Published in final edited form as:
Mov Disord. 2012 December ; 27(14): 1823–1826. doi:10.1002/mds.25226.

Common Variation in the *LRRK2* Gene is a Risk Factor for Parkinson's Disease

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Authors' Roles: 1. Research project: A. Conception and design, B. Acquisition of data, C. Analysis and interpretation of data. 2. Manuscript: A. Writing of the first draft, B. Review and Critique. 3. Other: A. Statistical analysis, B. Obtaining funding, C. Technical support, D. Supervision of data collection Mata: 1A, 1B, 1C, 2A, 3A, 3D; Checkoway: 1B, 2B, 3B; Hutter: 1A, 1C, 2B, 3B, 3C; Samii:1B, 2B; Roberts: 1B, 2B; Kim: 1B, 2B; Agarwal: 1B, 2B, 3C; Alvarez: 1B, 2B, 3B; Ribacoba: 1B, 2B, 3C; Pastor: 1B, 2B, 3C; Lorenzo-Betancor: 1B, 2B, 3C; Infante: 1B, 2B, 3B; Sierra: 1B, 2B, 3B; Gómez-Garre: 1B, 2B, 3B; Mir: 1B, 2B, 3B; Ritz: 1B, 2B, 3B, 3C; Rhodes: 1B, 2B; Colcher: 1B, 2B, 3B; Van Deerlin: 1B, 2B; Chung: 1B, 2B; Quinn: 1B, 2B; Yearout: 1B, 2B, 3C; Martinez: 1B, 2B; Farin: 1A, 1B, 2B, 3B, 3C, 3D; Wan: 1C, 2B, 3A; Edwards: 1C, 2B, 3A, 3B, 3D; Zabetian: 1A, 1B, 1C, 2A, 3B, 3D

Financial Disclosures for the preceding 12 months:
Dr. Mata is funded by grants from the Department of Veterans Affairs, NIH, and Parkinson's Disease Foundation.
Dr. Checkoway is funded by grants from NIH (NIEHS, NCI). He also serves as a paid consultant for the Alcoa Co., Pittsburgh, PA, the Electric Power Research Institute, Palo Alto, CA, ENVIRON, Amherst, MA, and the University of Minnesota Dept. of Environmental Health, Minneapolis, MN
Dr. Hutter is funded by grants from the NIH Dr. Samii has received honoraria from Teva and Boehringer-Ingelheim.
Dr. Roberts has no financial disclosures
Dr. Kim has not financial disclosures
Dr. Agarwal has received honoraria as a speaker for Teva, GSK and consultancy for Merz.
Dr. Mir and Dr. Gómez-Garre received support in the form of grants from the Ministerio de Ciencia e Innovación de España (SAF2007-60700); the Instituto de Salud Carlos III (PI10/01674, CP08/00174); the Consejería de Innovación, Ciencia y Empresa de la Junta de Andalucía (CVI-02526); the Consejería de Salud de la Junta de Andalucía (PI-0377/2007, PI-0741/2010), the Sociedad Andaluza de Neurología and the Jaques and Gloria Gossweiler Foundation. Dr. Gómez-Garre was also supported by the "Miguel Servet" program from the Instituto de Salud Carlos III.
Dr. Alvarez has no financial disclosures
Dr. Ribacoba has no financial disclosures
Dr. Pastor is funded by grant of the Spanish Ministry of Science and Innovation SAF2010- 22329-C02-01: 2011-2013.
Dr. Lorenzo-Betancor is funded by grant of the Spanish Ministry of Science and Innovation SAF2010-22329-C02-01: 2011-2013.
Dr. Infante is funded by grants from the "Fondo de Investigación Sanitaria-ISCIII" and CIBERNED-ISCIII
Dr. Sierra is funded by grants from "Fondo de Investigación Sanitaria-ISCIII" and IFIMAV
Dr. Ritz received funding from NIH grants R01-ES010544, U54-ES012078, P01-ES016732, and P50-NS038367, Department of Defense grant PC051037 and initial funding from a pilot grant by the American Parkinson Disease Association.
Dr. Rhodes is funded by NIH grants R01 ES010544, U54 ES012078, P01 ES016732, and P50 NS038367
Dr. Colcher has served as a consultant for Lundbeck pharmaceuticals and Teva pharmaceuticals.
Dr. Van Deerlin is funded by grants from the NIH,
Dr. Chung has no financial disclosures
Dr. Quinn has no financial disclosures
Ms. Yearout receives salary support from the Department of Veterans Affairs and NIH.
Ms. Martinez receives salary support from the Department of Veterans Affairs and NIH.
Dr. Farin is funded by grants from the NIH Ms. Wan receives salary support from the NIH.
Dr. Edwards is funded by grants from the NIH.
Dr. Zabetian is funded by grants from the American Parkinson Disease Association, Department of Veterans Affairs, NIH, Northwest Collaborative Care, and Parkinson's Disease Foundation.

Conflict of interest concerning the research related to the manuscript: None

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Abstract

Background—Common variants in the *LRRK2* gene influence risk of Parkinson's disease (PD) in Asians, but whether the same is true in European-derived populations is less clear.

Methods—We genotyped 66 *LRRK2* tagging single nucleotide polymorphisms (SNPs) in 575 PD patients and 689 controls from the Northwestern U.S. (Tier 1). PD-associated SNPs ($p<0.05$) were then genotyped in an independent sample of 3617 cases and 2512 controls from the U.S. and Spain (Tier 2). Logistic regression was used to model additive SNP genotype effects adjusted for age and sex among white individuals.

Results—Two regions showed independent association with PD in Tier 1, and SNPs in both regions were successfully replicated in Tier 2 (rs10878226, combined odds ratio [OR], 1.20; 95% confidence interval [CI], 1.08-1.33; $p=6.3\times10^{-4}$; rs11176013, OR, 0.89; CI, 0.83-0.95; $p=4.6\times10^{-4}$).

Conclusions—Our data suggest that common variation within *LRRK2* conveys susceptibility for PD in individuals of European ancestry.

Keywords

Parkinson's disease; *LRRK2*; SNP

Introduction

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene account for 1-2% of Parkinson's disease (PD) in individuals of European ancestry. Furthermore, two common single nucleotide polymorphisms (SNPs) within *LRRK2* (rs34778348 [G2385R] and rs33949390 [R1628P]) that are specific to Asians have consistently been demonstrated to associate with PD.[1-5] Whether or not common variation in *LRRK2* alters PD risk in populations of European origin is less clear. Initial studies of white PD case-control samples focused solely on *LRRK2* and using a tagging SNP approach yielded largely negative findings.[6, 7] Subsequent genome-wide association studies (GWAS) and GWAS meta-analyses from Europe and North America have yielded varying levels of support for an association between PD and *LRRK2* ranging from none[8-10] to marginal,[11] intermediate,[12, 13] or strong (surpassing the genome-wide significance threshold).[14, 15]

Here we present findings from an analysis of *LRRK2* in which a comprehensive set of tagging SNPs was examined in a PD case-control sample of 1264 subjects from the U.S. (Tier 1) with replication in a case-control sample of 6129 individuals from Spain and the U.S. (Tier 2).

Subjects and Methods

Subjects

The study population was divided into two tiers. Tier 1 was comprised of 575 PD patients and 689 controls from the Northwestern U.S. who were enrolled in the Parkinson's Genetic Research Study (PaGeR)[16] or in a population-based study of PD at the University of Washington and Group Health Cooperative (UW-GHC).[17] The mean age (±SD) at enrollment was 67.2 ± 10.3 years for cases and 68.9 ± 9.2 years for controls. Cases were 60.0% male and controls were 60.2% male. Tier 2 included 3617 patients with PD and 2512 controls; subjects were enrolled in studies from the U.S. (PaGeR, Parkinson's Environment and Genes Study [PEG],[18] University of Pennsylvania Center for Neurodegenerative Disease Research) or at academic centers from four regions of Spain (Asturias, Cantabria, Navarra and Andalucia). Cases were 63.4% male with a mean age at enrollment of 67.5 ± 11.0 years. Controls were 43.4% male with a mean age at enrollment of 66.7 ± 12.3 years.

Patients in UW-GHC and PEG met clinical diagnostic criteria for PD as previously described.[17,18] Patients in all other studies met UK PD Society Brain Bank clinical

diagnostic criteria for PD.[19] Controls who were unrelated to cases and had no history of a neurodegenerative disease were recruited in the same geographic locations as the cases. Only individuals who self-reported their race as white were included in the analysis.

The Institutional Review Board of each participating institution approved the study, and all participants provided informed consent.

Marker Selection and Genotyping

We partitioned *LRRK2* SNPs from the HapMap CEU panel into 50 "bins" using an r^2 threshold of 0.80 and a minor allele frequency cutoff of 5%. We then selected one tagging SNP from each bin and a second SNP from bins containing > 5 SNPs. In total, 66 SNPs were genotyped using Affymetrix GeneChip Universal 3K Tag Arrays (Tier 1) or TaqMan assays (Tier 2). If a SNP failed genotyping by TaqMan Assay for any reason, we substituted a highly correlated SNP from the same bin.

Data Analysis

We used logistic regression to model the association between PD and each SNP under an additive model adjusting for sex and age at enrollment using homozygotes for the major allele as the reference. For Tier 1 we used a nominal significance level of 0.05 to be more inclusive of potential PD-associated SNPs. We used fixed-effects meta-analysis to obtain a summary estimate and p-value combining Tier 1 and Tier 2 results.

Further details on SNP selection, genotyping and data analysis are provided in the Supplement.

Results

Of the 66 SNPs selected for screening in Tier 1, one (rs1491942) failed genotyping and three deviated significantly ($p<0.001$) from Hardy-Weinberg equilibrium in controls. These four SNPs were excluded from further analysis. Of the remaining 62 SNPs, three were significantly ($p<0.05$) associated with PD in Tier 1 (Figure 1 and Table 1). Two of the SNPs (rs7294619 and rs10878226), located in the promoter region, were highly correlated with one another ($r^2=0.98$) and tagged the same association signal. Thus, we selected only one of these two SNPs (the one with the lower *p* value, rs10878226) for replication in Tier 2. The third PD-associated SNP (rs11176013), a synonymous substitution (K1637K) in exon 34, appeared to represent an independent signal as it was only weakly correlated with the other two SNPs (rs7294619, $r^2=0.04$; rs10878226, $r^2=0.04$). Though we initially chose this SNP for replication, it failed TaqMan Assay design and was replaced by a highly correlated SNP (rs10878371, $r^2=1$). In Tier 2, after adjustment for age and sex both rs10878226 and rs10878371 were associated with PD (Table 1). Furthermore, both SNPs displayed the same direction of effect in Tiers 1 and 2. A meta-analysis showed strong evidence for an association for both SNPs (Table 1). We did not detect significant evidence of heterogeneity across study sites for either SNP using the Breslow-Day test ($p>0.36$), or by using "site" as a covariate in the logistic regression model (data not shown).

Discussion

Using an approach in which we systematically assayed common variation in a discovery sample and then successfully replicated findings in a large case-control sample, we observed an association between *LRRK2* SNPs and PD. The effect size seen in our sample was small (Table 1), but was consistent with that reported in previous positive studies of *LRRK2* from Europe and the U.S. in which the ORs ranged from 1.15-1.30.[11-14] In contrast, substantially larger effects sizes have been reported for the G2385R and R1628P SNPs in Asian PD case-

control samples, with ORs between approximately 2-3.[1-3] This might explain why association analyses of common *LRRK2* variants have produced more consistent results in Asians than in populations of European origin.

We detected evidence of two independent association signals in the study, one in the upstream region of the gene (tagged by rs10878226) and the other further downstream (tagged by rs11176013). Previous GWAS have not directly addressed the possibility of multiple distinct association signals within *LRRK2*. However, the strongest signal from the largest individual studies and meta-analyses published to date has come from the 5′ end of the gene. A web-based PD GWAS of 3,426 cases and 29,624 controls showed an association peak at a SNP located in intron 5 of *LRRK2* (rs10878246; $p=2.79 \times 10^{-6}$).[12] In two partially overlapping PD GWAS meta-analyses the *LRRK2* marker with the lowest *p*-value was rs1491942 which lies within intron 2 ($p=3.23 \times 10^{-8}$ and $p=6.44 \times 10^{-15}$, respectively). [14,15] The top SNPs from these studies were moderately correlated with rs10878226 (rs1491942, $r^2=0.51$; rs10878246, $r^2=0.44$) and thus all three SNPs might tag the same underlying functional variant(s).

An analysis of 121 *LRRK2* exonic variants in 6995 white PD patients and 5595 controls recently validated a protective haplotype comprised of three highly correlated variants (N551K-R1398H-K1423K) that was first identified in Asians.[1,20] We genotyped two of these SNPs (N551K and K1423K) in Tier 1 but neither showed significant association with PD ($p=0.52$ and $p=0.74$, respectively). Conversely, rs11176013 which tagged the downstream signal in our sample was not observed to associate with PD in the aforementioned study (OR, 1.02; CI, 0.94-1.11). The reason for discordance between studies is not clear, but potential explanations include insufficient power, effects of unrecognized population structure, and population-specific environmental interactions.

In Asians, there is evidence to suggest that at least two PD-associated SNPs directly modify Lrrk2 function and are in fact “true” risk variants. For example, G2385R and R1628P have both been shown to alter kinase activity in dopaminergic cell lines.[1] However, the identity of the risk variants responsible for the association signal at *LRRK2* in populations of European origin is not yet known. In our dataset, inspection of the bins tagged by rs10878226 and rs11176013 revealed no obvious candidate functional SNPs. The former contained a total of five SNPs, two in the upstream region (1-2 kb from the transcription start site) and three in intron 2. Neither of the upstream SNPs occurred within a transcription factor binding site as predicted by TF-SEARCH (http://www.cbrc.jp/research/db/TFSEARCH.html). The latter contained a total of 32 SNPs, two synonymous substitutions (K1637K and G1819G) and 30 intronic variants, and none of these occurred near intron-exon boundaries. Though one or more of these SNPs might still affect *LRRK2* expression or splicing, it is also possible that the risk variants in question reside in other bins or were not adequately captured by the tagging SNP set used in this study. Additional fine-mapping combined with functional assays will be necessary to address this issue in the future.

Our findings add to a growing body of evidence indicating that common variants in the *LRRK2* gene convey risk for PD in individuals of European origin. This suggests that in such populations, *LRRK2* is both a “causal” gene harboring infrequent mutations that result in autosomal dominant PD and a susceptibility gene in which polymorphisms exert a modest influence on disease risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Jaione Irigoyen, Sydney Thomas, and Sara Kath for assistance with subject recruitment, Elena Lorenzo, Elena Alonso, Ana Corao, Sarah Waldherr, and Haley Huston for technical support, and Dr. Kathy Montine for editorial assistance.

Funding sources for study: This work was supported by grants from the Department of Veterans Affairs (1I01BX000531), National Institutes of Health (P50 NS062684, P50 NS053488, P50 NS038367, P42ES004696, P30ES007033, and R01 NS065070), University of Washington (Royalty Research Fund), Spanish Ministry of Science and Innovation (SAF2006-10126: 2006- 2009 and SAF2010-22329-C02-01: 2011-2013), Fondo de Investigacion Sanitaria (FIS, PI1100228, PFIS, FI 11/00259, IFIMAV, WLA 04/11), Spanish Ministry of Science and Technology, European Social Fund, and the Asociación Parkinson Asturias.

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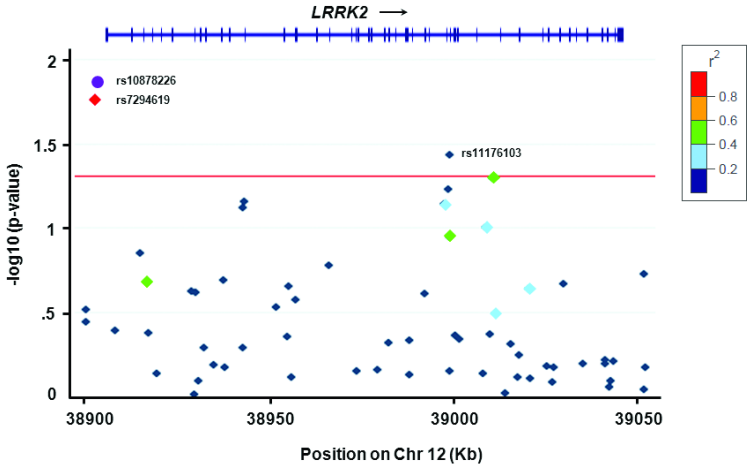

Figure 1.

Association plot of the 65 *LRRK2* SNPs successfully genotyped in Tier 1. The Y-axis denotes the association test result as -log(*p* value). The horizontal red line denotes the threshold for significance in Tier 1. The most significant SNP (rs10878226) is denoted by a circle. Color coding represents r^2 values between each SNP and rs10878226.

Table 1

LRRK2 SNPs associated with Parkinson's disease in Tiers 1 and 2

	Tier 1			Tier 2			Combined[c]	
SNP	MAF (case/control)	OR (95% CI)	*P*-value	MAF (case/control)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
rs10878226	0.15/0.12	1.34 (1.06-1.69)	0.014	0.13/0.11	1.17 (1.04-1.32)	0.007	1.20 (1.08-1.33)	6.3×10^{-4}
rs7294619[a]	0.15/0.12	1.32 (1.05-1.67)	0.017	--	--	--	--	--
rs11176013[b]	0.41/0.46	0.84 (0.72-0.99)	0.037	0.46/0.48	0.90 (0.84-0.97)	0.009	0.89 (0.83-0.95)	4.6×10^{-4}

CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism

[a] This SNP is highly correlated with rs10878226 (r^2=0.98) and therefore was not genotyped in Tier 2

[b] In Tier 2, rs10878371 was substituted as a proxy SNP (r^2=1)

[c] Meta-analysis combining Tier 1 and Tier 2. No significant heterogeneity was observed for any of the SNPs (Higgins $I^2 \leq 3\%$)

Mov Disord. Author manuscript; available in PMC 2013 December 01.