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Analysis of GWAS-linked variants in multiple system atrophy

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ABSTRACT

A recent genome-wide association study performed in European population identified 4 potentially interesting gene loci of multiple system atrophy (MSA), including the *EDN1* rs16872704, *MAPT* rs9303521, *FBXO47* rs78523330, and *ELOVL7* rs7715147. Because of the genetic heterogeneity, we aimed to explore the possible genetic association between above 4 single nucleotide polymorphisms (SNPs) and MSA in Chinese Han population from Mainland China, Taiwan, and Singapore. A total of 1847 subjects comprising 906 MSA patients and 941 unrelated healthy controls were genotyped by directly sequencing for these SNPs. No significant differences in the genotype distributions, minor allele frequency of *EDN1* rs16872704, *MAPT* rs9303521, *FBXO47* rs78523330, and *ELOVL7* rs7715147 between MSA patients and healthy controls, and between subtypes of MSA patients (MSA-C and MSA-P), were found. In conclusion, we demonstrated that genome-wide association study–linked SNPs in Caucasians do not confer a significant risk for MSA in the Chinese population.

1. Introduction

Multiple system atrophy (MSA) is a rare but fatal neurodegenerative disease, which affects an approximately 3–4 per 100,000 adults (Fanciulli and Wenning, 2015; Federoff et al., 2015). It is clinically characterized by levodopa-resistant parkinsonism, cerebellar ataxia, pyramidal signs, and autonomic dysfunction. Based on its more predominant clinical manifestation, MSA is commonly classified into 2 subtypes: MSA-P (parkinsonism) and MSA-C (cerebellar) (Stefanova et al., 2009). Abundant glial cytoplasmic inclusions formed by fibrillized α-synuclein proteins were described as the pathological features of the disease (Papp et al., 1989). Hence, MSA shares overlapping clinical manifestations and genetic background with Parkinson's disease (PD), another typical α-synucleinopathy (McCann et al., 2014).

Although MSA was originally considered as a sporadic and nongenetic disease, many studies have indicated that genetic factors are responsible for MSA (Stemberger et al., 2011). A recent genome-wide association study (GWAS) performed in 918 European MSA patients and 3864 healthy controls (HCs) identified 4 potential gene loci that might be associated with the risk of MSA. These include endothelin 1 (*EDN1*) rs16872704, f-box Protein 47 (*FBXO47*) rs78523330, microtubule-associated protein tau (*MAPT*) rs9303521, and ELOVL fatty acid elongase 7(*ELOVL7*) rs7715147 (Sailer et al., 2016). Considering the ethnic heterogeneity, we aimed to investigate the association between *EDN1* rs16872704, *MAPT* rs9303521, *FBXO47* rs78523330, and *ELOVL7* rs7715147 and MSA in Chinese population from China, Taiwan, and Singapore.

2. Materials and methods

A total of 1847 subjects comprising 906 MSA patients and 941 unrelated HCs were recruited. All the 906 MSA patients (716 from Mainland China, 150 from Taiwan, and 40 from Singapore) were diagnosed by experienced neurologists and met the criteria for probable MSA based on the "Second consensus statement on the diagnosis of multiple system atrophy" (Gilman et al., 2008). And the patients underwent routine genetic testing for *SCA1*, *2*, *3*, *6*, *7*, and *17* to rule out the diagnosis of

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Table 1
Clinical and demographic characteristics of MSA patients and HCs

	MSA	HCs	MSA-China	HC-China	MSA-Taiwan	HC-Taiwan	MSA-Singapore
Cases	906	941	716	809	150	132	40
Sex							
Male (%)	484 (53.4)	478 (50.8)	385 (53.8)	410 (50.7)	82 (49.4)	64 (48.5)	26 (65.0)
Female (%)	422 (46.6)	463 (49.2)	331 (46.2)	399 (49.3)	84 (50.6)	68 (51.5)	14 (35.0)
Study age (years, mean ± SD)	62.7±8.9	59.4±11.1	62.1±8.6	58.0±11.3	66.5±8.9	68.1±6.7	58.5±7.8
Age at onset (years, mean ± SD)	58.1±8.8[a]	-	57.4±8.7	-	61.9±8.2[b]	-	56.2±7.9
Subtypes							
MSA-C	510 (56.3)	-	408 (57.0)	-	62 (41.3)	-	50 (100)
MSA-P	496 (43.7)	-	308 (43.0)	-	88 (58.7)	-	-

Key: HCs, healthy controls; MSA, multiple system atrophy.
[a] Comparison between age at onset of MSA and age of HCs: $p = 0.004$.
[b] Comparison between age at onset of MSA and age of HC: $p < 0.001$.

spinocerebellar ataxia (SCA). A total of 941 (849 from Mainland China and 132 from Taiwan) unrelated Chinese currently HCs from the same residential areas were recruited. All the 4 single nucleotide polymorphisms (SNPs) were directly sequenced. The sequences of primers and reaction condition were shown in Supplementary Table 1.

3. Results

The clinical information of the MSA patients and HCs from different regions is detailed in Table 1.

There were no significant differences in the genotype distributions, minor allele frequency (MAF), and different genetic models of *EDN1* rs16872704 and *MAPT* rs9303521 between MSA and HCs after age and sex adjustment in the whole population study (Table 2) and each subpopulation, respectively (Supplementary Table 2). In addition, no significant differences in the genotype distributions, MAF, and different genetic models of the 2 SNPs were observed between subgroups regarding MSA subtypes (Supplementary Table 3) and sex distribution (Supplementary Tables 4 and 5). All the MSA patients and HCs exhibited AA at the *FBXO47* rs78523330 and CC at the *ELOVL7* rs7715147, except for only one female MSA-P patient from Mainland China carrying the CA heterozygote at the *ELOVL7* rs7715147 (data not shown).

4. Discussion

In our study, we were unable to replicate the result of the European GWAS, which identified 4 polymorphisms' potential association with Caucasian MSA, in an equivalent number of patients among ethnic Chinese from Mainland China, Taiwan, and Singapore.

In the central nervous system, *EDN1* from astrocytes seems to play a neurodeleterious role by inducing cerebral arterial constriction, causing cerebral microcirculation failure, hypoxia, and mitochondrial dysfunction, leading to excitotoxicity, inflammation, and astrogliosis (Hostenbach et al., 2016). In our present study, the MAF of rs16872704 in *EDN1* in HCs is similar to that in Caucasians; in addition, the calculated statistical power for the rs16872704 SNP was 99.4% in the present study. Therefore, it is reasonable to conclude that rs16872704 is unlikely to increase the risk for MSA in Chinese.

MAPT has been widely verified to play a crucial role in tauopathies, such as progressive supranuclear palsy (Höglinger et al., 2011) and PD (Simón-sánchez et al., 2009). Moreover, studies from American revealed significant associations between MSA and *MAPT* rs242557, rs3785883, and rs8070723 in 127 pathologically confirmed MSA cases (Labbe et al., 2016). But no association was found between *MAPT* rs242557 and MSA in our previous study based on a Chinese cohort (Chen et al., 2015a). Our present study had 97.6% power at an alpha of 0.05 for the rs9303521 variant.

FBXO47 functions in recognizing and binding to some phosphorylated proteins, and promoting protein ubiquitination and degradation (Simon-Kayser et al., 2005). Previous study found abnormal ubiquitination of proteins is involved in MSA (Deger et al., 2015). ELOVL7 may participate in the production of saturated and polyunsaturated very long chain fatty acids, which might contribute to the unique neuropathology of MSA (Bleasel et al., 2014; Tamura et al., 2009). It is likely that *FBXO47* and *ELOVL7* may play a role in the pathogenesis for MSA; however, we found no associations with their polymorphic variants in our population.

The discrepancy between our study and the European study can be explained by ethnic specificity. For example, our previous studies indicated that the variants in *SNCA* and *COQ2*, which were associated with MSA in Caucasian and Japanese population, are unlikely to be associated with the risk for Chinese MSA patients (Chen et al., 2015b,c). Furthermore, in PD, another neurodegenerative disease that shares clinical characteristics with MSA, GWAS demonstrate some differences in the genetic contribution to PD between European population and Asian population (Foo et al., 2017). Therefore, these 4 SNPs associated with the risk for MSA in European are unlikely to increase the risk for MSA in Chinese population.

5. Conclusion

In a large MSA cohort, we found no association of *EDN1* rs16872704, *MAPT* rs9303521, *FBXO47* rs78523330, and *ELOVL7* rs7715147 variants with MSA in our Chinese population. Further studies in other populations will be of interest.

Disclosure statement

The authors declare that they have no conflict of interest.

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