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Letter to the Editor

Association of Parkinson disease to *PARK16* in a Chilean sample☆

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Parkinson's disease (PD) is one of the most common neurodegenerative disorders worldwide with a prevalence of ~3% in persons over the age of 65 years. Genetic causes of PD have been identified using both linkage and association approaches [1]. Recently, two genome-wide association (GWA) studies in PD using Asian and Caucasian patients and controls of Japanese and European origin have identified common susceptibility variants reaching genome-wide significance [2,3]. Among several other loci, the Japanese study described variants with *p*-values between 10^{-7} and 10^{-12} which are located at a new susceptibility locus on chromosome 1q32 called *PARK16* [3]. Analysis of *PARK16* in the European sample also showed significant association with PD for rs823128 at *PARK16* (*p*-value of 7×10^{-8}) [2].

To determine the contribution of *PARK16* to PD in a different ethnic background, we investigated association of this locus with PD in a case-control sample from Chile.

1. Material and methods

After giving informed consent, Chilean PD patients fulfilling UK Brain Bank diagnostic criteria (with the exception that positive family history was not regarded an exclusion criterion) were recruited from PD organizations located in Santiago, Concepcion, Puchuncavi, Ventanas, and Melipilla. In the patient cohort, 23.67% of all individuals had a positive family history. Control subjects were healthy volunteers from the same geographic area and were examined by a neurologist to confirm the absence of any neurological disease (Table 1). Young control individuals were excluded from the analysis if they reported first-degree relatives with PD.

Genotyping was performed using the melting curve technique on a LightCycler 480 (RocheDiagnostics) with a call rate of >95%. All genotyped SNPs were compatible with Hardy-Weinberg Equilibrium (HWE) (Table 2) [4]. To search for association in our dataset, we applied a logistic regression analysis with an additive coding model for each SNP.

2. Results and discussion

We first investigated rs823128 since this SNP showed a significant association with PD in both above mentioned studies [2,3], and could replicate the association in our Chilean sample (heterozygous odds ratio (OR) 0.56; 95% confidence interval (95% CI) 0.37–0.87; $p = 0.0093$; Table 2). We observed a lower minor allele frequency (MAF) in the Chilean PD patients than in controls (9.3% versus 16.5%). The observed genotype distribution in the Chilean population is similar to the one observed in the Japanese study group where 9% of patients and 14% of controls carried the minor allele. In contrast, this variant is less common in the European population with 3% vs. 4% in patients and controls.

Second, we analyzed rs947211, a SNP with a higher MAF. This SNP revealed no association with PD in our sample (Table 2). Additionally, we adjusted our analysis for gender without substantial changes in the results (data not shown).

One possible cause for this apparent discrepancy between these two SNPs is that the strength of the association between rs947211 and PD (i.e. effect size) is substantially smaller than for rs823128. In line with this hypothesis, *PARK16* did not reach the significance level in the European GWAS or its replication [2]. However, combining samples from stage I and II did reveal association with rs823128 showing the strongest association. Interestingly, rs947211 did not reach significance in this study. This indicates that the effect size of rs947211 in the European population may be too small to be detected. Thus, due to the limited sample size of the Chilean sample and the small effect size, rs947211 showed no association with PD in the Chilean sample. Specifically, the power of our sample was only 22% for a two-sided test, a 5% significance level for detecting an association between PD and rs823128 using the allele frequency of 0.17 as observed in the present control sample and an odds ratio of 0.66 as reported by Simon-Sanchez et al. [2]. Furthermore, the power was only 20% for a replication of rs947211 using a two-sided test, a 5% significance level using the allele frequency of 50% and an odds ratio of 1.30 as reported by Satake et al. [3]. Alternatively, the structure of the linkage disequilibrium (LD) blocks within the *PARK16* locus may have led to the lack of association between PD and rs947211 in the Chilean population. In this regard, a previous study suggested that *PARK16* seems to have multiple independent association signals which can be explained by the presence of several linkage disequilibrium (LD) blocks containing the SNPs with significant association to PD [3]. Thus, the susceptibility allele contributing to the pathogenesis of PD may reside within the LD block containing rs823128, which is independent of the LD block including rs947211.

In conclusion, our data suggest that rs823128, within the *PARK16* locus, contributes to PD also in ethnic backgrounds other than Asian and Caucasian.

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Table 1
Case-Control dataset originally included for association in this study.

Patient Data								Control Data					
Sample Origin	Inclusion Criteria[a]	No of Patients	Ethnic Background	Gender		Age ± S.D.[b]	Age of onset ± S.D.[b]	Sample Origin	No of Controls	Ethnic Background	Gender		Age ± S.D.[b]
				Male	Female						Male	Female	
Santiago, Concepcion, Puchuncavi, Ventanas, and Melipilla	UBBCDC	169	Chilean	83	86	68 ± 11.4 (15–87)	60 ± 11.51 (41–85)	Healthy volunteers from same areas	195	Chilean	62	133	66 ± 10.77 (21–90)

[a] UBBCDC, UK Brain Bank Clinical Diagnostic Criteria.
[b] age and standard deviation (S.D.) are given in years.

Table 2
Statistical analysis of SNPs within PARK16 included in this study.

SNP		Controls		Cases		Controls		Cases		Odds ratio	(95% CI)	p
rs-number	Genotype	n	Percentage	n	Percentage	REH[a]	(95% CI[b])	REH	(95% CI)			
rs823128	A/A	138	71.50	139	83.73	0.6526	(0.3608–1.1807)	0.4877	(0.1626–1.4631)	1.0000		**0.0093**
	A/G	46	23.84	23	13.86					0.5631	(0.3652–0.8681)	
	G/G	9	4.66	4	2.41					0.3170	(0.1334–0.7536)	
rs947211	A/A	40	20.51	23	13.69	0.9163	(0.6797–1.2354)	1.2152	(0.9097–1.6233)	1.0000		0.2473
	A/G	92	47.18	88	52.38					1.1933	(0.8845–1.6098)	
	G/G	63	32.31	57	33.93					1.4240	(0.7824–2.5916)	

[a] Relative excess heterozygosity for testing compatibility with Hardy-Weinberg equilibrium.
[b] Two-sided; CI: Confidence Interval.

Conflict of interest

The authors report no conflicts of interest.

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