). No significant differences were found for all SNPs when alleles or genotypes were compared between non-APOE ε4 AD and control subjects.

For rs8070723 in MAPT, all subjects in this study were identified as AA homozygous.

4. Discussion

STX6, MOBP, MAPT, and EIF2AK3 were all implicated by PSP pathology and shown to have genetic and expression effects on tauopathy of the neurodegenerative diseases (Höglinger et al., 2011; Zou et al., 2012). To explore whether these genes cause susceptibility to LOAD, the most common tauopathy, we analyzed STX6, MOBP, MAPT, and EIF2AK3 loci in a Han Chinese data set of 1592 subjects. In this large case-control study, we found preliminary evidence that rs242557 at the MAPT locus might be associated with LOAD (OR, 1.175), and this association appeared to be stronger for

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>AD (796)</th>
<th>Control (796)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male:female</td>
<td>400:396</td>
<td>408:388</td>
<td>0.668</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>75.28 ± 6.57⁣</td>
<td>74.81 ± 6.96</td>
<td>0.166</td>
</tr>
<tr>
<td>MMSE score</td>
<td>12.12 ± 5.56</td>
<td>28.26 ± 1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE ε4 carrier (n)</td>
<td>200</td>
<td>122</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Key: AD, Alzheimer’s disease; MMSE, Mini Mental State Examination.

* Mean age at onset.

* Mean age at examination.
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