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Research Report

Association study of *semaphorin* 5A with risk of Parkinson's disease in a Chinese Han population

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disorder with genetic risk factors. *Semaphorin* 5A (*SEMA5A*) was recognized as a risk factor for PD through high resolution whole genome association study by Maraganore et al. We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay to check two single nucleotide polymorphisms (SNPs) within *SEMA5A* in 340 PD patients and 222 PD free cases of Chinese Han ancestry and tested by gene sequencing. We found that the *SEMA5A* variant genotype (allele) of rs7702187 and rs3798097 had no association with the risk of PD in our sample. The AC haplotype was associated with a significant increased risk of PD and the AT haplotype showed an associated decreased risk of PD compared with the most common haplotype TC. Our findings suggested that haplotypes of *SEMA5A* may be involved in PD risk in the Chinese Han population.

1. Introduction

Parkinson's disease is a common neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of neuronal intracellular Lewy bodies. The clinical features of PD are resting tremor, rigidity, bradykinesia and postural instability. The environmental and genetic risk factors play important roles in pathogenesis of PD, but the exact mechanism has not yet been known. Mutations of several genes such as α-synuclein, parkin, LRRK2 and PINK1 have been identified as causatives of rare familial PD (Polymeropoulos et al., 1997; Valente et al., 2001, 2004; Nichols et al., 2005). The identification of PD risk genes will greatly expand our knowledge of the genetic and molecular pathogenesis of this disorder.

Semaphorin 5A locates in chromosome 5p15.2. It is a transmembrane protein belonging to the member of semaphorin protein family. The extracellular domain of *SEMA5A* contains seven thrombospondin (TSP) type-1 repeats in addition to the sema domain (Adams et al., 1996). It is essential for the development of the extraembryonic tissues and the cardiovascular system and can elicit multiple

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functional responses such as axon growth, cell adhesion and differentiation, cell–cell signaling and nervous system development through its functional receptor plexin-B3 (Oster et al., 2003; Pineda et al., 2005; Artigiani et al., 2004). In the nervous system, *SEMA5A* is expressed by oligodendrocytes and inhibits axonal growth (Goldberg et al., 2004).

Recently, a high resolution whole genome association study of PD by Maraganore et al. showed that a SNP rs7702187 within *SEMA5A* was apparently associated with PD and had the lowest *p*-value (OR 1.74, $p=7.62\times10^{6}$) (Maraganore et al., 2005). Clarimon et al. evaluated rs7702187 and other four SNPs in two independent case control series from Finland and Taiwan, and found that rs7702187 was a decreased risk while rs3798097 was an increased risk with PD in the Taiwanese population but not in the Finland population (Clarimon et al., 2006). Bialecka et al. performed a case control study in Polish Caucasians and Asians from Singapore and reached a conclusion that rs7702187 was not a marker of PD risk (Bialecka et al., 2006). Elbaz et al. examined all the 13 SNPs found in the original genome wide association study, wherein most participants were of white, non-Hispanic descent, but did not lend support to Maraganore et al (Elbaz et al., 2006).

In our case control study, we selected two SNPs including rs7702187 and rs3798097, whose effects on PD risk were argued, to evaluate the association between *SEMA5A* and the risk of PD in Chinese Han population.

2. Results

2.1. SNP analysis

The observed genotype frequencies for these two polymorphisms were all in Hardy–Weinberg equilibrium in cases and controls. The genotype distributions of *SEMA5A* in the cases and the controls were shown in Table 1. The frequencies of mutant homozygote and heterozygote have no significant difference with the frequencies of wild-type homozygote in two polymorphisms ($p>0.05$). The frequencies of A allele of rs7702187 and T allele of rs3798097 were: 0.22 versus 0.21, 0.10 versus 0.09, in PD patients and healthy controls respectively. We did not find genotype associations between rs7702187 and rs3798097, and the risk of PD.

2.2. Linkage disequilibrium (LD) and haplotype analysis

In the LD analysis, we found that rs7702187 was in low LD with rs3798097 ($D'=0.4557$, $r^2=0.0792$).Three haplotypes with frequencies >5% were derived from the observed genotypes of these two *SEMA5A* polymorphisms. The distributions of *SEMA5A* haplotypes were significantly different between cases and controls ($p<0.05$).The AC haplotypes harboring two *SEMA5A* variant alleles were more common in cases than in controls and were associated with a 1.78-fold increased risk of PD (95%CI 1.26–2.52, $p<0.05$), compared with the most common haplotype TC. The AT haplotype was more common in controls than in cases, which was associated with 0.38-fold decreased risk of PD (95%CI 0.22–0.67. $p<0.05$) (Table 2).

3. Discussion

In our hospital based case control study, we investigated the association of two SNPs of *SEMA5A* with risk of PD in a Chinese Han ancestry population including 340 PD patients and 222 controls. We found that *SEMA5A* genotypes were not associated with the risk of PD in our population. AC haplotype of *SEMA5A* was associated with a significantly increased risk of PD while AT haplotype with a decreased risk of PD. These findings indicate that haplotype containing one mutant allele may serve as a risk modifier while haplotype containing two mutant alleles may serve as a protective modifier. The two polymorphisms may be involved in PD development.

The relationship between *SEMA5A* and risk of PD was first introduced by Maraganore et al. In his study, rs7702187 allele in *SEMA5A* was identified as a significant risk predictor for PD which produced a possibility to study *SEMA5A* polymorphism. To date, there were several studies that investigated the role of *SEMA5A* variants in PD susceptibility. Clarimon et al. reported A homozygote of rs7702187 had a significantly decreased risk of PD compared with T homozygote or heterozygote, and rs3798097 had a significantly increased association with PD in

Table 1 – Logistic regression analyses on association between rs7702187, rs3798097 genotypes and risk 0f PD

Genotype	Cases N=340 N (%)	Controls N =222 N (%)	OR (95%CI)	*p* value
rs7702187 T>A				
TT	220 (64.7)	145 (65.3)	1.00 (reference)	
AT	92 (27.1)	63 (28.4)	0.96 (0.66–1.41)	0.85
AA	28 (8.2)	14 (6.3)	1.32 (0.67–2.59)	0.51
AA+AT	120 (35.3)	77 (34.7)	1.03 (0.72–1.47)	0.93
A allele	0.22	0.21		
rs3798097 C>T				
CC	276 (81.2)	186(83.8)	1.00 (reference)	
CT	61 (18.0)	34(15.3)	1.21 (0.76–1.91)	0.49
TT	3 (0.8)	2(0.9)	1.01 (0.17–6.11)	1.00
CT+TT	64 (18.8)	36(16.2)	1.20 (0.77–1.88)	0.50
T allele	0.10	0.09		