Research Article

SNCA Gene, but Not MAPT, Influences Onset Age of Parkinson’s Disease in Chinese and Australians

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Background. α-Synuclein (SNCA) and microtubule-associated protein tau (MAPT) are the two major genes independently, but not jointly, associated with susceptibility for Parkinson’s disease (PD). The SNCA gene has recently been identified as a major modifier of age of PD onset. Whether MAPT gene synergistically influences age of onset of PD is unknown. Objective. To investigate independent and joint effects of MAPT and SNCA on PD onset age. Methods. 412 patients with PD were recruited from the Australian PD Research Network (123) and the Neurology Department, Ruijin Hospital Affiliated to Shanghai Jiaotong University, China (289). MAPT (rs17650901) tagging H1/H2 haplotype and SNCA (Rep1) were genotyped in the Australian cohort, and MAPT (rs242557, rs3744456) and SNCA (rs11931074, rs894278) were genotyped in the Chinese cohort. SPSS regression analysis was used to test genetic effects on age at onset of PD in each cohort. Results. SNCA polymorphisms associated with the onset age of PD in both populations. MAPT polymorphisms did not enhance such association in either entire cohort. Conclusion. This study suggests that, in both ethnic groups, SNCA gene variants influence the age at onset of PD and α-synuclein plays a key role in the disease course of PD.

1. Introduction

Parkinson’s disease (PD) is the most common neurodegenerative movement disorder in the elderly (approximately 2% of the population aged over 60) with an average age of onset of 60 years and a variety of different subtypes [1, 2]. Patients with young disease onset often have a benign disease course and a lower rate of dementia compared to those with later disease onset [3], and previous studies show that genetic factors influence both the age of onset [4, 5] and clinical subtypes of PD [6–8]. These clinical variations are not due to mutations in PD causative genes [9].

The two most consistently identified susceptibility genes for sporadic PD are the α-synuclein (SNCA) and microtubule-associated protein tau (MAPT) genes [10, 11] which play independent, but not joint, effects on the risk of developing PD [12, 13], although there are significant differences in the variants associated with PD between Asian and Caucasian populations [14]. In addition, we have shown that in Caucasians the SNCA and MAPT genes act synergistically to influence the rate of progression of PD (certain genotypes have a 5.8-increased risk for developing a more rapid disease progression) when analysing one microsatellite (Rep1 or D4S3481 with three common alleles, that is, 259 bp, 261 bp, and 263 bp or alleles 0, 1, and 2) marker of SNCA gene and a rs17650901 SNP of MAPT gene (lies in exon 1 and its A-allele tags the MAPT H1 haplotype [15]) in an Australian cohort [7]. A recent study showed that among 17 genome-wide association studies- (GWAS-) linked loci in mainland China, only two SNPs (rs1931074 and rs894278) of the SNCA gene associate with the risk for sporadic PD after adjusting for age and sex [16]. The rs894278 SNP is
Table 1: Subjects demographic information.

<table>
<thead>
<tr>
<th>PD cohorts</th>
<th>N</th>
<th>Female : male</th>
<th>Ethnic origin</th>
<th>Age (y/o) (mean ± SD)*</th>
<th>Onset (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australians</td>
<td>123</td>
<td>57 : 66</td>
<td>Caucasian</td>
<td>68 ± 9</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>Chinese</td>
<td>289</td>
<td>119 : 170</td>
<td>Han</td>
<td>63 ± 9</td>
<td>58 ± 10</td>
</tr>
</tbody>
</table>

N: number; y/o: years old; SD: standard deviation; *P < 0.001.

located in intron 4, and the rs11931074 remains distal to the untranslated region of SNCA [17]. The MAPT gene does not appear to be associated with PD susceptibility in the Chinese [16], possibly due to ethnicity and the extremely low frequency of the H2 MAPT haplotype in mainland China [18]. However, the MAPT H1c subhaplotype (tagged by the rs242557 A-allele [19]) and other SNPs (e.g., rs3744456) are associated with increased expression of tau (especially four repeat transcripts) in human brain tissue [20, 21] and in vivo experiments [22]. These different MAPT SNPs might be associated with PD risk in the Chinese.

It has recently been shown that the SNCA gene is a major modifier of age of PD onset [23]. However it remains unclear whether the MAPT gene also modified age of PD onset and whether there is a synergistic effect of both SNCA and MAPT on the age of onset of PD. This study is to investigate independent and joint effects of MAPT and SNCA on PD onset age. Understanding the influence of variations in these genes on clinical features of PD in different ethnic populations would further consolidate the molecular pathophysiologic mechanisms underpinning PD.

2. Methods

2.1. Study Subjects. 412 patients satisfying the Queen Square Brain Bank Criteria for PD and without autosomal dominant family history of PD were recruited consecutively from the Australian Parkinson’s Disease Research Network, Australia (Caucasian: n = 123, 66 male, 57 female) and the movement disorders clinic, Department of Neurology, Ruijin Hospital Affiliated to School of Medicine, Shanghai Jiaotong University, China (Han: n = 289, 170 male, 119 female) (Table 1). The average age at recruitment (± standard deviation) was 68 ± 9.0 years in Australia and 63 ± 9.4 years in China. The studies were approved by the appropriate institutional ethics committees of the University of New South Wales and the School of Medicine, Shanghai Jiaotong University. Blood from each patient was taken with consent for genetic analyses. Genomic DNA was extracted from peripheral blood by a standardized phenol/chloroform extraction method.

2.2. Clinical Information. At recruitment, a standard questionnaire was completed to obtain detailed clinical information, such as gender, age at onset, age at enrolment, medication administration, and family history. The age of onset of PD was defined when at least two of the three main signs of PD, that is, rigidity, tremor, and bradykinesia, had developed [24]. The average age at onset (±standard deviation) was 60 ± 11 years in the Australian cohort (range 32–83 years) and 58 ± 10 years in the Chinese cohort (range 34–82 years).

2.3. Genetic Analysis. Due to population-specific heterogeneity in PD [25], MAPT (rs17650901) and SNCA Rep1 (D4S3481) were genotyped in the Australian cohort [7, 15, 26], and MAPT (rs2425577 and rs3744456) and SNCA (rs11931074, rs894278) were genotyped in the Chinese cohort [22] (see supplementary Table 1 in supplementary material available online at http://dx.doi.org/10.1155/2015/135674). The rate of genotype calls was ≥95% for all SNPs. For those variants identified by restriction fragment length polymorphism (RFLP), the genotype results were further confirmed via direct PCR product sequencing on random samples. An online tool (http://www.genes.org.uk/software/cubex/) [27] was used to assess linkage disequilibrium in the selected SNPs.

2.4. Statistical Analyses. Different models of inheritance were adopted for analysing each polymorphic effect on age at PD onset using one-way ANOVA, where onset age was considered as a continuous variable. As more males have PD, SPSS regression analyses were then used adjusting for gender to minimize this effect. After examining the effects of single polymorphisms on onset age in all subjects, gene–gene interactions were assessed in each cohort using adjusted regression models, and a P value of <0.05 was considered as significant.

3. Results

Our results showed that the SNCA gene, but not the MAPT gene, associated with age of PD onset in the cohorts assessed. No synergic genetic effects were detected on age of PD onset between SNCA and MAPT polymorphisms in either the Australian or Chinese cohort. There was a weak linkage disequilibrium between SNCA rs11931074 and rs894278 (D’ = 0.72) and there was no linkage disequilibrium between MAPT rs2425577 and rs3744456 (D’ = 0.44) in the Chinese cohort.

3.1. SNCA, but Not MAPT Gene, Associates with Age of PD Onset. SPSS-ANOVA analysis showed that polymorphisms in SNCA only, but not MAPT gene, associated with the age of onset of PD in both populations sampled (Table 2). In the Australian cohort, the genotype of SNCA D4S3481 associated with onset age of PD. The genetic associations were consistent with recessive models of inheritance of SNCA D4S3481 allele 1, although dominant and additive models of allele 0 and allele 1 also had significant effects on the age of PD onset (Table 2).
Table 2: SNCA but not MAPT gene associates with age of PD onset (Random-Effects Models).

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>SNPs</th>
<th>Genetic Inheritance Model</th>
<th>Number</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australians (123 cases)</td>
<td>SNCA D4S3481</td>
<td>Genotypes (00, 01, 02, 11, 12, 22)</td>
<td>14, 34, 6, 51, 15, 3</td>
<td>3.953</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allele 0 carrier status (2, 1, 0)</td>
<td>14, 40, 69</td>
<td>5.606</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dominant (2 + 1, 0)</td>
<td>54, 69</td>
<td>11.291</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recessive (2, 1 + 0)</td>
<td>14, 109</td>
<td>1.996</td>
<td>0.160</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allele 1 carrier status (2, 1, 0)</td>
<td>51, 49, 23</td>
<td>8.408</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dominant (2 + 1, 0)</td>
<td>100, 23</td>
<td>8.742</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recessive (2, 1 + 0)</td>
<td>51, 72</td>
<td>13.840</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allele 2 carrier status (2, 1, 0)</td>
<td>3, 21, 99</td>
<td>1.966</td>
<td>0.145</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Dominant (2 + 1, 0)</td>
<td>24, 99</td>
<td>1.853</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>MAPT rs17650901</td>
<td>Dominant (GG + AG versus AA)</td>
<td>86 versus 37</td>
<td>3.272</td>
<td>0.073</td>
</tr>
<tr>
<td>Chinese (289 cases)</td>
<td>SNCA rs11931074</td>
<td>Dominant (GG + GT versus TT)</td>
<td>172 versus 117</td>
<td>0.638</td>
<td>0.425</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recessive (GG versus GT + TT)</td>
<td>46 versus 243</td>
<td>0.358</td>
<td>0.550</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additive (GG versus GT versus TT)</td>
<td>46 versus 126 versus 117</td>
<td>0.374</td>
<td>0.689</td>
</tr>
<tr>
<td></td>
<td>SNCA rs894278</td>
<td>Dominant (GG + GT versus TT)</td>
<td>182 versus 107</td>
<td>0.665</td>
<td>0.415</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recessive (GG versus GT + TT)</td>
<td>47 versus 242</td>
<td>5.20</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additive (GG versus GT versus TT)</td>
<td>47 versus 135 versus 107</td>
<td>2.592</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>MAPT rs2425577</td>
<td>Dominant (GG + GA versus AA)</td>
<td>190 versus 99</td>
<td>0.583</td>
<td>0.446</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recessive (GG versus GA + AA)</td>
<td>55 versus 234</td>
<td>0.026</td>
<td>0.871</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additive (GG versus GA versus AA)</td>
<td>55 versus 135 versus 99</td>
<td>0.297</td>
<td>0.744</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*rs3744456</td>
<td>Dominant (CC + CG versus GG)</td>
<td>77 versus 212</td>
<td>1.574</td>
</tr>
</tbody>
</table>

*Only dominant inheriting pattern is adopted due to rare minor allele frequency of the homozygote.

Table 3: Association between SNCA and age of onset of Parkinson’s disease after adjusting for gender.

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Polymorphism</th>
<th>N</th>
<th>Genetic Inheritance Model</th>
<th>Genotype</th>
<th>N</th>
<th>Age at onset (s.e.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australians</td>
<td>SNCA D4S3481</td>
<td>123</td>
<td>Recessive</td>
<td>No allele 1-one allele 1</td>
<td>72</td>
<td>57 (12)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Two allele 1</td>
<td>51</td>
<td>64 (8)</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>SNCA rs894278</td>
<td>289</td>
<td>Recessive</td>
<td>G/G</td>
<td>47</td>
<td>55 (2)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T/T-G/T</td>
<td>242</td>
<td>58 (1)</td>
<td></td>
</tr>
</tbody>
</table>

N = number; s.e. = standard error.

In the Chinese cohort, only SNCA rs894278 SNP associated with PD onset age, which followed a recessive inheritance model for allele G.

3.2. Genetic Effects of SNCA Gene on Age of Onset of PD. After adjusting for gender, SPSS regression analysis showed that SNCA polymorphisms were still associated with the onset age of PD, although the effect observed for the SNCA D4S3481 allele 1 in Australians is more obvious compared with the SNCA rs894278 SNP in the Chinese. Australians carrying two SNCA D4S3481 allele 1 had a delayed onset of PD by about seven years (P = 0.002), while the Chinese with a SNCA rs894278 GG genotype had an earlier onset by about three years (P = 0.015) (Table 3 and supplementary figure).

4. Discussion

Whether a person might develop PD (susceptibility of PD) and when a patient with PD starts to show the symptoms (PD onset) are two distinct questions. It is not surprising that the data derived from two distinct ethnic cohorts show that polymorphisms in the SNCA gene can influence the age of PD onset, while polymorphisms in the MAPT gene do not, although MAPT gene has been shown directly or indirectly (by regulating other PD risk genes) to be associated with PD in both populations [28–30].

Our data showing that the SNCA gene affects age of PD onset in Australian and Chinese cohorts is consistent with a recent report using a very large sample cohort [23] and also with other similarly sized population studies in Spain.
These data may suggest that a reduction in biologically functional α-synuclein, whether through aggregation or reduced expression, could precipitate the neurodegeneration in PD [45, 46]. The merit of this study is the interrogation of two populations independently, with comparable results in both cohorts. Our data suggest that different therapeutic strategies should be considered based on polymorphisms in the SNCA gene of individual patients and that maintaining a certain level of biologically functional α-synuclein is an important consideration in targeting α-synuclein for therapies [44, 47].

Our results emphasize that a better understanding of genome-wide risk factors on the clinical quantitative traits in patients with PD, that is, age at onset and severity of motor and nonmotor symptoms, may assist with future personalised medicine for PD.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Yue Huang and Gang Wang contributed equally to the work.

Acknowledgments

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