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Supplementary Material

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Penetrance estimate of *LRRK2* p.G2019S Mutation in Individuals of Non-Ashkenazi Jewish Ancestry

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Abstract

Background—Penetrance estimates of the *LRRK2* p.G2019S mutation for Parkinson’s disease (PD) vary widely (24%–100%). The p.G2019S penetrance in individuals of Ashkenazi Jewish ancestry has been estimated as 25%, adjusted for multiple covariates. It is unknown whether penetrance varies among different ethnic groups. The objective of this study was to estimate the penetrance of p.G2019S in individuals of non-Ashkenazi Jewish ancestry and compare penetrance between Ashkenazi Jews and non-Ashkenazi Jews to age 80.

Methods—The kin-cohort method was used to estimate penetrance in 474 first-degree relatives of 69 non-Ashkenazi Jewish *LRRK2* p.G2019S carrier probands at eight sites from the Michael J. Fox *LRRK2* Cohort Consortium. An identical validated family history interview was administered to assess age at onset of PD, current age, or age at death for relatives in different ethnic groups at each site. Neurological examination and *LRRK2* genotype of relatives were included, when available.

Results—Risk of PD in non-Ashkenazi Jewish relatives who carry a *LRRK2* p.G2019S mutation was 42.5% (95% CI: 26.3 – 65.8%) to age 80 which is not significantly higher than the previously estimated 25% (95% CI: 16.7 – 34.2%) in Ashkenazi Jewish carrier relatives. The penetrance of PD to age 80 in *LRRK2* p.G2019S mutation carrier relatives was significantly higher than the non-carrier relatives, as seen in Ashkenazi Jewish relatives.

Conclusions—The similar penetrance of *LRRK2* p.G2019S estimated in Ashkenazi Jewish carriers and non-Ashkenazi Jewish carriers confirms that p.G2019S penetrance is 25–42.5% at age 80 in all populations analyzed.

Keywords

LRRK2; penetrance; Parkinson's disease

1. INTRODUCTION

p.Gly2019Ser (p.G2019S) is the most frequently reported mutation in *LRRK2* and occurs in 1% of patients with sporadic PD and 4% of patients with familial PD¹, and is higher among Ashkenazi Jewish PD patients (14.3%–18.8%)^{2–5} and North African Berbers (39.3%)⁶. Estimating the risk of developing disease, PD, for individuals who carry a mutation, p.G2019S, (penetrance) by a certain age has important implications for both genetic counseling and clinical trial planning. The penetrance estimates of *LRRK2* p.G2019S for the development of PD vary widely (24%–100%)⁷ because of the use of different ethnic groups, gender, recruitment methods, statistical methods, and the presence of genetic or environmental modifiers of age at onset.

We previously estimated the penetrance of *LRRK2* p.G2019S in 2270 first-degree Ashkenazi Jewish relatives from the Michael J. Fox Ashkenazi Jewish *LRRK2* Consortium, including family history data on 652 Ashkenazi Jewish relatives of 129 PD probands with p.G2019S mutation and 1,618 Ashkenazi Jewish relatives of 345 PD probands without the p.G2019S mutation⁸ without adjusting for covariates. We subsequently proposed statistical methods to account for multiple covariates simultaneously in order to refine the penetrance estimate⁹. We re-estimated the adjusted penetrance of *LRRK2* p.G2019S in the Ashkenazi Jewish population as 25% (95% CI: 16.7–34.2%)⁹ to age 80 and found it to be similar to that reported initially⁸.

Here, in order to determine whether the penetrance of *LRRK2* p.G2019S differs by ethnicity (i.e., Ashkenazi Jews versus non-Ashkenazi Jews), we expanded the data collection to individuals without reported Ashkenazi Jewish ancestry (i.e., non-Ashkenazi Jews) through the Michael J. Fox *LRRK2* Consortium. We aimed to compare the penetrance of p.G2019S in individuals without reported Ashkenazi Jewish ancestry (i.e., non-Ashkenazi Jews) to the penetrance estimate derived from the individuals of Ashkenazi Jewish ancestry, adjusted for multiple covariates. The penetrance estimates were used to design a hypothetical PD protective trial testing disease modification.

2. METHODS

2.1. Participants

Our study builds on the Michael J. Fox *LRRK2* Cohort Consortium established in 2009¹⁰ to examine the genetic and environmental factors associated with disease onset in first-degree relatives of PD probands with p.G2019S mutations (relatives of carrier probands) and relatives of PD probands without p.G2019S mutations (relatives of non-carrier probands). Written informed consent was obtained from each proband and institutional review boards at each site approved the protocol. All PD probands were required to have four non-Ashkenazi Jewish grandparents. We used the same valid and reliable structured family history

questionnaires¹¹ across sites and the ascertainment scheme did not depend on sampling based on reporting a positive family history of PD. The PD probands were contacted once and completed a valid family history interview, either in person or over the telephone, and provided information on each of their first-degree relatives. PD probands were genotyped for *LRRK2* p.G2019S. Most of the relatives were not genotyped due to lack of resources to collect blood samples in all family members or death of older relatives (e.g., parents). Key information for each relative included demographics such as year of birth, current age or age at death, gender, ethnicity, PD status, age at onset of PD, and genotype if known. The PD proband in each family was excluded from the penetrance estimation to avoid ascertainment bias¹².

Sixty-nine non-Ashkenazi Jewish PD probands were recruited at eight sites and family history interviews were obtained on 474 first-degree non-Ashkenazi Jewish relatives including: the French PD Genetic network, France ($n=173$ relatives from 21 PD probands), Barcelona, Spain ($n=151$ relatives from 24 PD probands), and six other smaller sites contributing 150 relatives from 24 PD probands (California and Indiana, USA; Tübingen, Germany; Milan, Italy; San Sebastian, Spain; Toronto, Canada) (See supplementary Table 1 and 2 and supplementary Figure 1). Probands recruited from Indiana University were seen at multiple sites within the USA. There were 389 relatives recruited from clinic-based samples and 85 from population-based or community-based samples. The characteristics of relatives and PD probands are presented in Table 1, supplementary Table 1, 2, and 3.

Here, we estimate the penetrance of *LRRK2* p.G2019S in the non-Ashkenazi Jewish population using 474 relatives of 69 carrier probands, adjusting for multiple covariates⁹. We compare the penetrance estimate of *LRRK2* p.G2019S in first-degree relatives of non-Ashkenazi Jewish PD probands to Ashkenazi Jewish PD probands and used a newly developed statistical method that accounts for covariates (e.g., demographics or risk factors of PD) simultaneously⁹, thereby improving the precision of the estimates.

2.2. Statistical Analysis

Demographics and disease characteristics of first-degree non-Ashkenazi Jewish relatives were compared among recruitment sites (France, Spain, and all other sites combined). Demographic and disease characteristics of families and PD probands with and without *LRRK2* p.G2019S mutations were compared using Student's t-tests, Wilcoxon-Mann-Whitney test, Chi-square test, Fisher's exact test, and Kruskal Wallis test, where appropriate. The difference in age at onset of PD between clinic-based and population or community-based samples was tested by log-rank test.

Our method allows incorporation of information such as genotypes of relatives in the model. Fifty-one relatives from 31 families were known to carry *LRRK2* p.G2019S mutations and 38 relatives from 26 families were known to be non-carriers of *LRRK2* p.G2019S. The genotypes of the remaining 385 relatives were unknown. When most of the genotypes in relatives are not observed, the kin-cohort method^{9,12} estimates the probability of missing *LRRK2* p.G2019S carrier status in the relatives using the mutation status in PD probands and Mendelian inheritance patterns with the prevalence of mutation in relatives. The method incorporates this estimated probability with age at PD diagnosis in the first-degree relatives

to estimate the age-specific cumulative risk of PD in p.G2019S carriers and non-carriers, using an expectation-maximization algorithm¹³ developed to handle missing relatives' genotype data. We assumed healthy non-Ashkenazi Jewish relatives have 0.4% prevalence of *LRRK2* p.G2019S mutation⁴. Covariates in PD probands and relatives such as PD proband's sex, relative's sex, site of enrollment, and recruitment method were adjusted simultaneously to improve the accuracy of the penetrance estimation through a Cox proportional hazard model⁹. A bootstrap resampling method was used to compute confidence intervals of the estimated age-specific penetrance accounting for correlation among relatives in the same family^{9,14}.

We conducted several comparisons based on the estimated penetrance in the non-Ashkenazi Jewish relatives. First, we compared the penetrance of *LRRK2* p.G2019S to age 80 with the PD risk in non-carrier relatives. Second, we examined whether the penetrance of *LRRK2* p.G2019S differed by sex. Third, we estimated the penetrance in parents and siblings. Fourth, we examined the effect of covariates on PD risk.

Next, we compared the penetrance at age 80 in non-Ashkenazi Jewish carrier relatives with previously obtained penetrance in Ashkenazi Jewish carrier relatives⁹ using Wald test at 5% significance level.

Lastly, we use penetrance estimates to calculate the sample size needed for a hypothetical two-arm PD prevention trial comparing the likelihood of diagnosis of PD (phenoconversion). Our penetrance estimates provide design parameters for the placebo arm by computing the probability of developing PD within the next 5 years for subjects who have not developed PD by a given age. Assuming a certain effect size, we estimate the sample size to test the null hypothesis of no difference in the proportion of PD phenoconverters between the placebo arm and the intervention arm to achieve 80% power (a two-sided test with significance level = 0.05)⁹. We considered two scenarios for the effect size of the intervention: in scenario 1, the intervention was assumed to reduce the risk of PD to that observed in the non-carrier relatives, essentially eliminating the effect of the mutation completely (100%) and assuming the intervention has no effect on non-carrier relatives; in scenario 2, the intervention was assumed to manifest half of the effect as in scenario 1 (50%).

3. RESULTS

3.1. Demographics

The demographic and clinical characteristics of first-degree non-Ashkenazi Jewish relatives stratified by the recruitment site and the PD proband's mutation status are reported in Table 1, supplementary Table 2 and 3, respectively. The flow chart and distribution of the study population are reported in supplementary Figure 1 and supplementary Table 4.

Among the 474 non-Ashkenazi Jewish first-degree relatives of p.G2019S carrier PD probands (i.e., 127 parents, 220 siblings, and 127 children), 45 had PD (i.e., 22 parents, 23 siblings, and 0 children). The mean age at onset of PD, defined as onset of motor symptoms of PD, was similar in male and female relatives. Gender distribution was similar across the

three non-Ashkenazi Jewish site groups. There was no significant difference between clinic-based and community- or population-based samples on the age at onset of PD. Among 69 carrier PD probands in the non-Ashkenazi Jewish cohort, 9 PD probands (13%) had families with multiple PD affected individuals. When adjusted for family size, 11% of family members of carrier PD probands were affected by PD on average (Standard deviation=0.14), which is similar to the Ashkenazi Jewish cohort where 10% of family members of Ashkenazi Jewish carrier PD probands were affected by PD on average (Standard deviation=0.17).

3.2. Penetrance of *LRRK2* p.G2019S

Penetrance estimates (cumulative risk of PD) of *LRRK2* p.G2019S in the non-Ashkenazi Jewish relatives are presented in Table 2 and Supplementary Table 5. The penetrance of p.G2019S to age 80 in non-Ashkenazi Jewish carrier relatives (42.5%, 95% CI: 26.3 – 65.8%) was significantly higher than the non-carrier relatives (2.7%, 95% CI: 0.1 – 10.7%, $p<0.001$; Figure 1) (Hazard ratio of carriers to non-carriers: 20.85, 95% CI: 4.75–829.19, $p=0.005$), similar to what we have seen in the Ashkenazi Jewish population. The large confidence interval for the hazard ratio is due to the low hazard rate in the non-carrier relatives. When the male and female relatives were examined separately, the p.G2019S penetrance to age 80 in carrier male relatives (35.2%, 95% CI: 17.8 – 58.4%) was not significantly different from female carrier relatives (49.3%, 95% CI: 30.3 – 74.3%; Supplementary Figure 3A) (Hazard ratio of male to female: 0.64, 95% CI: 0.32–1.14, $p=0.11$; Table 3). When non-Ashkenazi Jewish parents and siblings of probands were examined separately, the penetrance of p.G2019S to age 80 in carrier parents (39.6%, 95% CI: 21.9 – 67.9%) was not significantly different from carrier siblings (45.7%, 95% CI: 26.9 – 67.2%, $p=0.52$; supplementary Figure 4A).

When examining the effect of the PD proband's sex, site of enrollment, and recruitment method that may modify the PD risk, none of the prognostic factors that we controlled significantly influenced PD risk. The risk of PD was similar between male and female probands and there was no difference between sites. Moreover, the risk of PD was similar between the clinic-based sample and the population-based or community-based sample (see Table 3). The penetrance estimates in non-Ashkenazi Jewish French and Spanish relatives (the two largest sites) were similar to one another and to the rest of the non-Ashkenazi Jewish (see supplementary Table 5 and supplementary Figure 5A).

Lastly, we compared the penetrance estimates in non-Ashkenazi Jewish relatives to Ashkenazi Jewish relatives (Table 4 and supplementary Table 6). The penetrance of *LRRK2* p.G2019S for the development of PD to age 80 in non-Ashkenazi Jewish carrier relatives (42.5%, 95% CI: 26.3 – 65.8%) was not significantly different from previously estimated in Ashkenazi Jewish carrier relatives (25%, 95% CI: 16.7 – 34.2%)⁹ ($p=0.947$). There was no significant difference in penetrance comparing non-Ashkenazi Jewish to Ashkenazi Jewish when stratified by sex.

3.3. Sample size estimation for clinical trial testing disease modification

The effects size and sample size estimates are presented in supplementary Table 7. In scenario 1, a sample size of $n=111$ per arm is required to detect a risk difference in PD conversion of 7.5% (2.3% – 12.7%) between placebo arm and intervention arm with a baseline age of 60. In scenario 2, a sample size of $n=632$ per arm is required to detect the difference of 3.8% (1.1% – 6.4%) to detect half of the risk reduction between placebo arm and intervention arm with a baseline age of 60. Therefore, a larger sample size is needed for a prevention trial to detect a smaller risk differences with sufficient power.

When we considered a study of 3 year duration at age 60, a sample size of $n=211$ per arm was required to detect a risk difference of 4.0% in scenario 1 and $n=1,216$ per arm was required to detect the difference of 2.0% in scenario 2, which require a larger sample size. We also considered the same sample size calculation with an average recruitment baseline age of 70, which leads to a larger required sample size to detect the smaller risk difference.

4. DISCUSSION

We have determined that the p.G2019S penetrance for the development of PD to age 80 in non-Ashkenazi Jewish carrier relatives is 42.5% (95% CI: 26.3 – 65.8%) which is similar to previously estimated in Ashkenazi Jewish carrier relatives 25% (95% CI: 16.7 – 34.2%)⁹. Estimates of *LRRK2* p.G2019S penetrance have been reviewed in previous studies, and range from 24%–100%⁷. Clark et al. 2006³ reported a lifetime penetrance of 24% up to age 80 (95% CI: 13.5 – 43.7%) in 2,975 carrier and non-carrier relatives of 459 PD cases and 2,044 relatives of 310 control probands using the kin cohort method¹⁵, similar in Ashkenazi Jewish and non-Ashkenazi Jewish cases. In contrast, Healy et al. 2008¹ reported a risk of 28% at age 59, 51% at 69 and 74% at 79 for the p.G2019S mutation in 1,045 mutation carriers from 133 families from 24 populations worldwide. The upper bound of the confidence interval for the current study is 65.8%, which is lower than the 74% reported by Healy et al. Our recent study of *LRRK2* p.G2019S penetrance in Ashkenazi Jews included 474 PD probands from three site groups. The lifetime risk of PD was estimated to be 26% by age 80⁸, and after adjusting for demographic or clinical characteristics of PD probands or relatives, the lifetime risk of PD was estimated to be 25% by age 80⁹, almost identical to the earlier report in Clark et al. 2006³. A recent study in Tunisia¹⁶, North Africa, known to have a high burden of *LRRK2* p.G2019S parkinsonism, estimated the penetrance in *LRRK2* p.G2019S carriers to be 91% by age 80. The high *LRRK2* p.G2019S penetrance may have arisen due to the exclusion of asymptomatic carrier relatives from their estimation^{1,16}.

Strengths of our study include first, the use of the sampling scheme that recruits probands regardless of their family history of PD. This differs from other studies that included only families with multiple relatives who developed PD. Second, to date, this is the first and largest study to use the identical family history interview in different ethnic groups at multiple sites to assess the age-specific risk of PD⁸. By using a valid and reliable family history interview¹¹, we were able to estimate the non-Ashkenazi Jewish *LRRK2* p.G2019S penetrance among several ethnic groups, including five sites in Europe and two in the U.S. This aids in the comparison of penetrance estimates to previous PD populations. Third, the probands were recruited from clinic-based, population-based or community-based cohorts,

but most of the patients were sampled through clinical centers. Additional recruitment of patients in population-based or community-based samples would allow extension of penetrance estimates to broader groups. Lastly, we controlled for covariates simultaneously. This methodology facilitates obtaining more accurate and refined penetrance estimates.

One limitation of this study is the relatively small number of non-Ashkenazi Jewish participants, leading to a wide confidence interval for the penetrance estimates. The upper limit of the 95% confidence interval for the penetrance in Ashkenazi Jewish carrier relatives is 34.2%, which is slightly below the estimated penetrance in non-Ashkenazi Jewish carrier relatives (42.5%). It is conceivable that with a larger sample size, a lower penetrance in Ashkenazi Jews compared to non-Ashkenazi Jews could be significant. For example, we would need at least 1,806 non-Ashkenazi Jewish relatives to detect a significant difference in penetrance between non-Ashkenazi Jewish carrier relatives (42.5%) and Ashkenazi Jewish carrier relatives (the upper confidence limit of Ashkenazi Jewish carrier relatives reaches 34.2%). The PD probands were recontacted for the family history interview sometimes years after initial recruitment. The validated family history was administered only once. We were unable to contact all PD probands in the previous study. The reasons for a small number of non-Ashkenazi Jewish PD probands and relatives in our study includes the short recruitment period and practical difficulties in reaching probands and relatives. Another limitation is that the actual genotype information was not available in all relatives. Although we used our new kin-cohort method to include the actual genotypes in relatives, when available, higher precision would be expected if the estimation were based on the actual relatives' genotype. An additional limitation is that we did not control for environmental risk factors in the relatives (e.g., cigarette smoking¹⁷) or common mutations that are associated with PD such as mutations in the glucocerebrosidase (*GBA*)¹⁸ gene in the non-Ashkenazi Jews. However, none of the non-Ashkenazi Jewish PD probands who were genotyped for the *GBA* mutation carried the *GBA* mutations ($n=36$). Excluding the remaining 33 probands with missing *GBA* mutation status would lead to a small sample size, therefore, we included all the probands into the analysis. In terms of the non-carrier group, our cumulative risk of *LRRK2* p.G2019S to age 80 in non-Ashkenazi Jewish non-carriers (2.7%, 95% CI: 0.1 – 10.7%) was slightly but not significantly higher than the general population (1.7%)¹⁹ and lower than Ashkenazi Jewish non-carrier relatives (11.0%, 95% CI: 8.0 – 14.7%, $p=0.008$)⁹. We did not include 22 non-Ashkenazi Jewish relatives of 3 non-carrier probands since we do not have sufficient samples to represent relatives from non-carriers. Our estimation of the PD risk in the non-carrier group is obtained solely from relatives of *LRRK2* carrier probands, which may explain a slightly higher PD risk as compared to the general population. The significantly higher PD risk in Ashkenazi Jewish non-carriers than non-Ashkenazi Jewish non-carriers ($p=0.013$) may indicate that there are other genetic modifiers in Ashkenazi Jewish population that may increase the PD risk.

The number of non-Ashkenazi Jewish samples required to achieve a power of 80% for a 3-year prevention trial is large (scenario 2). To design an efficient trial, investigators need to enrich samples based on other risk factors in addition to *LRRK2* p.G2019S mutation. International studies such as Parkinson's Progression Markers Initiative²⁰ were launched to identify additional biomarkers for predicting PD susceptibility and progression in the

prodromal phase, so that individuals at the highest risk for PD can be identified and recruited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Table 1

Demographics and disease characteristics of non-Ashkenazi Jewish first-degree relatives of *LRRK2* p.G2019S carrier probands.

Relatives (n=474)	Relatives of p.G2019S carrier probands
Age (years, SD, n)	57.0 (20.4) n=429
Age at onset PD (years, SD, n)	67.6 (10.7) n=45
Male (n=228)	
Age (years, SD, n)	57.1 (21.0) n=211
Age at onset PD (years, SD, n)	68.3 (9.2) n=17
Female (n=246)	
Age (years, SD, n)	56.9 (19.8) n=218
Age at onset PD (years, SD, n)	67.1 (11.7) n=28
Parents (n=127)	
Age (years, SD, n)	75.4 (13.5) n=105
Age at onset PD (years, SD, n)	69.4 (12.2) n=22
Siblings (n=220)	
Age (years, SD, n)	58.4 (18.0) n=197
Age at onset PD (years, SD, n)	65.8 (8.9) n=23
Children (n=127)	
Age (years, SD, n)	39.6 (12.8) n=127
Age at onset PD (years, SD, n)	- (-) n=0

Abbreviations: SD= standard deviation; PD=Parkinson disease.

Table 2

Cumulative risk of PD to age 80 in non-Ashkenazi Jewish first-degree relatives of *LRRK2* p.G2019S carrier probands.

Relatives*	Cumulative Risk in p.G2019S carrier relatives to age 80 (%)	Cumulative Risk in p.G2019S non-carrier relatives to age 80 (%)	Cumulative Risk in p.G2019S carrier relatives to age 80 compared to non-carrier relatives to age 80	Relatives with PD (n)
Total (n=474)	42.5 (26.3 – 65.8)	2.7 (0.1 – 10.7)	$p<0.001$	45
Male Relatives (n=228)	35.2 (17.8 – 58.4)	2.1 (0.1 – 7.8)	$p=0.001$	17
Female Relatives (n=246)	49.3 (30.3 – 74.3)	3.2 (0.1 – 13.4)	$p<0.001$	28

* 89 non-Ashkenazi Jewish relatives were genotyped for the *LRRK2* G2019S mutations with 51 carrier relatives from 31 families and 38 non-carriers from 26 families. The genotype for the rest of 385 relatives were unknown.

Table 3

Estimated hazard ratios of Parkinson's disease onset in non-Ashkenazi Jewish first-degree relatives of *LRRK2* p.G2019S carrier probands.

Variable	Estimated Hazard ratio	Lower limit	Upper limit	p-value
Relative's sex (Male vs Female)	0.635	0.322	1.137	0.114
Prognostic factors				
Proband's sex (Male vs Female)	0.900	0.456	1.691	0.695
Sites				
France vs Others	0.885	0.331	2.254	0.776
Barcelona-Spain vs Others	0.707	0.259	1.696	0.388
France vs Barcelona-Spain	1.252	0.498	3.110	0.576
Recruitment scheme				
Clinic vs Community or Population based sample	0.887	0.271	3.667	0.955

The Cox proportional hazards model is λ (Carrier status, Relative's sex, Proband's sex, Site, Recruitment scheme) = $\lambda_0(t) \exp(\beta \text{ Carrier status} + \eta_1 \text{ I(Relative's sex=Male)} + \gamma_1 \text{ I(Proband's sex=Male)} + \gamma_2 \text{ I(Site=France)} + \gamma_3 \text{ I(Site=Barcelona-Spain)} + \gamma_4 \text{ I(Recruitment scheme=Clinic-based)})$.

Table 4

Comparing Cumulative Risk of PD to Age 80 between non-Ashkenazi Jewish and Ashkenazi Jewish first-degree relatives of *LRRK2* p.G2019S carrier probands.

Relatives	G20109S mutation carrier status	Cumulative Risk in non-Ashkenazi Jewish* relatives to age 80 (%)	Cumulative Risk in Ashkenazi Jewish** relatives to age 80 (%) ⁹	Cumulative Risk in non-Ashkenazi Jewish relatives to age 80 compared to Ashkenazi Jewish relatives to age 80
All	Carriers	42.5 (26.3 – 65.8)	25.0 (16.7–34.2)	$p=0.106$
	Non-carriers	2.7 (0.1 – 10.7)	11.0 (8.0–14.7)	$p=0.013$
Male	Carriers	35.2 (17.8 – 58.4)	21.5 (9.0–35.6)	$p=0.268$
	Non-carriers	2.1 (0.1 – 7.8)	15.2 (10.5–20.6)	$p<0.001$
Female	Carriers	49.3 (30.3 – 74.3)	28.5 (18.8–39.4)	$p=0.098$
	Non-carriers	3.2 (0.1 – 13.4)	6.6 (4.0–9.7)	$p=0.394$

* 89 non-Ashkenazi Jewish relatives were genotyped for the *LRRK2* G2019S mutations with 51 carrier relatives from 31 families and 38 non-carriers from 26 families. The genotype for the rest of 385 relatives were unknown.

** 158 Ashkenazi Jewish relatives were genotyped for the *LRRK2* G2019S mutations with 90 carrier relatives from 59 families and 68 non-carriers from 47 families. The genotype for the rest of 2,112 relatives were unknown.