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

Soraya Bardien, PhD1,*, Janine Blanckenberg, PhD1, Lize van der Merwe, PhD2,3, Matthew J. Farrer, PhD4, and Owen A. Ross, PhD5

1Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, University of Stellenbosch, Cape Town, South Africa
2Biostatistics Unit, Medical Research Council, Cape Town, South Africa
3Department of Statistics, University of the Western Cape, Cape Town, South Africa
4Department of Medical Genetics, University of British Columbia, Vancouver, Canada
5Department of Neuroscience, Mayo Clinic College of Medicine, Jacksonville, Florida, USA

Keywords
Parkinson’s disease; LRRK2 gene; case-control association studies; South African population

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. PD-susceptibility alleles in LRRK2 appear to be ethnic-specific with G2385R, R1628P and A419V identified in Asian populations, whereas M1646T is found in Caucasians. A haplotype protecting against development of PD is present in Chinese (N551K-R1398H) and Caucasians (N551K-R1398H-K1423K). 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 were genotyped using the MassArray iPLEX platform (Sequenom, San Diego, CA, USA). Statistic 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.

*Correspondence to: Dr Soraya Bardien, Division of Molecular Biology and Human Genetics, University of Stellenbosch, PO Box 19063, Tygerberg, 7505, Cape Town, South Africa; sbardien@sun.ac.za.

Relevant conflicts of interest/financial disclosures: For SB, JB, LvdM and OAR nothing to report. MJF has received speaker fees from Genetech and Teva and he occasionally consults with Isis Pharmaceuticals, H.Lundbeck A/S and GlaxoSmithKline. The Mayo Clinic holds patents related to past gene discoveries including LRRK2, and methods of treating neurodegenerative disease, from which MJF receives royalties.
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.

Acknowledgments

We thank all the study participants and also gratefully acknowledge Prof. Jonathan Carr, Alexandra Soto-Ortolaza and Sr. Debbie Lombard for their valuable contributions to this research project.

Funding agencies: This work was supported by the Michael J Fox Foundation, Mayo Clinic Morris K. Udall Parkinson’s Disease Research Center of Excellence (NINDS P50NS072187) and the South African Medical Research Council.

Authors’ Roles:

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

Janine Blanckenberg: Writing of sections of the manuscript.

Lize van der Merwe: Design and execution of statistical analyses and interpretation of results.

Matthew J. Farrer: Research project conception and execution.

Owen A. Ross: Research project conception, organization and execution.

All authors provided critical review of the manuscript and contributed to the final draft.

References


<table>
<thead>
<tr>
<th>SNP</th>
<th>Amino acid</th>
<th>Afrikaner Caucasian MAF (%)</th>
<th>P-value</th>
<th>‘non-Afrikaner' Caucasian MAF (%)</th>
<th>P-value</th>
<th>Mixed ancestry MAF (%)</th>
<th>P-value</th>
<th>Black African MAF (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10878245</td>
<td>L153L</td>
<td>37.1</td>
<td>0.691</td>
<td>35.5</td>
<td>0.019</td>
<td>65.7</td>
<td>0.064</td>
<td>75.0</td>
<td>0.527</td>
</tr>
<tr>
<td>rs33958906</td>
<td>P1542S</td>
<td>3.2</td>
<td>0.799</td>
<td>1.1</td>
<td>0.013</td>
<td>0.018</td>
<td>0.238</td>
<td>0.238</td>
<td>-</td>
</tr>
<tr>
<td>rs1176013</td>
<td>K1637K</td>
<td>45.2</td>
<td>0.317</td>
<td>38.5</td>
<td>0.023</td>
<td>52.9</td>
<td>0.053</td>
<td>50.0</td>
<td>0.476</td>
</tr>
<tr>
<td>rs11564148</td>
<td>S1647T</td>
<td>24.6</td>
<td>0.890</td>
<td>29.3</td>
<td>0.039</td>
<td>28.6</td>
<td>0.648</td>
<td>13.4</td>
<td>0.004</td>
</tr>
<tr>
<td>rs10878371</td>
<td>G1819G</td>
<td>43.7</td>
<td>0.170</td>
<td>39.5</td>
<td>0.032</td>
<td>1.7</td>
<td>0.032</td>
<td>1.4</td>
<td>0.114</td>
</tr>
<tr>
<td>rs34637584</td>
<td>G2019S</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
<td>0.032</td>
<td>1.4</td>
<td>0.114</td>
<td>1.4</td>
<td>0.114</td>
</tr>
<tr>
<td>rs10878405</td>
<td>E2108E</td>
<td>36.1</td>
<td>24.7</td>
<td>32.7</td>
<td>0.036</td>
<td>0.022</td>
<td>32.8</td>
<td>0.133</td>
<td>0.010</td>
</tr>
<tr>
<td>rs33962975</td>
<td>G2389G</td>
<td>7.9</td>
<td>12.5</td>
<td>8.1</td>
<td>0.026</td>
<td>18.6</td>
<td>0.042</td>
<td>3.1</td>
<td>0.454</td>
</tr>
</tbody>
</table>

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.