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SNP rs11931074 of the SNCA gene may not be associated with multiple system atrophy in Chinese population

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Background: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by poorly levodopa-responsive parkinsonism, cerebellar ataxia, and autonomic dysfunction. Pathogenic mechanisms remain obscure, but the neuropathological hallmark is the presence of α-synuclein-positive glial cytoplasmic inclusions. Previous studies suggested that a single nucleotide polymorphism (SNP), rs11931074, in the α-synuclein gene, SNCA, had highly significant association with an increased risk of the development of MSA in the Caucasian subjects. In contrast, a Korean study failed to identify an association with disease risk. Methods: To study the effect of rs11931074 on MSA risk in a Chinese population, we conducted a case–control study and genotyped SNP rs11931074 by Sanger sequencing in 96 Chinese patients with MSA and 120 healthy controls. Moreover, we performed a meta-analysis on the topic. Results: There was no statistical difference in genotypes or allele frequencies of SNP rs11931074 between MSA and control groups in our cohort. The results of meta-analysis showed that the risk allele T of rs11931074 was associated with MSA (pooled odds ratio = 1.26, 95% confidence interval = 1.07–1.49, P = 0.006). Conclusions: Despite a positive result of the meta-analysis, the significant difference in frequency of allele T of rs11931074 between Asian and Caucasian subjects indicates that population heterogeneity at rs11931074 may exist.

KEYWORDS: multiple system atrophy, SNCA gene, single nucleotide polymorphisms, meta-analysis

Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disease, with two subtypes: MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C) [1]. The MSA-P subtype is more common than the MSA-C subtype in Caucasian subjects (58% vs. 42%), while the MSA-C subtype (83.8%) is predominant in Asian populations compared to the MSA-P subtype (16.2%) [2, 3]. The primary neuropathologic feature of MSA is widespread and abundant α-synuclein-positive glial cytoplasmic inclusions in the central nervous system. The α-synuclein protein is encoded by the SNCA gene, and its misfolded form and dysfunction contribute to the pathogenesis of MSA [4]. Thus, genetic studies on MSA have mainly focused on the SNCA gene.

Initially, coding region sequencing, gene dosage measurements, and tagging SNPs approaches failed to demonstrate a significant association of SNCA variants with MSA [5–7]. However, in 2009, Scholz and colleagues reported that genetic variants within the SNCA locus were associated with an increased risk for developing MSA in Caucasian individuals [8]. That result was subsequently replicated by other groups [9,10]. In contrast, a Korean study reported higher frequencies of rs11931074 in their healthy controls and failed to identify an association with disease risk [11].

In this study, we conducted a case–control study and genotyped SNP rs11931074 by Sanger sequencing to investigate the effect of rs11931074 on MSA risk in the Chinese population. In addition, we conducted a meta-analysis on this SNP to verify whether it was associated with susceptibility to MSA.
Materials and methods

Subjects

MSA subjects (n = 96) were recruited from the Department of Neurology in Xiangya Hospital of Central South University, the State Key Laboratory of Medical Genetics, and the Neurodegenerative Disorders Research Center of Central South University. All patients underwent a set of standardized neurological examinations by two or three neurologists who specialized in movement disorders. The diagnosis of patients with MSA was based on the current consensus criteria established by Gilman and colleagues [1]. The patient group included 69 male patients and 27 female patients. The control group (n = 120) was composed of the majority of patients' spouses and other healthy individuals recruited from the Health Examining Center of Xiangya Hospital of Central South University. Individuals who had major organ dysfunction, neurological diseases, or a family history of movement disorders were excluded from the study. This study was approved by the local ethics committee. Written informed consent was obtained from each participant.

Samples preparation and polymerase chain reaction (PCR)

Blood samples for each participant were collected into ethylenediaminetetraacetate (EDTA) anticoagulation tubes, and leukocyte genomic DNA samples were extracted employing standard phenol–chloroform methods. In controls and patients with MSA, we amplified the region in \( SNCA \) containing rs11931074 by PCR (primers and PCR cycling parameters are listed in Supplementary Table 1S). The genotypes of the SNP for PCR products were determined by Sanger sequencing using an ABI 3730XL automated sequencer (Applied Biosystems, Inc.).

Statistical analyses

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 16.0; SPSS Inc., Chicago, IL). We assessed the baseline levels in patients with MSA and controls using the \( \chi^2 \) test and the \( t \)-test. Differences of allele and genotype frequencies of SNP rs11931074 between groups were analyzed using the \( \chi^2 \) test. \( p < 0.05 \) was regarded as statistically significant.

Meta-analysis

The PubMed/MEDLINE, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) were searched for all relevant articles with the following search terms: “SNCA” or “rs11931074” and “multiple system atrophy” or “olivopontocerebellar atrophy” or “Shy-Drager syndrome” or “striatonigral degeneration”. The search was updated until March 2014. To expand our search, references of the retrieved articles were also screened for additional studies. The following criteria were used to identify relevant studies for the meta-analysis: (1) clinical diagnosis of MSA was established according to the first or second consensus statement on the diagnosis of multiple system atrophy [1,12]; (2) a case–control study design was used; (3) rs11931074 and MSA were tested for association; (4) available genotype/allele data of rs11931074 were provided; (5) control subjects were shown to be healthy without history of neurodegenerative diseases. Articles were excluded if they: (1) were written in languages other than English or Chinese; (2) provided insufficient information for extraction of data; (3) were based on the same data set as another publication. All the data were extracted independently by four investigators (ZFS, XXS, HRP, and ZC) according to the inclusion criteria listed above. Disagreements were resolved in a consensus meeting.

We used a fixed-effect model for statistical pooling of the data. Pooled data are presented with 95% confidence intervals (CI). An I-squared statistic was used to test for heterogeneity between studies. Publication bias was not assessed due to the small number of studies in this review. Meta-analyses were performed using RevMan4.2. \( p < 0.05 \) was considered statistically significant.

Results

The rs11931074 was in Hardy–Weinberg equilibrium in both cases and controls (\( p > 0.05 \)). Clinical and demographic data in our study are provided in Supplementary Table 2S. There was no significant difference in age or sex between the case and control groups. Based on the current consensus criteria [1], there were 58 patients with MSA-C and 38 patients with MSA-P (63 patients with probable MSA and 33 patients with possible MSA). We found no significant differences between patients and controls in allele and genotype frequencies under all genetic models (dominant, recessive, and additive models) for the SNP rs11931074. The odds ratio (OR) was 1.06 (95% confidence interval [CI], 0.57–1.95) under a recessive model. We also tested for differences in allele and genotype frequencies in patients with MSA-P and patients with MSA-C, relative to controls, and found no significant differences between each group and controls under all genetic models (Table 1).

In our meta-analysis, a total of 162 publications were obtained by the computer literature search. After reviewing
Table 1. Allele and genotype frequencies of SNP rs11931074 in patients with MSA and controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>Genotype</th>
<th>n (%)</th>
<th>$P^1$</th>
<th>$P^2$</th>
<th>$P^3$</th>
<th>$P^4$</th>
<th>Odds Ratio (95% CI)$^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA</td>
<td>GG</td>
<td>23 (24.0)</td>
<td></td>
<td>0.64</td>
<td></td>
<td></td>
<td>1.06 (0.57–1.95)</td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>48 (50.0)</td>
<td></td>
<td>0.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>25 (26.0)</td>
<td></td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSA-C</td>
<td>GG</td>
<td>13 (22.4)</td>
<td></td>
<td>0.41</td>
<td></td>
<td></td>
<td>1.24 (0.62–2.51)</td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>28 (48.3)</td>
<td></td>
<td>0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>17 (29.3)</td>
<td></td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSA-P</td>
<td>GG</td>
<td>10 (26.3)</td>
<td></td>
<td>0.83</td>
<td></td>
<td></td>
<td>0.80 (0.33–1.93)</td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>20 (52.6)</td>
<td></td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>8 (21.1)</td>
<td></td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>GG</td>
<td>33 (27.5)</td>
<td></td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>57 (47.5)</td>
<td></td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>30 (25.0)</td>
<td></td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.62</td>
<td></td>
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</tr>
</tbody>
</table>

There was no significant difference between MSA group, MSA-C subgroup, MSA-P subgroup, and controls in allele and genotype frequencies of SNP rs11931074.

$^1$, $^2$, $^3$, $^4$ represent analyses under allele, dominant, additive, and recessive models, respectively.

MSA, multiple system atrophy; CI, confidence interval.

titles, abstracts, or full text, 159 articles were excluded, and a meta-analysis of SNP rs11931074 in patients with MSA was performed in three case–control studies and our present study for a total of 1510 cases with MSA and 9986 controls. No heterogeneity between studies was found ($p > 0.10, I^2 < 50\%$). We found a significant association between SNP rs11931074 and MSA risk (allelic model, pooled OR = 1.26 for T allele, 95% CI = 1.07–1.49, $p = 0.006$); however, both studies on Asian populations were negative results for SNP rs11931074 (Figure 1).

Discussion

SNP rs11931074 is located 7.2 kb downstream from the 3’ end of SNCA and has been reported to be associated with Parkinson’s disease [13, 14]. Recently, studies also demonstrated that SNP rs11931074 was most associated with an increased risk for developing MSA in Caucasian subjects [8–10]. The frequency of the minor allele (T) was about 10% for patients with MSA compared with 8% for healthy controls, resulting in an odds ratio of 6.2 [8]. In contrast, Yun and colleagues failed to identify this association with a higher frequency of 58% for the minor allele (T) in both MSA and controls in a Korean population [11].

The frequency of minor allele T of rs11931074 in Han Chinese in Beijing HapMap sample (HAPMAP-CHB) was about 45%; that is high relative to European populations, but low relative to other Asian populations (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=11931074). We have shown that the plasma $\alpha$-synuclein levels in patients with MSA were significantly elevated compared with that in healthy controls [15]. Moreover, we have also found that the frequency of allele T of rs11931074 was significantly elevated in patients with Parkinson’s disease, and was correlated with serum $\alpha$-synuclein [16]. Taken together, these findings suggest that further investigation of the association between the allele T of rs11931074 and MSA risk is warranted.

This study, however, did not detect an association between rs11931074 and MSA risk in Chinese patients under any genetic model. When applying a recessive model with a possible association [8], we also failed to observe a significant association with risk for MSA. Since the MSA-C subtype is more common in Asian populations [3], we further studied allele and genotype frequencies of SNP rs11931074 under all genetic models, separately, for the MSA-C and MSA-P subtypes. Again, no significant difference in allele and genotype frequencies of SNP rs11931074 was found in patients with either subtype relative to controls. The frequency of
allele T of rs11931074 in our controls was 48.8%, consistent with that of HAPMAP-CHB. Although the small sample size limited the statistical power of our study, the frequency of allele T of rs11931074 in our patients with MSA was 51.0%, which was quite different with that in Caucasian population (10% for patients) [8] and indicated that allele T of rs11931074 may not be a risk for MSA in Chinese population. Despite a pooled positive result of the meta-analysis (pooled OR = 1.26), both studies on Asian populations found no association, while the studies on European populations did find an association, indicating that population heterogeneity at the SNP rs11931074 may exist. Notably, the Multiple System Atrophy Research Collaboration recently found that a common variant (V343A) and multiple rare variants in the COQ2 gene were associated with sporadic MSA, and that the V343A variant was exclusively observed in the Japanese population instead of in European and North American populations [17], which also suggested a different genetic risk for MSA in Asian and European populations. The enrollment of more individuals and the application of advanced genetic tools such as genome-wide association studies and next generation sequencing may be necessary to study the genetic factors involved in MSA in different populations.

Conclusion

We studied for the first time in a Chinese population the effect of rs11931074 of SNCA on MSA risk. In general, our study indicated that allele T of rs11931074 may not be a risk for MSA in Chinese population, which supported that population heterogeneity at the SNP rs11931074 may exist.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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