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α-Synuclein polymorphism and Parkinson's disease in a tau homogeneous population

Hee Jin Kim *MD*, Jong-Min Kim *MD PhD*, Jee-Young Lee *MD*, *Sung Sup Park *MD PhD*, Beom S Jeon *MD PhD*

*Departments of Neurology, and *Laboratory Medicine, Seoul National University College of Medicine, MRC, Clinical Research Institute, Seoul National University Hospital and Bundang Hospital, Seoul, South Korea*

Abstract

Background & Objective: The *MAPT* H1 haplotype and *SNCA* single nucleotide polymorphism (SNP) rs356219 have been reported to have a synergistic effect on the risk of Parkinson's disease (PD). Because the H1/H1 genotype has been reported to predominate in Korean population, we investigated the polymorphism of rs356219 in 878 PD patients and 559 controls. *Methods:* The *SNCA* SNP rs356219 was analyzed in 878 PD patients and in 559 healthy Korean subjects. *Results:* The G allele of *SNCA* SNP rs356219 was found to contribute to PD susceptibility with odds ratios (ORs) similar to those reported previously. However, the ORs were not as large as that of the *SNCA* rs356219 plus *MAPT* H1/H1 combination reported in the literature, which cast doubt on the existence of a synergistic effect between the two genotypes in our population.
Conclusions: This study supports that the G allele of the *SNCA* SNP rs356219 contributes to PD susceptibility as reported previously, but it does not support the presence of a synergistic interaction between *SNCA* and *MAPT*.

INTRODUCTION

Recently the microtubule-associated protein tau (*MAPT*) gene H1 haplotype and the α-synuclein *(SNCA)* rs356219 polymorphism were reported to synergistically increase the risk of Parkinson's disease (PD).[1] The *MAPT* gene encodes the microtubule associated protein tau, which is involved in microtubule assembly and stabilization. The possession of one of these risk genotypes increased the risk of developing PD marginally, whereas the possession of both approximately doubled the risk, which suggests that *MAPT* and *SNCA* interact during the pathogenesis of PD.[1]

It has been reported that in the Korean population the prevalence of the H1/H1 genotype of *MAPT* is overwhelming.[2] In this previous study, 53 patients with neurological disorders and 100 controls were tested, and all were found to possess the H1/H1 haplotype, which is consistent with the suggestion that the H2 haplotype is almost exclusively Caucasian in origin.[3] This homogeneity of the *MAPT* haplotype in the Korean population obviates the need to stratify subjects by *MAPT* haplotype during studies on the risks posed by the single nucleotide polymorphisms (SNPs) of *SNCA* on the development of PD. In the present study, we investigated whether the rs356219 SNP of *SNCA* is a risk factor of sporadic PD in the Korean population, and to determine whether the risk presented by synergism between the *MAPT* H1 haplotype and *SNCA* rs356219 is as large as that reported by Goris and colleagues.[1]

METHODS

Subjects

Gene samples were obtained from the gene bank at the Movement Disorder Division of Seoul National University Hospital. All patients and controls were native Koreans. Blood samples were collected after obtaining written informed consent from each participant. The institutional review board of Seoul National University Hospital approved this genetic study. PD was diagnosed according to the United Kingdom Parkinson Disease Society Brain Bank criteria, but the positive family history criterion was excluded.[4]

The *LRRK2* G2019S, *SCA2*, and *SCA17* genes and *SNCA* multiplication were screened in all PD patients, as previously described[5-8], and the *parkin*, *DJ-1*, *Pink1* genes in PD patients with age

Address correspondence to: Dr Beom S. Jeon, MD, Seoul National University Hospital, Department of Neurology, Chongno-Ku Yunkeun-Dong 28, Seoul, 110-744, South Korea. Tel: 82-2-2072-2876; fax: 82-2-3672-7553; e-mail: brain@snu.ac.kr

of onset less than 40. Those who were found to be positive were excluded.

A total of 878 PD patients were included in the present study. The patient group comprised 383 men and 495 women. Mean patient age at sampling was 64.2±9.0 years (range, 33-91) and mean age at onset was 56.6±9.5 years (range, 23-85). Early-onset PD was defined as age of onset of ≤ 50 years, and 241 patients were younger than 50 at PD onset. There were 34 patients with a positive family history, defined having other affected first-degree relatives.

DNA samples from 559 healthy subjects (259 men and 300 women) without a family history of parkinsonism, were analyzed. DNA from healthy subjects was obtained from the gene database at the Department of Laboratory Medicine, Seoul National University Hospital. The mean age of controls at time of sampling was 58.5±10.6 years (range, 37-85).

Genetic analysis

Venous blood samples were drawn and genomic DNA was extracted using standard techniques. One SNP located in the 3'region of *SNCA* (rs356219) and *MAPT* SNP rs9468 were selected based on past reports.[1,9-10] The genotyping of SNPs was performed using the TaqMan fluorogenic 5' nuclease assay (ABI, Foster City, CA, USA). The final volume used for PCR (polymerase chain reaction) was 5ul, and contained 10ng of genomic DNA and 2.5ul TaqMan Universal PCR Master Mix, with 0.13ul of 40X Assay Mix. PCR was performed using 384-well plates and a Dual 384-Well GeneAmp PCR System 9700 (ABI, Foster City, CA), and the endpoint fluorescent readings were performed on an ABI PRISM 7900 HT Sequence Detection System (ABI). Duplicate samples and negative controls were included to ensure the accuracy of genotyping. The Chi-squared test was used to compare categorical variables. Statistical significance was accepted at the 5% level.

RESULTS

In order to confirm the uniformity of *MAPT* H1 haplotype among in the Korean population, *MAPT* SNP rs9468 was analyzed in 173 PD patients and 191 controls. All except one had homozygous H1/H1 at the *MAPT* rs9468 SNP.

We analyzed the SNP rs356219 in the *SNCA* 3'region in a total of 878 PD patients and 559 controls. No deviations of the genotype frequencies from Hardy–Weinberg equilibrium were detected in either cases or controls. SNP rs356219 was in almost complete linkage disequilibrium (D'=1). The G allele had a higher frequency in PD patients than in controls (0.63 vs 0.53), and was found to be associated with an increased risk of PD (OR of 1.53 in the recessive model, Table 1). A comparison of genotypes between the early-onset and late-onset groups revealed no significantly differences (data not shown). Furthermore, analyses of genotypic groups of the SNP in PD patients revealed no significant differences in terms of demographic or clinical variables (data not shown).

DISCUSSION

This study supports that the G allele of the *SNCA* SNP rs356219 contributes to PD susceptibility in the Korean population as reported previously.[1,9-10] The OR in the recessive model was similar to those previously found (1.53 vs 1.4-1.5).[1,9-10] Considering that virtually all subjects in our population had the *MAPT* H1/H1 haplotype, the OR for the G allele of the *SNCA* SNP rs356219 (by the recessive model) in our population was lower than that of the United Kingdom population when *MAPT* H1/H1 and *SNCA* rs356219 were combined (1.53 vs 2.14).[1] Because the H1/H1 haplotype of *MAPT* overwhelmingly predominates in the Korean population[2], we are unable to comment on the effect of *MAPT* H1/H1 haplotype on PD susceptibility. However, it appears that there is no synergistic effect between *MAPT* H1/H1 haplotype and *SNCA* rs356219 in our population.

We found no differences in clinical features between genotypic groups of the *SNCA* rs356219 in terms of age at onset, gender distribution, or disease severity. Thus, although the *SNCA* rs356219 may increase the risk of PD development, they do not appear to have any obvious effects on symptoms or disease progression in our population.

In summary, this study supports that the G allele of *SNCA* rs356219 contributes to PD susceptibility. However, it does not appear that there is a synergistic interaction between *MAPT* H1 haplotype and *SNCA* rs356219 in our population.

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Table 1: Analysis of allele frequencies

SNP	Genotype		MAF	Allele G versus allele A		Dominant model		Recessive model	
	Case	Control				(GG + GA versus AA)		(GG versus GA + AA)	
	GG/GA/AA	GG/GA/AA	Case/Control	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
rs356219	337/423/117	162/263/133	0.37/0.47	1.51(1.29-1.75)	$1x10^{-7}$	2.03(1.54-2.68)	$3x10^{-7}$	1.53(1.22-1.92)	$3x10^{-4}$

MAF, minor allele frequency; OR, Odds ratio; CI, Confidence interval.

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The authors report no conflicts of interest.

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