Penetrance of Parkinson's disease in *LRRK2* p.G2019S carriers is modified by a polygenic risk score

Hirotaka Iwaki MD[1,2], Cornelis Blauwendraat PhD[1], Mary B. Makarious BSc [1], Sara Bandrés-Ciga PhD[1], Hampton L. Leonard MS[1], J. Raphael Gibbs PhD[1], Dena G. Hernandez PhD[1], Sonia W. Scholz MD[1], Faraz Faghri MS[1], International Parkinson's Disease Genomics Consortium (IPDGC), Mike A. Nalls Ph.D[1,2], Andrew B. Singleton Ph.D[1]

1) Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA
2) Data Tecnica International, Glen Echo, MD, USA

Corresponding author

Andrew B. Singleton, Ph.D.

Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health

35 Convent Drive, Bethesda, MD, USA 20892

Phone Number: 301-435-7606

Fax Number: 301-451-7295

Word count

Running title

PRS for penetrance of PD with LRRK2 p.G2019S

Keywords

LRRK2; G2019S; Parkinson's disease; Polygenic risk score; Genetics

Financial Disclosure

Hirotaka Iwaki: Grants, Michael J Fox Foundation, Mike A. Nalls: Consultancies, Lysosomal Therapies Inc., Vivid Genomics Inc., Kleiner Perkins Caufield & Byers, Neuron23, Inc., Michael J. Fox Foundation

Abstract

Background: While the LRRK2 p.G2019S mutation has been demonstrated to be a strong risk factor for Parkinson's Disease (PD), factors that contribute to penetrance among carriers, other than aging, have not been well identified.

Objectives: To evaluate whether a cumulative genetic risk identified in the recent genome-wide study is associated with penetrance of PD among p.G2019S mutation carriers.

Methods: We included p.G2019S heterozygote carriers with European ancestry in three genetic cohorts in which the mutation carriers with and without PD were selectively recruited. We also included the carriers from two datasets: one from a case-control setting without selection of mutation carriers, and the other from a population sampling. The associations between PRS constructed from 89 variants reported in Nalls et al. and PD were tested and meta-analyzed. We also explored the interaction of age and PRS.

Results: After excluding 8 homozygotes, 833 p.G2019S heterozygote carriers (439 PD and 394 unaffected) were analyzed. PRS was associated with a higher penetrance of PD (OR 1.34, 95% C.I. [1.09, 1.64] per +1 SD, P = 0.005). In addition, associations with PRS and penetrance were stronger in the younger participants (main effect: OR 1.28 [1.04, 1.58] per +1 SD, P = 0.022; interaction effect: OR 0.78 [0.64, 0.94] per +1 SD and +10 years of age, P = 0.008).

Conclusions: Our results suggest that there is a genetic contribution for penetrance of PD among p.G2019S carriers. These results have important etiologic consequences and potential impact on the selection of subjects for clinical trials.

Introduction

Parkinson's disease (PD) is a complex genetic disorder, where rare and highly damaging variants as well as common risk variants play a role in its etiology.[1] The *LRRK2* p.G2019S (rs34637584) mutation is one of the major known contributors to PD.[2,3] The p.G2019S mutation has an estimated prevalence of approximately 1% in the PD population of European ancestry, with much higher frequencies being reported for North African Berber Arab populations and European subpopulations with high Ashkenazi Jewish ancestry.[4–7] The p.G2019S mutation is not fully penetrant, with risk of PD for carriers increasing with age. At age 80 years, 25% to 42.5%

of carriers will have PD.[7,8] Critical question that remain centers on what the determinants of p.G2019S penetrance are. Previously, it has been reported that a variant in *DNM3*, encoding the vesicular transport protein dynamin 3, is a potential *LRRK2* p.G2019S age-at-onset modifier, lowering the age at onset by approximately 8 years.[9] However, other reports have not replicated this finding and instead nominated variants in *SNCA* as modifiers of *LRRK2* mutation penetrance.[10] The underlying pathogenic mechanism of *LRRK2*-linked PD is currently unknown, but a great deal of focus has been placed on the ability of the p.G2019S mutation to increase LRRK2 kinase activity, especially since loss-of-function mutations do not seem to be contributing to disease.[11,12]

In the last several years, genome-wide association studies (GWAS) have identified an ever-increasing number of risk loci for PD. Individually, each of these loci confers modest effects on risk for disease. Polygenic risk score (PRS) represents known cumulative genetic risk across these loci in each assayed individual. PRS reveals that, collectively, these risk variants confer considerable risk for disease, with those in the top decile of genetic risk being sixfold more likely to have PD than those in the lowest decile of genetic risk in the European population.[1] PRS is also highly correlated with age at onset of PD,[13,14] and is associated with penetrance of damaging *GBA* variants.[15] Here, we investigate the influence of the latest PD PRS on age at onset and penetrance of PD in p.G2019S carriers using several large cohorts.

Methods

Whole genome sequencing

Genetics and clinical data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). (For up-to-date information on the PPMI study, visit www.ppmi-info.org.) In this study, we included three genetic cohorts: Parkinson's Progression Markers Initiative Genetic Cohort (PPMI_GC), Parkinson's Progression Markers Initiative Genetic Registry (PPMI_GR), and the LRRK2 Consortium Cohort (LCC), hereafter collectively named the *Genetic Cohort Dataset*. These cohorts selectively included people with specific high-risk genetic variants, such as carrying p.G2019S, for both cases and unaffected individuals. Whole genome sequencing (WGS) data was generated at the Laboratory of Neurogenetics (LNG) at the National Institutes of Health, and detailed methods are available from the study website. After downloading, subsequent genotypes

were filtered to exclude minor allele frequency of less than 0.01, missing rate more than 5%, and the test for Hardy–Weinberg equilibrium threshold of 1.0E-4 in controls. Following quality control, 185 carriers of p.G2019S (PD/Non-PD = 88/97) in PPMI_GC, 75 (38/37) in PPMI_GR, and 175 (107/68) in LCC were included in the analysis. Among them, 7 individuals (3 in PPMI_GC, 3 in PPMI_GR, and 1 in LCC, all cases) were homozygotes.

Genotype data from the International Parkinson Disease Genomics Consortium

Aggregated genotype data was obtained from the International Parkinson Disease Genomics Consortium (IPDGC), as previously described.[1] In brief, genotypes were processed using standard pipelines and imputed using the HRC imputation panel r1.1 2016[16] via the Michigan imputation server under the default setting with phasing using the EAGLE option.[17] Genotypes were filtered for imputation quality $R^2 > 0.8$. Following quality control criteria similar to that applied to the Genetic Cohort Dataset, a total of 227 carriers were included in the analysis, of which 208 were PD cases and 19 were controls. Among them, one PD patient was homozygous. For composing PRS, we used a threshold of $R^2 > 0.3$ to obtain dosages of more risk-associated alleles because only 64 variants were passed with the cutoff of 0.8 in R^2.

UK Biobank data

The United Kingdom (UK) Biobank (UKBB) is a large, long-term biobank study in the UK that includes genetic data and a wide range of phenotypes of approximately 500,000 individuals.[18] PD case-control status was based on multiple field codes, including 41202, 41204, 40002, and 20002. *LRRK2* p.G2019S was directly genotyped in the UK Biobank cohort (rs34637584, n = 314), and the concordance rate in the whole-exome sequencing data[19] was 100%. After applying the same quality control steps as above, 179 carriers were identified, of which 6 were reported to be PD cases; all were heterozygotes.

Polygenic risk score calculation

PRS was calculated incorporating the risk loci previously associated with PD.[1] In the calculation of PRS, risk allele dosages were summed with weights as their published beta estimates, giving greater weight to alleles with higher estimates. Then, PRS were standardized to each cohort level. For the UKBB and IPDGC imputed genotype data, not all 89 variants were available due

to lower imputation scores (R^2 > 0.8 for UKBB and R^2 > 0.3 for IPDGC); therefore, 88 variants in UKBB and a median of 89 variants (range: 82–89) in IPDGC were used.

Statistical analysis

Our primary analysis was to test the association between PRS and PD odds using a fixed effect meta-analysis model among the mutation carriers. First, a logistic regression model was applied for the main effect of PRS for the Genetic Cohort Dataset (PPMI_GC/PPMI_GR/LRRK2), IPDGC dataset, and UKBB dataset separately. The data were adjusted for age, sex, cohort, and PCs representing population structure. Across all datasets, the linear age upon recruitment was used for carriers without PD and the age at diagnosis for carriers with PD, whereas the age at onset was used for the IPDGC dataset and the age at recruitment for the UKBB dataset. The age data were centered—the original value subtracted by the mean age at each cohort—to accommodate square age variable in the later step. To adjust for population structure, PC1–10 were used for the Genetic Cohort Dataset and IPDGC dataset, and PC1–5 were used for the UKBB dataset because of its size.

In the secondary analysis, the interaction between age and PRS for PD odds was tested. In this analysis, we excluded the UKBB dataset because of the small number of PD cases. We meta-analyzed the dataset level ORs for the main effect and the interaction effect between age and PRS as in the similar model above, but we further adjusted for square age in the Genetic Cohort Dataset and IPDGC dataset. Square age was significantly associated with the PD odds in these two datasets; as the UKBB dataset cannot accommodate the variable because of too few PD cases, we thus could not include square age in the primary analysis.

Also, the association of PRS on age at diagnosis (Genetic Cohort Dataset) or age at onset (IPDGC dataset) for the carriers with PD was analyzed in an exploratory manner. Adjusted covariates included age, square age, sex, cohorts, and PC1–10.

There were 8 homozygotes of p.G2019S mutation in the analysis set, and we excluded them from all analyses. Analyses were conducted by using R version 3.5.1(https://cran.r-project.org/), with a significance level of 0.05 (two-sided). With the sample size here, we had 90% power for the primary analysis and 35% power for the exploratory analysis on age at onset/diagnosis, assuming that the associations were the same as in the previous report conducted in a general case-control setting in the European population.[1]

Patients Consent

Participants' information and genetic samples were obtained under appropriate written consent and with local institutional and ethical approvals for all cohorts and datasets in this study.

Results

Data overview

Table 1 is a summary of participants with and without the *LRRK2* p.G2019S mutation in the datasets under study. The IPDGC dataset consists of 14,225 cases and 16,543 controls with known *LRRK2* p.G2019S status; only 1.4% of the cases had the *LRRK2* p.G2019S mutation, and 0.11% of the controls carried the mutation. The prevalence of PD in carriers is consistent with results from a previous report of 1% of PD patients carrying the mutation.[7] Among the 362,884 participants passing filtering criteria in the UKBB, 0.049% were carriers of the *LRRK2* p.G2019S mutation. While the overall prevalence of PD in this dataset was 0.33%, 3.36% of carriers had PD, indicating an approximately 10 times higher crude risk of PD associated with the mutation. This is consistent with the crude relative risk of 13 in UKBB. In total, of 3 datasets there were 8 homozygotes reported as PD cases. They had a higher PRS and older age at diagnosis compared to heterozygous PD cases (Supplemental Table 1), although the differences were not statistically significant. Because of the small number of homozygotes, we excluded them from downstream analyses.

Genetic risk score modifies penetrance of LRRK2 p.G2019S

The unadjusted plots of PRS among cases and unaffected individuals in the Genetic Cohort Dataset showed that the mean of the PRS was higher in cases among carriers (Figure 1). The means of PRS in cases were also higher than those in controls among noncarriers in the IPDGC and UKBB datasets (Supplemental Figure 1). Meta-analysis results of the three datasets showed that a higher PRS was significantly associated with a higher odds ratio of PD (OR 1.34, 95% C.I. [1.09, 1.64] per + 1SD [per standard deviation of increase from the cohort mean, P = 0.005]; Figure 2A).

Stronger association of genetic risk score for PD penetrance in younger carriers

In the secondary analysis examining the interaction between PRS and age, the main effect of PRS as well as the interaction between PRS and age were significantly associated with the odds of PD, but in the opposite direction (main effect: OR 1.28 [1.04, 1.58] per +1 SD, P = 0.022; interaction effect: OR 0.78 [0.64, 0.94] per +1 SD and +10 years of age, P = 0.008; Figure 2B). This suggests that in the studied cohorts, the magnitude of association between PRS and PD odds were stronger when the age of the participants was younger. We added post-hoc analyses stratified by age (<55 years old, 55-65 years old and 65< years old) to illustrate the stronger association of PRS in younger age in carriers. (Figure 3). The analyses examining the main effect and interaction effect among nonmutation carriers in the IPDGC dataset showed that these effects were also significant in nonmutation carriers (the main term for +1 SD in PRS: OR 1.6, P = 2.5E-245; the interaction term of +1 SD in PRS and +10 years in age: 0.94, P = 1.4E-9). However, the magnitude of the interaction effect was smaller than that in *LRRK2* p.G2019S carriers, and the magnitudes of associations were significantly different between carriers and non-carriers in the test of homogeneity (P = 0.044).

Genetic risk score and age at onset/diagnosis in LRRK2 p.G2019S cases

Previously, we have shown that PRS is inversely correlated with age at onset in PD cases.[13] In the current study, there was insufficient evidence that PRS was significantly associated with age at onset/diagnosis of PD in *LRRK2* p.G2019S carriers. The directionality was the same as in the general population previously studied (–0.801 [–0.959, –0.643] per +1 SD in PRS), but the association did not reach significance level (Supplemental Figure 2). As mentioned in the power calculation analyses in Methods, this is an underpowered study, and therefore additional data is needed to confirm these results.

Exploratory analysis for the individual Parkinson's disease-associated variants

While the power of the study is not sufficient, the motivation for this analysis was to qualitatively assess whether any of the risk variants could be strong penetrance modifiers. The Q-Q plot for the observed and expected P in -log10 scale showed an upper deviation from the expected line (lambda value of 1.34), indicating the contribution of these variants for the PD risk

in p.G2019 LRRK2 heterozygous carriers. However, no single association stood out as a possible penetrance modifier after adjusting for multiple tests (Supplemental Figure 3). Furthermore, when the estimates for the associations of carriers and noncarriers of individual variants were compared, there were 10 variants whose tests of homogeneity were rejected at a significance level of 0.05 (Supplemental Figure 4, Supplemental Table 2). Additionally, *GBA* mutations in *LRRK2* p.G2019S carriers (Supplemental Table 3) were analyzed, but there was no clear enrichment of *GBA* mutations in cases versus controls or for younger age at onset among cases.

Discussion

The aggregated genetic risks in the form of PRS that were constructed from the recent case-control GWAS of European population was significantly associated with the risk of PD among heterozygous *LRRK2* p.G2019S mutation carriers in our study. Furthermore, the magnitude of the association was larger in the younger population, and this interaction between age and PRS was significantly larger than in noncarriers. Conversely, the age at onset or the age at diagnosis among carriers with PD was not significantly associated with PRS, likely due to the small study size rather than a truly null association. Additionally, although age at onset and age at diagnosis is highly correlated, clinical site variation and differences in assessing this could affect the analysis. Therefore, more data are required to conclusively determine this point.

When we investigated specific variants of interest for PD, such as *GBA* coding variants and PD GWAS variants, no significant differences were identified, although relatively small numbers of *GBA* coding variants did not seem to affect *LRRK2* penetrance, which is in line with previous results.[20] The effect size of 10 PD GWAS variants were heterogeneous between p.G2019S carriers and noncarriers at an unadjusted significance level of 0.05. We need more data to formally assess these different associations for PD between carriers and noncarriers, but genes in these loci are good candidates as potential interactors. Interestingly, rs823118 has a larger effect size and is a locus that harbors an *RAB7L1*, which is a *LRRK2* interactor.[21] Also the effect size of rs1293298 (*CTSB* locus) is opposite compared to general PD, where the rs1293298 locus was recently shown to be a potential genetic modifier of *GBA*-associated PD.[15]

The primary limitation of this study is the size, despite including several large cohorts. *LRRK2* p.G2019S is rare in the general population, and therefore actively recruiting carriers would be a good strategy to increase power for studies such as ours. To investigate the penetrance of

carriers, recruitment only focusing on carriers are very effective, as shown in Table 1. More initiatives and future collaboration with clinical trials only targeting *LRRK2* p.G2019S mutations are warranted. Currently, there are at least three clinical trials targeting *LRRK2*-linked PD: two use kinase inhibition, and the third focuses on reducing the protein load. As these trials move forward, important considerations are whether the disease mechanisms that cause *LRRK2*-linked PD are generalizable to typical PD, and whether it is possible to identify which *LRRK2* mutation carriers will or will not express disease. Previously, we have shown that active randomization on genetic components of PD is important for successful clinical trials because unbalanced genetic risk may lead to the heterogeneity of intervention arms and lower the power of that trial.[22] Our results suggest that actively balancing PRS is similarly important for a disease modifying/preventing trial targeting p.G2019S carriers.

Taken together, we show that penetrance and likely age at onset of *LRRK2* is modified by PD PRS, implying a clear genetic influence.

Acknowledgements

We would like to thank all of the subjects who donated their time and biological samples to be a part of this study. We also would like to thank all members of the International Parkinson Disease Genomics Consortium (IPDGC). See for a complete overview of members, acknowledgements and funding http://pdgenetics.org/partners. This work was supported in part by the Intramural Research Program of the National Institute on Aging, National Institutes of Health, Department of Health and Human Services; project ZO1 AG000949.

Data used in preparation of this article were obtained from the MJFF sponsored LCC and PPMI database (www.ppmi-info.org/data). For up to date information on these studies, visit www.michaeljfox.org/lcc and www.ppmi-info.org. PPMI – a public-private partnership – is funded by The Michael J. Fox Foundation for Parkinson's Research and funding partners, including AbbVie, Allergan, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers Squibb, Celgene, Denali Incorporated, GE Healthcare, Genentech, GlaxoSmithKline, Eli Lilly and Company, Lundbeck, Merck & Co., Meso Scale Discovery, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier Laboratories, Takeda, Teva, UCB, Verily, Voyager Therapeutics, and Golub Capital (www.ppmi-info.org/fundingpartners). LCC is

coordinated and funded by The Michael J. Fox Foundation for Parkinson's research. The investigators within the LCC contributed to the design and implementation of the LCC and/or provided data and/or collected biospecimens, but did not necessarily participate in the analysis or writing of this report. The full list of LCC investigators can be found at www.michaeljfox.org/lccinvestigators.

Appendix

Supplemental Figure 1. PRS of case and control in IPDGC and UKBB

Supplemental Figure 2. Age at onset/diagnosis and the PRS

Supplemental Figure 3. The QQ plot for the population risk variants.

Supplemental Figure 4. Population risk variants whose effect sizes are heterogeneous between carriers and non-carriers

Supplemental Table 1. Homozygous carriers of LRRK2 p.G2019S

Supplemental Table 2. Variants whose effect on the risk are homogeneous between carriers and non-carriers

Supplemental Table 3 Contingency Table for GBA protein coding variants in LRRK2 p.G2019S carriers

IPDGC collaborator's list

Authors' Role

1) Research project

1A. Conception: CB, IPDGC, AS

1B. Organization: HI, CB, IPDGC

1C. Execution;HI, CB, IPDGC

2) Statistical Analysis

2A. Design: HI, CB

2B. Execution:HI, CB

2C. Review and Critique: All

3) Manuscript:

3A. Writing of the first draft: HI, CB,

3B. Review and Critique: All

Financial Disclosure

Hirotaka Iwaki: Grants, Michael J Fox Foundation, Mike A. Nalls: Consultancies, Lysosomal Therapies Inc., Vivid Genomics Inc., Kleiner Perkins Caufield & Byers, Neuron23, Inc., Michael J. Fox Foundation

References

1. Nalls MA, Blauwendraat C, Vallerga CL, et al. Expanding Parkinson's disease genetics: novel risk loci, genomic context, causal insights and heritable risk. bioRxiv. Epub 2019.
2. Nichols WC, Pankratz N, Hernandez D, et al. Genetic screening for a single common LRRK2 mutation in familial Parkinson's disease. Lancet. 2005;365:410–412.
3. Gilks WP, Abou-Sleiman PM, Gandhi S, et al. A common LRRK2 mutation in idiopathic Parkinson's disease. Lancet. 2005;365:415–416.
4. Bras JM, Guerreiro RJ, Ribeiro MH, et al. G2019S dardarin substitution is a common cause of Parkinson's disease in a Portuguese cohort. Mov Disord. 2005;20:1653–1655.
5. Ozelius LJ, Senthil G, Saunders-Pullman R, et al. LRRK2 G2019S as a Cause of Parkinson's Disease in Ashkenazi Jews. N Engl J Med. 2006;354:424–425.
6. Lesage S, Dürr A, Tazir M, et al. LRRK2 G2019S as a Cause of Parkinson's Disease in North African Arabs. N Engl J Med. 2006;354:422–423.
7. Healy DG, Falchi M, O'Sullivan SS, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 2008;7:583–590.
8. Lee AJ, Wang Y, Alcalay RN, et al. Penetrance estimate of LRRK2 p.G2019S mutation in individuals of non-Ashkenazi Jewish ancestry. Mov Disord. 2017;32:1432–1438.
9. Trinh J, Gustavsson EK, Vilariño-Güell C, et al. DNM3 and genetic modifiers of age of onset in LRRK2 Gly2019Ser parkinsonism: a genome-wide linkage and association study. Lancet Neurol. 2016;15:1248–1256.
10. Fernández-Santiago R, Garrido A, Infante J, et al. α-synuclein (SNCA) but not dynamin 3 (DNM3) influences age at onset of leucine-rich repeat kinase 2 (LRRK2) Parkinson's disease in Spain. Mov Disord. 2018;33:637–641.

11. Blauwendraat C, Reed X, Kia DA, et al. Frequency of Loss of Function Variants in LRRK2 in Parkinson Disease. JAMA Neurol. 2018;75:1416.
12. Whiffin N, Armean M I, Kleinman A, et al. Human loss-of-function variants suggest that partial LRRK2 inhibition is a safe therapeutic strategy for Parkinsons disease. bioRxiv. Epub 2019.:1–34.
13. Blauwendraat C, Heilbron K, Vallerga CL, Bandres-Ciga S, Coelln R von, Pihlstrøm L. Parkinson disease age at onset GWAS: defining heritability, genetic loci and α-synuclein mechanisms. Mov Disord. 2019;in press.
14. Nalls MA, Escott-Price V, Williams NM, et al. Genetic risk and age in Parkinson's disease: Continuum not stratum. Mov Disord. 2015;30:850–854.
15. Blauwendraat C, Reed X, Nalls M, Krohn L, Heilbron K. Genetic modifiers of risk and age at onset in GBA positive Parkinson's disease and Lewy body dementia. preprint. Epub 2019.
16. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet. 2016;48:1279–1283.
17. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. Nat Genet. 2016;48:1284–1287.
18. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562:203–209.
19. Van Hout V C, Ioanna T, Beckman D J, et al. Whole Exome Sequencing and Characterization of Coding Variation in 49,960 Individuals in the UK Biobank. bioRxiv. Epub 2019.
20. Yahalom G, Greenbaum L, Israeli-Korn S, et al. Carriers of both GBA and LRRK2 mutations, compared to carriers of either, in Parkinson's disease: Risk estimates and genotype-phenotype correlations. Parkinsonism Relat Disord. 2019;62:179–184.
21. Beilina A, Rudenko IN, Kaganovich A, et al. Unbiased screen for interactors of leucine-rich repeat kinase 2 supports a common pathway for sporadic and familial Parkinson disease. Proc Natl Acad Sci. 2014;111:2626–2631.
22. Leonard H, Blauwendraat C, Krohn L, et al. Genetic variability and potential effects on clinical trial outcomes: perspectives in Parkinson's disease. bioRxiv 2018.

Figures

Figure 1: PRS of cases and controls in genetic cohorts

Legend: The means of PRS in cases were higher than unaffected among LRRK2 p.G2019S mutation carriers. LCC, LRRK2 Consortium Cohort; PPMI_GC, Parkinson's Progression Markers Initiative Genetic Cohort; PPMI_GR, Parkinson's Progression Markers Initiative Genetic Registry.

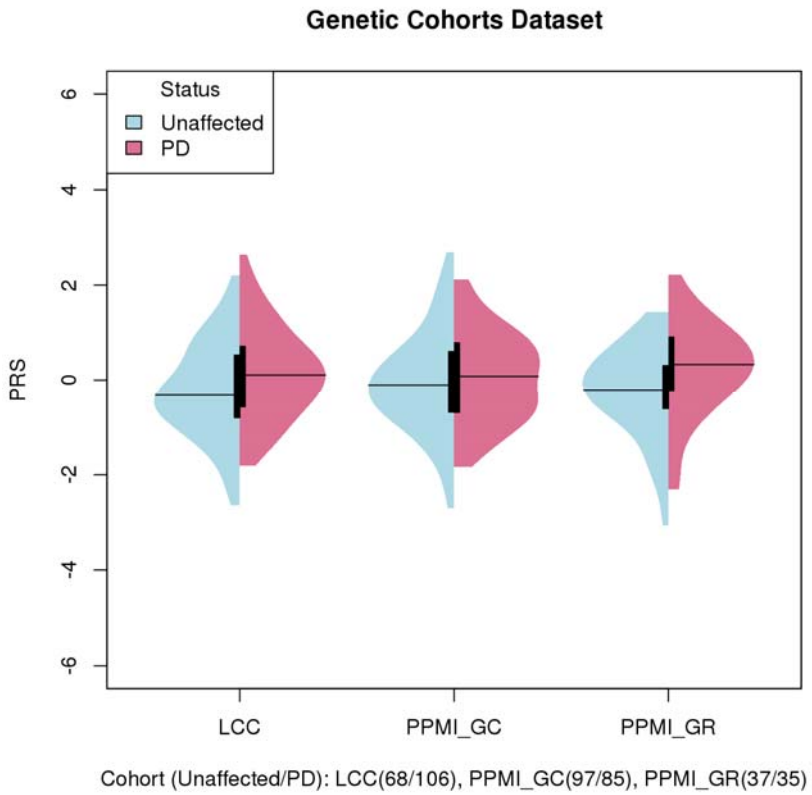


Figure 2: Meta-analysis for PRS, and its interaction with age on penetrance

Legend:

A. Primary analysis of testing the association between PRS and PD showed that PRS was significantly associated with the PD odds.
B. Secondary analysis model with PRS and the interaction between PRS and age showed that the main effect of PRS as well as the interaction between PRS and age were significantly associated with the odds of PD, but in the opposite direction. Compared to

the interaction effect among non-carriers in IPDGC, the magnitude of the interaction among the mutation carriers was large.

OR, Odds ratio; I_sq, I square (%); Q-test, P-value for the test of Heterogeneity; IPDGC, International Parkinson Disease Genomics Consortium. Odds ratio were adjusted for study, age, square age, sex and PC1-10

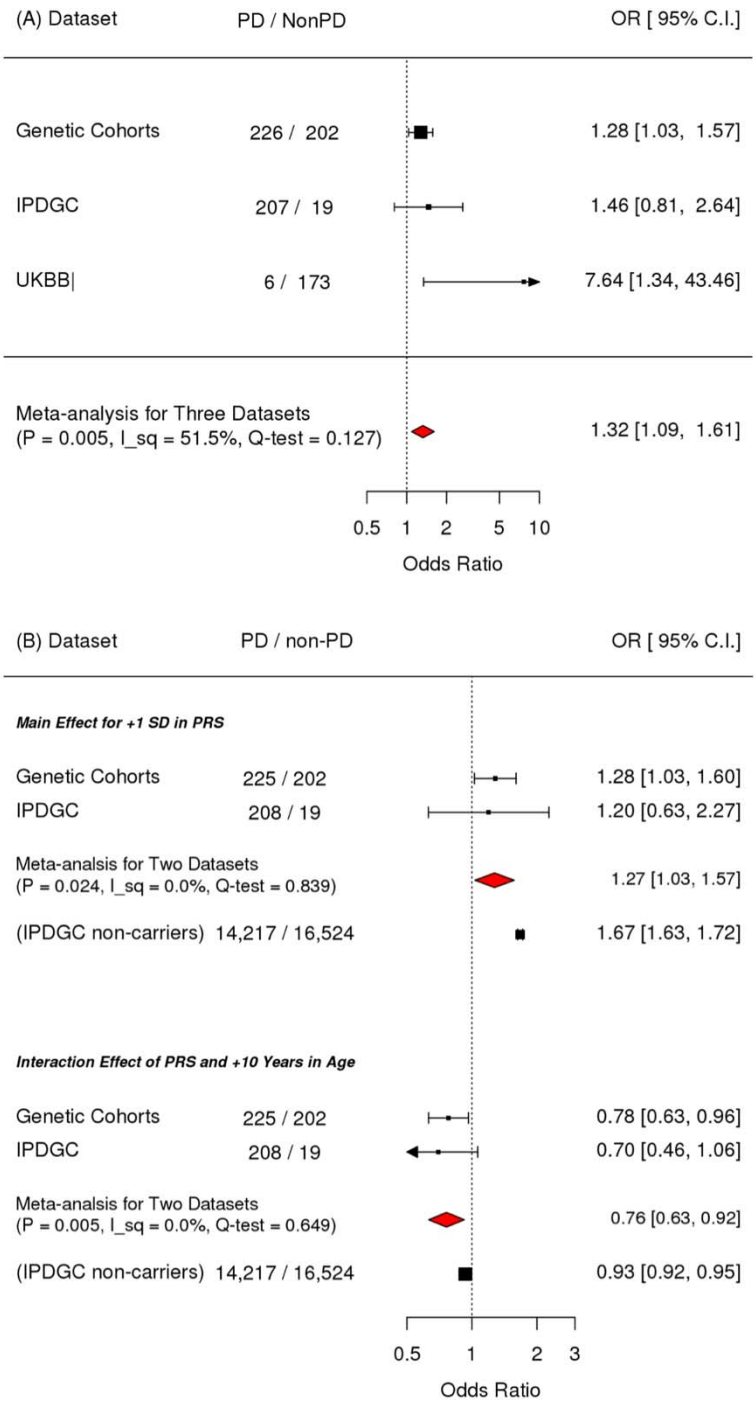
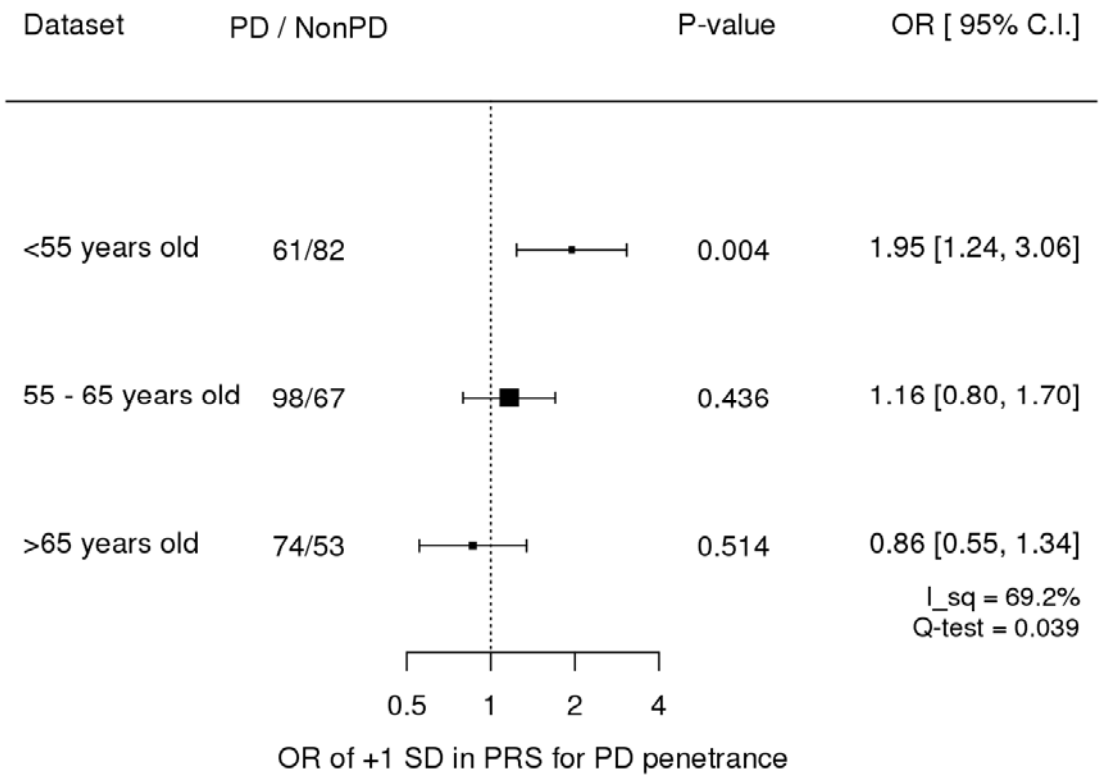


Figure 3: Age stratified associations of PRS on penetrance in Genetics Cohorts Dataset

Legend: Age stratified analysis showed that PRS was significantly associated with the younger age. OR, Odds ratio; I_sq, I square (%); Q-test, P-value for the test of Heterogeneity. Odds ratio were adjusted for study, age, square age, sex and PC1-10



Tables

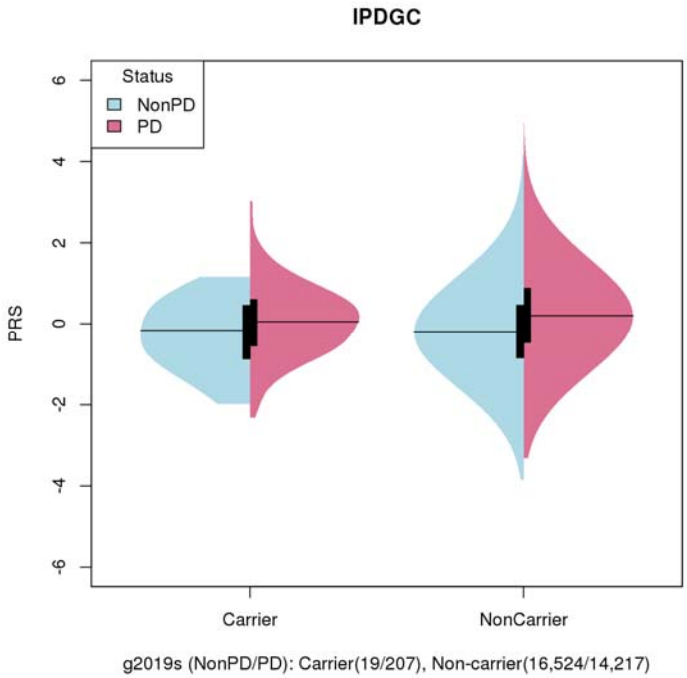
Table1: Overview of data.

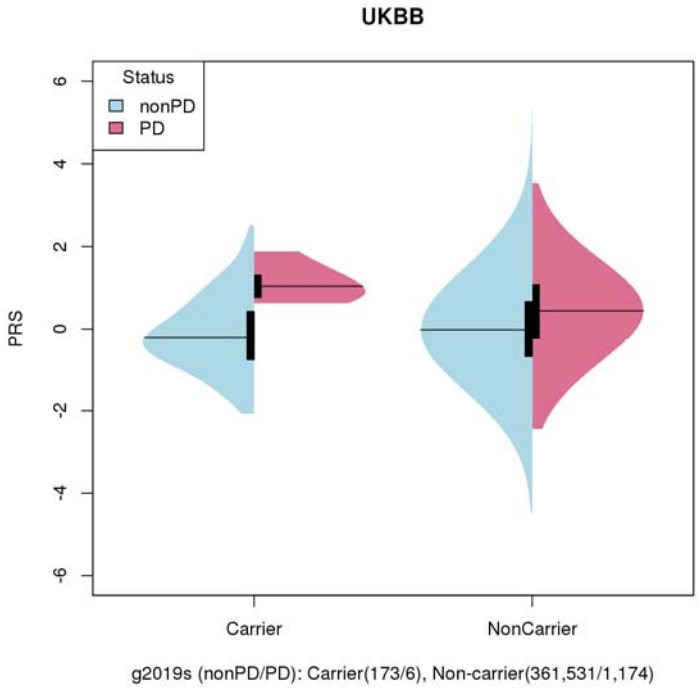
	p.G2019S carriers (N of Homozygotes)		p.G2019S noncarriers		
Datasets and Cohorts	**Unaffected**	**PD**	**Control**	**PD**	**TOTAL**
Genetic Cohort Dataset (WGS)					
PPMI Genetic Cohort (PPMI_GC)	97 (0)	88 (3)	-	-	185
PPMI Genetic Registry (PPMI_GR)	37 (0)	38 (3)	-	-	75
LRRK2 Consortium Cohort (LCC)	68 (0)	107 (1)	-	-	175
General Case/Control cohort (genotyped)					
IPDGC (11 cohorts)	19 (0)	208 (1)	16,524	14,217	30,968
General population cohort (genotyped)					
UK Biobank	173 (0)	6 (0)	361,531	1,174	362,884
TOTAL	394 (0)	447 (8)	378,055	15,391	394,287

IPDGC, International Parkinson Disease Genomics Consortium

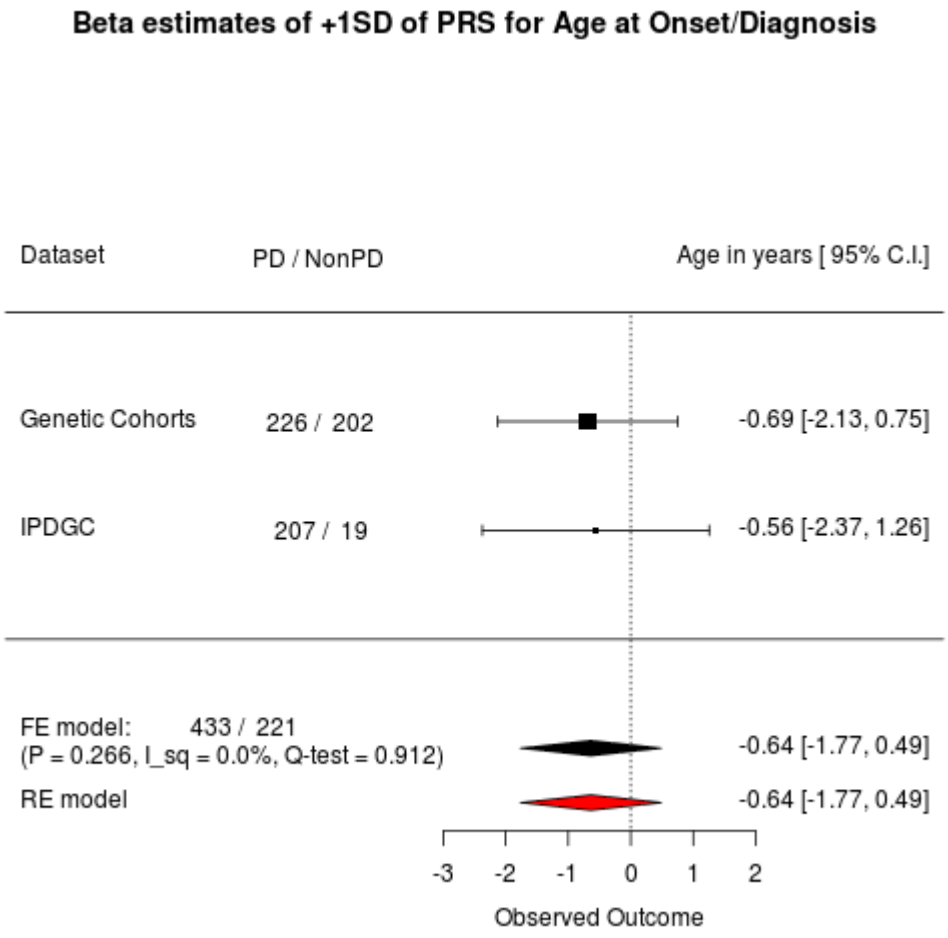
Appendix for "LRRK2 penetrance is modified by Parkinson disease genetic risk score"

Supplemental Figure 1: PRS of case and control in IPDGC and UKBB

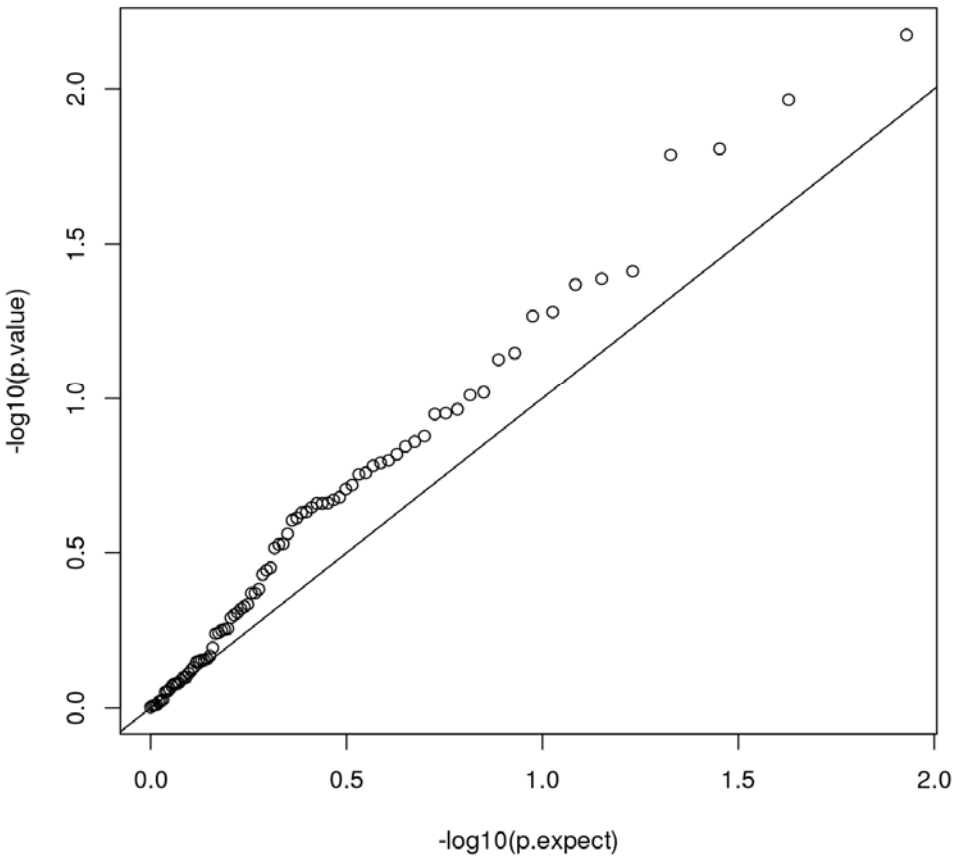




Supplemental Figure 2 Age at onset/diagnosis and the PRS

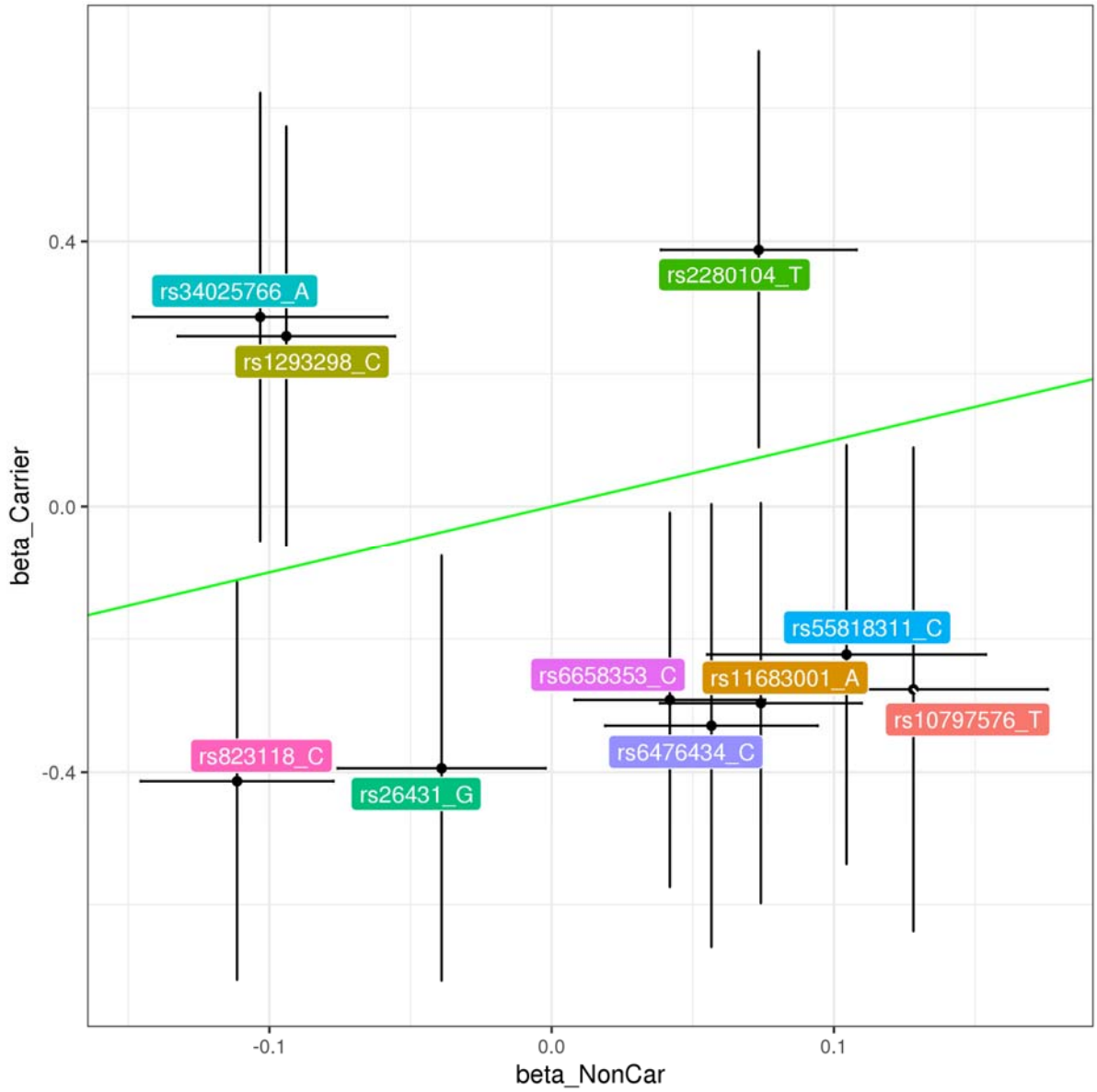


Supplemental Figure 3. The QQ plot for the population risk variants.



Black line: The expected line of plots under null. The upper deviation from the line indicates the heritability by the population risk variants in the LRRK2 carriers.

Supplemental Figure 4. Population risk variants whose effect sizes are heterogeneous between carriers and non-carriers



Green line: expected line, Error bar: 95% C.I.

Supplemental Table 1. Homozygous carriers of LRRK2 p.G2019S

	Genetic Cohort Datasets	IPDGC
n	7	1
Case	7	1
Female	4	0
Age at diagnosis /onset(IPDGC)	65.68 (2.98)	61.00 (NA)
PRS (mean (SD))	0.36 (1.17)	-1.17 (NA)

Supplemental Table 2. Variants whose effect on the risk are homogeneous between carriers and non-carriers

			Carrier		Non Carrier		Nearest Gene	Nearest QTL
SNP_A1	A1_freq	QEp	Beta	SE	Beta	SE		
rs11683001_A	0.33	0.017	-0.296	0.154	0.074	0.018	MAP4K4	MAP4K4
rs6658353_C	0.50	0.021	-0.291	0.144	0.042	0.017	FCGR2A	FCGR2A
rs6476434_C	0.27	0.024	-0.330	0.170	0.057	0.019	UBAP2	PRSS3
rs34025766_A	0.16	0.025	0.285	0.172	-0.103	0.023	LCORL	DCAF16
rs26431_G	0.30	0.030	-0.394	0.163	-0.039	0.019	PAM	PAM
rs1293298_C	0.26	0.031	0.256	0.161	-0.094	0.020	CTSB	CTSB
rs10797576_T	0.14	0.031	-0.276	0.186	0.128	0.024	SIPA1L2	-
rs2280104_T	0.37	0.040	0.387	0.152	0.073	0.018	BIN3	BIN3
rs55818311_C	0.32	0.044	-0.223	0.161	0.104	0.025	SPPL2B	-
rs823118_C	0.42	0.049	-0.413	0.152	-0.111	0.017	NUCKS1	NUCKS1

Supplemental Table 3 Contingency Table for *GBA* protein coding variants in *LRRK2* p.G2019S carriers

	Genetic Cohorts		IPDGC	
	Unaffected	PD	Unaffected	PD
N	202	226	19	207
p.N370S				
Heterozygotes (%)	8 (4.0)	9 (4.0)	1 (5.9)	9 (4.7)
Homozygotes (%)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
p.T408M, Heterozygotes (%)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
p.E326K, Heterozygotes (%)	4 (2.0)	5 (2.2)	0 (0.0)	5 (2.4)

IDPGC collaborators' list

United Kingdom: Alastair J Noyce (Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, QMUL, London, UK and Department of Molecular Neuroscience, UCL, London, UK), Rauan Kaiyrzhanov (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Ben Middlehurst (Institute of Translational Medicine, University of Liverpool, Liverpool, UK), Demis A Kia (UCL Genetics Institute; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Manuela Tan (Department of Clinical Neuroscience, University College London, London, UK), Henry Houlden (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Huw R Morris (Department of Clinical Neuroscience, University College London, London, UK), Helene Plun-Favreau (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Peter Holmans (Biostatistics & Bioinformatics Unit, Institute of Psychological Medicine and Clinical Neuroscience, MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff, UK), John Hardy (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Daniah Trabzuni (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK; Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, 11211 Saudi Arabia), John Quinn (Institute of Translational Medicine, University of Liverpool, Liverpool, UK), Vivien Bubb (Institute of Translational Medicine, University of Liverpool, Liverpool, UK), Kin Y Mok (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Kerri J. Kinghorn (Institute of Healthy Ageing, University College London, London, UK), Nicholas W Wood (UCL Genetics Institute; and Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Patrick Lewis (University of Reading, Reading, UK), Sebastian Schreglmann (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Ruth Lovering (University College London, London, UK), Lea R'Bibo (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Claudia Manzoni (University of Reading, Reading, UK), Mie Rizig (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Mina Ryten (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Sebastian Guelfi (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Valentina Escott-Price (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK), Viorica Chelban (Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Thomas Foltynie (UCL Institute of Neurology, London, UK), Nigel Williams (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff, UK), Karen E. Morrison (Faculty of Medicine, University of Southampton, UK), Carl Clarke (University of Birmingham, Birmingham, UK and Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK).

France: Alexis Brice (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Fabrice Danjou (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Suzanne Lesage (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Jean-Christophe Corvol (Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS, UMR 7225, Sorbonne Universités, UPMC University Paris 06, UMR S 1127, Centre d'Investigation Clinique Pitié Neurosciences CIC-1422, AP-HP, Pitié-Salpêtrière Hospital, Paris, France), Maria Martinez (INSERM UMR 1220; and Paul Sabatier University, Toulouse, France),

Germany: Claudia Schulte (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Kathrin Brockmann (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Javier Simón-Sánchez (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany), Peter Heutink (DZNE, German Center for Neurodegenerative Diseases and Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany), Patrizia Rizzu (DZNE, German Center for Neurodegenerative Diseases), Manu Sharma (Centre for Genetic Epidemiology, Institute for

Clinical Epidemiology and Applied Biometry, University of Tubingen, Germany), Thomas Gasser (Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, and DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany),

United States of America: Mark R Cookson (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA), Sara Bandres-Ciga (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Cornelis Blauwendraat (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), David W. Craig (Department of Translational Genomics, Keck School of Medicine, University of Southern California, Los Angeles, USA), Kimberley Billingsley (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Derek Narendra (Inherited Movement Disorders Unit, National pInstitute of Neurological Disorders and Stroke, Bethesda, MD, USA), Faraz Faghri (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA; Department of Computer Science, University of Illinois at Urbana-Champaign, Urbana, IL, USA), J Raphael Gibbs (Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA), Dena G. Hernandez (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Kendall Van Keuren-Jensen (Neurogenomics Division, TGen, Phoenix, AZ USA), Joshua M. Shulman (Departments of Neurology, Neuroscience, and Molecular & Human Genetics, Baylor College of Medicine, Houston, Texas, USA; Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, Texas, USA), Hirotaka Iwaki (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Hampton L. Leonard (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Mike A. Nalls (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, USA; CEO/Consultant Data Tecnica International, Glen Echo, MD, USA), Laurie Robak (Baylor College of Medicine, Houston, Texas, USA), Jose Bras (Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan, USA), Rita Guerreiro (Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan, USA), Steven Lubbe (Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA), Steven Finkbeiner (Departments of Neurology and Physiology, University of California, San Francisco; Gladstone Institute of Neurological Disease; Taube/Koret Center for Neurodegenerative Disease Research, San Francisco, CA, USA), Niccolo E. Mencacci (Northwestern University Feinberg School of Medicine, Chicago, IL, USA), Codrin Lungu (National Institutes of Health Division of Clinical Research, NINDS, National Institutes of Health, Bethesda, MD, USA), Andrew B Singleton (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA), Sonja W. Scholz (Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA), Xylena Reed (Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA). Roy N. Alcalay (Department of Neurology, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, USA, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, USA)

Canada: Ziv Gan-Or (Montreal Neurological Institute and Hospital, Department of Neurology & Neurosurgery, Department of Human Genetics, McGill University, Montréal, QC, H3A 0G4, Canada), Guy A. Rouleau (Montreal Neurological Institute and Hospital, Department of Neurology & Neurosurgery, Department of Human Genetics, McGill University, Montréal, QC, H3A 0G4, Canada), Lynne Krohn (Montreal Neurological Institute and Hospital, Department of Neurology & Neurosurgery, Department of Human Genetics, McGill University, Montréal, QC, H3A 0G4, Canada),

The Netherlands: Jacobus J van Hilten (Department of Neurology, Leiden University Medical Center, Leiden, Netherlands), Johan Marinus (Department of Neurology, Leiden University Medical Center, Leiden, Netherlands)

Spain: Astrid D. Adarmes-Gómez (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Miquel Aguilar (Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mutua de Terrassa, Terrassa, Barcelona.), Ignacio Alvarez (Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mutua de Terrassa, Terrassa, Barcelona.),Victoria Alvarez (Hospital Universitario Central de Asturias, Oviedo), Francisco Javier Barrero

(Hospital Universitario San Cecilio de Granada, Universidad de Granada), Jesús Alberto Bergareche Yarza (Instituto de Investigación Sanitaria Biodonostia, San Sebastián), Inmaculada Bernal-Bernal (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Marta Blazquez (Hospital Universitario Central de Asturias, Oviedo), Marta Bonilla-Toribio (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Juan A. Botía (Universidad de Murcia, Murcia), María Teresa Boungiorno (Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mutua de Terrassa, Terrassa, Barcelona.) Dolores Buiza-Rueda (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Ana Cámara (Hospital Clinic de Barcelona), Fátima Carrillo (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Mario Carrión-Claro (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Debora Cerdan (Hospital General de Segovia, Segovia), Jordi Clarimón (Memory Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona and Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Madrid),Yaroslau Compta (Hospital Clinic de Barcelona), Monica Diez-Fairen (Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mutua de Terrassa, Terrassa, Barcelona.), Oriol Dols-Icardo (Memory Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, and Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Madrid), Jacinto Duarte (Hospital General de Segovia, Segovia), Raquel Duran (Centro de Investigacion Biomedica, Universidad de Granada, Granada), Francisco Escamilla-Sevilla (Hospital Universitario Virgen de las Nieves, Instituto de Investigación Biosanitaria de Granada, Granada), Mario Ezquerra (Hospital Clinic de Barcelona), Cici Feliz (Departmento de Neurologia, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain), Manel Fernández (Hospital Clinic de Barcelona), Rubén Fernández-Santiago (Hospital Clinic de Barcelona), Ciara Garcia (Hospital Universitario Central de Asturias, Oviedo), Pedro García-Ruiz (Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid), Pilar Gómez-Garre (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Maria Jose Gomez Heredia (Hospital Universitario Virgen de la Victoria, Malaga), Isabel Gonzalez-Aramburu (Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander) ,Ana Gorostidi Pagola (Instituto de Investigación Sanitaria Biodonostia, San Sebastián), Janet Hoenicka (Institut de Recerca Sant Joan de Déu, Barcelona), Jon Infante (Hospital Universitario Marqués de Valdecilla-IDIVAL and University of Cantabria, Santander, and Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Silvia Jesús (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Adriano Jimenez-Escrig (Hospital Universitario Ramón y Cajal, Madrid), Jaime Kulisevsky (Movement Disorders Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, and Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED)), Miguel A. Labrador-Espinosa (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Jose Luis Lopez-Sendon (Hospital Universitario Ramón y Cajal, Madrid), Adolfo López de Munain Arregui (Instituto de Investigación Sanitaria Biodonostia, San Sebastián), Daniel Macias (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Irene Martínez Torres (Department of Neurology, Instituto de Investigación Sanitaria La Fe, Hospital Universitario y Politécnico La Fe, Valencia), Juan Marín (Movement Disorders Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, and Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED)), Maria Jose Marti (Hospital Clinic Barcelona), Juan Carlos Martínez-Castrillo (Instituto Ramón y Cajal de Investigación Sanitaria, Hospital Universitario Ramón y Cajal, Madrid), Carlota Méndez-del-Barrio (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Manuel Menéndez González (Hospital Universitario Central de Asturias, Oviedo), Marina Mata (Department of Neurology, Hospital Universitario Infanta Sofía, Madrid, Spain) Adolfo Mínguez (Hospital Universitario Virgen de las Nieves, Granada, Instituto de Investigación Biosanitaria de Granada), Pablo Mir (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Elisabet Mondragon Rezola (Instituto de Investigación Sanitaria Biodonostia, San Sebastián),

Esteban Muñoz (Hospital Clinic Barcelona), Javier Pagonabarraga (Movement Disorders Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, and Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED)), Pau Pastor (Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mutua de Terrassa, Terrassa, Barcelona.), Francisco Perez Errazquin (Hospital Universitario Virgen de la Victoria, Malaga), Teresa Periñán-Tocino (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Javier Ruiz-Martínez (Hospital Universitario Donostia, Instituto de Investigación Sanitaria Biodonostia, San Sebastián), Clara Ruz (Centro de Investigacion Biomedica, Universidad de Granada, Granada), Antonio Sanchez Rodriguez (Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander), María Sierra (Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander), Esther Suarez-Sanmartin (Hospital Universitario Central de Asturias, Oviedo), Cesar Tabernero (Hospital General de Segovia, Segovia), Juan Pablo Tartari (Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mutua de Terrassa, Terrassa, Barcelona), Cristina Tejera-Parrado (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Eduard Tolosa (Hospital Clinic Barcelona), Francesc Valldeoriola (Hospital Clinic Barcelona), Laura Vargas-González (Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville), Lydia Vela (Department of Neurology, Hospital Universitario Fundación Alcorcón, Madrid), Francisco Vives (Centro de Investigacion Biomedica, Universidad de Granada, Granada).

Austria: Alexander Zimprich (Department of Neurology, Medical University of Vienna, Austria)

Norway: Lasse Pihlstrom (Department of Neurology, Oslo University Hospital, Oslo, Norway), Mathias Toft (Department of Neurology and Institute of Clinical Medicine, Oslo University Hospital, Oslo, Norway)

Estonia: Sulev Koks (Department of Pathophysiology, University of Tartu, Tartu, Estonia; Department of Reproductive Biology, Estonian University of Life Sciences, Tartu, Estonia), Pille Taba (Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia)

Israel: Sharon Hassin-Baer (The Movement Disorders Institute, Department of Neurology and Sagol Neuroscience Center, Chaim Sheba Medical Center, Tel-Hashomer, 5262101, Ramat Gan, Israel, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel)

Finland: Kari Majamaa (Institute of Clinical Medicine, Department of Neurology, University of Oulu, Oulu, Finland; Department of Neurology and Medical Research Center, Oulu University Hospital, Oulu, Finland), Ari Siitonen (Institute of Clinical Medicine, Department of Neurology, University of Oulu, Oulu, Finland; Department of Neurology and Medical Research Center, Oulu University Hospital, Oulu, Finland), Pentti Tienari (Clinical Neurosciences, Neurology, University of Helsinki, Helsinki, Finland, Helsinki University Hospital, Helsinki, Finland)

Nigeria: Njideka U. Okubadejo (University of Lagos, Lagos State, Nigeria), Oluwadamilola O. Ojo (University of Lagos, Lagos State, Nigeria),

Kazakhstan: Coordinator - Rauan Kaiyrzhanov **(**Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK), Chingiz Shashkin (Kazakh National Medical University named after Asfendiyarov, Almaty, Kazakhstan), Nazira Zharkinbekova (South Kazakhstan Medical Academy, Shymkent, Kazakhstan), Vadim Akhmetzhanov (Astana Medical University, Astana Kazakhstan), Akbota Aitkulova (National Center for Biotechnology, Astana, Kazakhstan; Al-Farabi Kazakh national university. Almaty Kazakhstan), Elena Zholdybayeva (National Center for Biotechnology, Astana, Kazakhstan), Zharkyn Zharmukhanov (National Center for Biotechnology, Astana, Kazakhstan), Gulnaz Kaishybayeva (Scientific and practical center “Institute of neurology named after Smagul Kaishibayev”, Almaty, Kazakhstan), Altynay Karimova (Scientific and practical center “Institute of neurology named after Smagul Kaishibayev”, Almaty, Kazakhstan), Dinara Sadykova (Astana Medical University, Astana, Kazakhstan).