Letter to the Editor

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Conflicting Results Regarding the Semaphorin Gene (*SEMA5A*) and the Risk for Parkinson Disease

To the Editor:

The strongest variant (*rs7702187*) associated with Parkinson disease (PD [MIM 168600]) reported in the whole-genome association study by Maraganore et al.[1] was evaluated in two independent case-control series of patients from Finland and Taiwan, as were four other variants located within *SEMA5A* (MIM 609297). The Finnish series comprised 146 patients with sporadic PD (mean age 67.2 years, range 38–88 years; 41% women) and 135 neurologically normal, healthy control subjects (mean age 65.8 years, range 37–80 years; 64% women). All individuals were recruited from the neurological outpatient clinics of the Helsinki University Central Hospital and Seinäjoki Central Hospital. The Taiwanese series consisted of 303 patients with sporadic PD (mean age 61.9 years, range 24–91 years; 46.2% women) and 171 control individuals (mean age 60.1 years, range 31–86 years; 43.9% women). Patients were selected from the neurological clinic of Chang-Gung Memorial Hospital. Individuals with evidence of secondary parkinsonism or with atypical features such as early dementia, ophthalmoplegia, early autonomic failure, and pyramidal signs were not included in this study. All patients included in the study fulfilled PD diagnosis criteria.[2] All participants signed an informed consent form.

Taqman Assays-by-Design SNP Genotyping Assays (Applied Biosystems) were employed for allelic discrimination of all SNPs. Differences in allele and genotype distributions were analyzed using the χ^2 test, and two-tailed *P* values are presented. Haplotype frequency comparisons between cases and controls were performed with PHASE version 2.1 software.[3] One thousand permutations were performed for each comparison. The COCAPHASE module of the UNPHASED statistical package was used for linkage-disequilibrium (LD) analyses.[4] Power calculations were performed with PS version 2.1.30.[5]

Allele and genotype frequency information for each of the markers is shown in table 1. None of the markers showed any significant association with disease in the Finnish series. However, we were able to replicate the reported association with marker *rs7702187* in the Taiwanese cohort (odds ratio [OR] = 1.53, 95% CI 1.12–2.10, $P = .007$). Genotype analysis showed that individuals homozygous for the A allele had a significantly decreased risk of PD compared with those heterozygous or homozygous for the T allele (OR = 0.60, 95% CI 0.41–0.88, $P = .009$). A significant association was also

Table 1

Genotype and Allele Frequency Distribution of the Polymorphisms Analyzed across *SEMA5A* on Chromosome 5

dbSNP Accession Number	Position	Genotype Frequency				Minor-Allele Frequency		OR	*P* (95% CI)[a]
		Control 11	Control 12	Case 11	Case 12	Control	Case		
Finnish series:									
rs3798097	9595529	.49	.35	.51	.35	.34	.32	.910	.610 (.63–1.31)
rs368226	9470056	.90	.10	.91	.09	.05	.05	.921	.838 (.42–2.02)
rs7702187	9385281	.69	.29	.74	.22	.16	.15	.901	.657 (.57–1.43)
rs1806151	9207659	.25	.50	.27	.53	.50	.47	1.160	.424 (.81–1.67)
rs786843	9093141	.68	.29	.66	.31	.18	.18	1.055	.814 (.67–1.65)
Taiwanese series:									
rs3798097	9595529	.81	.16	.88	.10	.11	.07	.586	**.025 (.37–.94)**
rs368226	9470056	.51	.37	.49	.42	.30	.30	.995	.976 (.74–1.33)
rs7702187	9385281	.61	.35	.49	.44	.22	.30	1.534	**.007 (1.12–2.10)**
rs1806151	9207659	.62	.34	.62	.35	.21	.22	.958	.805 (.68–1.35)
rs786843	9093141	.89	.10	.88	.12	.06	.06	1.057	.846 (.61–1.65)

[a] Values in bold denote statistical significance.

Table 2

Haplotype Frequency Distribution in Finnish and Taiwanese Series

	Frequency			
	Finnish[a]		Taiwanese[b]	
Haplotype	Control	Cases	Control	Cases
CCACC	.252	.267	.391	.339
CCAGC	.212	.203	.069	.081
TCAGC	.104	.096	.010	.005
TCACC	.103	.109	.049	.024
CGACG	.010	.013	.164	.163
CCTCC	.038	.046	.105	.162
Other[c]	.281	.267	.097	.227

Note.—The order of SNPs is *rs3798097*, *rs368226*, *rs7702187*, *rs1806151*, and *rs786843*.

[a] Global significance for haplotype frequency differences: $P = .9$

[b] Global significance for haplotype frequency differences: $P = .091$

[c] Other haplotypes with frequencies <5%.

found for the *rs3798097* marker, which is located in the 5′ UTR region of *SEMA5A* (OR for the C allele was 1.71, 95% CI 1.06–2.73, $P = .025$).

Both populations showed a complete lack of LD for any pairs of neighboring polymorphisms (all D' values were <0.5, independently of diagnostic group). Haplotype frequency comparisons did not reveal any significant differences between patients and controls in the Finnish series ($P = .901$) or between patients and controls in the Taiwanese series ($P = .091$) (table 2).

The present results point to differential risk effects of *SEMA5A* marker alleles across populations. In the Taiwanese population, we have found an associated risk in the same locus as the one reported elsewhere[1] but in an opposite direction. That is, the at-risk allele that we report was found to be protective in the sample from Minnesota described by Maraganore et al.[1] This could be due to the effect of LD between this polymorphism and another "true" risk variant within the gene. The lack of association shown in the Finnish population could be related to genetic heterogeneity, or, alternatively, the Finnish series might not be large enough to assess genes with modest effects (this sample has a 60% power to detect risks of 1.7, at $\alpha = 0.05$).

The replication of an association with *SEMA5A* in a Taiwanese population makes it a good candidate for further analyses in different populations.

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Web Resources

The URLs for data presented herein are as follows:

dbSNP, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=snp (for *SEMA5A* markers)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/entrez/Omim/ (for PD and *SEMA5A*)

References

1. Maraganore DM, de Andrade M, Lesnick TG, Strain KJ, Farrer MJ, Rocca WA, Pant PVK, Frazer KA, Cox DR, Ballinger DG (2005) High-resolution whole-genome association study of Parkinson disease. Am J Hum Genet 77:685–693
2. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181–184
3. Stephens M, Donnelly P (2003) A comparison of Bayesian methods for haplotype reconstruction from population genotype data. Am J Hum Genet 73:1162–1169
4. Dudbridge F (2003) Pedigree disequilibrium tests for multilocus haplotypes. Genet Epidemiol 25:115–121
5. Dupont WD, Plummer WD Jr (1998) Power and sample size calculations for studies involving linear regression. Control Clin Trials 19:589–601

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