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Patient-Control Association Study of the *LRRK2* Gene in South African Parkinson's Disease Patients

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The leucine-rich repeat kinase 2 (*LRRK2*) gene is of interest to Parkinson's disease (PD) as it has been implicated in both familial and sporadic forms of the disorder.[1] PD-susceptibility alleles in *LRRK2* appear to be ethnic-specific with G2385R,[2] R1628P[3] and A419V[4] identified in Asian populations, whereas M1646T is found in Caucasians.[4] A haplotype protecting against development of PD is present in Chinese (N551K-R1398H)[5] and Caucasians (N551K-R1398H-K1423K).[4] Further studies are necessary to investigate the contribution of *LRRK2* to PD-susceptibility in various populations worldwide.

To this end we investigated whether variants in *LRRK2* were associated with PD in a South African patient series comprising 205 PD patients and 378 controls of different ethnicities: Caucasian, Mixed ancestry, Xhosa-speaking Black African and Indian/Asian (Supplementary Table 1). For the purposes of our study the Afrikaner Caucasian individuals, hereafter referred to as Afrikaner, were analyzed separately from the 'non-Afrikaner' Caucasians. All *LRRK2* exonic variants, published or reported up to April 1, 2010[4] were genotyped using the MassArray iPLEX platform (Sequenom, San Diego, CA, USA). Statistical analyses were performed using R (www.r-project.org) and R package haplo.stats. Logistic regression was used to assess individual single nucleotide polymorphisms (SNPs) and haplotype associations with PD. With group sizes of 64 patients and 93 controls (similar to our Afrikaner group), a significance level of 5%, and assuming a control frequency of 5%, we had 80% power to detect an additive allelic odds ratio of 3.1.

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Of the 117 variants genotyped, 30 were polymorphic in at least one ethnic group. All variants were in Hardy-Weinberg equilibrium. In this exploratory analysis a number of novel associations with PD were found (Table 1; Supplementary Table 2), although an association with a variant common to all ethnic groups was not detected. The M1646T variant was not present in the Black African individuals. Furthermore, this variant was not associated with PD in any of the other ethnic groups; this may be related to small sample sizes or possibly due to differences in genetic substructure (Supplementary Fig. 1). The previously-identified protective haplotype (N551K-R1398H-K1423K) did not show a significant association with PD. However, of interest is the fact that greater diversity in the haplotype structure was observed in the Black African and Mixed ancestry individuals (five haplotypes) than the Caucasians (two haplotypes) (Supplementary Table 3) which is important for future association studies.

Previous mutation-screening studies on *LRRK2* in African populations found that upwards of 30% of PD patients in North African Berber Arabs harbor the pathogenic G2019S mutation. In contrast, the present study found G2019S to be relatively uncommon in the South African population (4/205, 2%) reflecting the fact that extensive genetic diversity across different African populations exists.[7]

Taken together, our findings further support the idea that genetic risk factors in *LRRK2* for PD are ethnic-specific. While it is acknowledged that the group sizes are small, this study is of interest as it is the first case-control association study on *LRRK2* in a sub-Saharan African population. It would be important for this work to be duplicated in diverse populations to see how the results compare and contrast.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' Roles:

Soraya Bardien: Research project execution, writing and editing of the manuscript.

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Table 1

Case-control association results for the *LRRK2* variants that showed evidence for association in at least one South African ethnic group.

			Afrikaner Caucasian				'non-Afrikaner' Caucasian				Mixed ancestry				Black African			
			MAF (%)		P-value		MAF (%)		P-value		MAF (%)		P-value		MAF (%)		P-value	
SNP	Amino acid	MA	PD	CON	Add	Dom	PD	CON	Add	Dom	PD	CON	Add	Dom	PD	CON	Add	Dom
rs10878245	L153L	T	37.1	39.2	0.691	0.838	35.5	47.3	**0.019**	0.111	65.7	52.4	0.064	0.244	75.0	69.7	0.527	0.795
rs33958906	P1542S	T	3.2	2.7	0.799	0.799	1.1	6.4	**0.013**	**0.018**	0	1.2	0.238	0.238	-	-		
rs11176013	K1637K	A	45.2	51.1	0.317	0.703	38.5	50.5	**0.023**	0.205	52.9	39.4	0.053	0.070	50.0	43.4	0.476	0.289
rs11564148	S1647T	A	24.6	25.3	0.890	0.923	29.3	29.7	0.932	0.890	28.6	25.9	0.648	0.748	0	13.4	**0.004**	**0.004**
rs10878371	G1819G	T	43.7	51.6	0.170	0.479	39.5	50	**0.039**	0.207	52.9	40.4	0.077	0.076	50.0	43.9	0.505	0.314
rs34637584	G2019S	A	-	-			1.7	0	**0.032**	**0.032**	1.4	0	0.114	0.114	-	-		
rs10878405	E2108E	A	36.1	24.7	**0.036**	**0.022**	32.7	32.8	0.988	0.826	17.6	26.5	0.133	0.139	0	10.6	**0.010**	**0.010**
rs33962975	G2385G	G	7.9	12.5	0.182	0.219	8.1	14.1	0.056	0.070	18.6	8.4	**0.026**	**0.042**	3.1	6.1	0.454	0.454

MA, minor allele in the combined groups; MAF, minor allele frequency; The '–' indicates that the MA is not present.

Frequencies are given separately for PD cases (PD) and controls (CON).The P-values are from logistic regression models testing additive allelic effect (Add) or Dominant (Dom) minor allele effect within each ethnic group.

Significant p-values were taken as $p < 0.05$, without correction for multiple testing, and are shown in bold font. If correction for multiple testing (for 30 tests) had been taken into account a significant p-value would have been $p < 0.0017$.