Published Ahead of Print on April 23, 2008 as 10.1212/01.wnl.0000304039.11891.29

Genotype–phenotype correlations between *GBA* mutations and Parkinson disease risk and onset

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ABSTRACT

Background: Mutations in *GBA* and *LRRK2* genes have been implicated in Parkinson disease (PD), particularly in Ashkenazi Jews.

Methods: An Israeli Ashkenazi cohort of 420 patients with PD, 333 elderly controls, and 3,805 young controls was screened for eight *GBA* mutations, which are associated with mild (N370S, R496H) and severe (84GG, IVS2 + 1, V394L, D409H, L444P, RecTL) Gaucher disease. Patients with PD and elderly controls were also genotyped for *LRRK2* G2019S.

Results: *GBA* carrier frequency was 17.9% in patients with PD compared to 4.2% in elderly and 6.35% in young controls. The proportion of severe mutation carriers among patients with PD–*GBA* carriers was 29% compared to 7% among young controls. Severe and mild *GBA* mutations increased the risk of developing PD by 13.6- and 2.2-fold, and affected the average age at PD onset (AAO), 55.7 and 57.9 years, compared to 60.7 years in patients without known *GBA* or *LRRK2* mutations.

Conclusions: These data demonstrate genotype–phenotype correlations between different *GBA* mutations and Parkinson disease (PD) risk and AAO in Ashkenazi Jews. Additionally, an earlier AAO was observed in *LRRK2* G2019S carrier patients with PD. Finally, these data demonstrate that a surprisingly high frequency, more than one third of our patient population, carried a mutation in *GBA* or *LRRK2*. **Neurology® 2008;70:1–1**

GLOSSARY

AAO = age at onset; **ANOVA** = analysis of variance; **GD** = Gaucher disease; **HWE** = Hardy-Weinberg equilibrium; **PD** = Parkinson disease.

Clinical observations, neuropathologic evidence, and genetic studies in the last decade have implicated mutations in the β-glucocerebrosidase (*GBA*) gene in parkinsonian phenotypes and in Parkinson disease (PD) susceptibility. Mutations and rearrangements in *GBA* cause Gaucher disease (GD), a recessively inherited deficiency of the lysosomal enzyme, glucocerebrosidase. GD is most common in the Ashkenazi Jewish population, where the 1226A > G (N370S) mutation predominates. Common *GBA* mutations have been classified as null, severe, or mild, based on their phenotypic effect. Severe and null mutations cause neuronopathic forms of GD, while mild mutations are conventionally associated with the nonneuronopathic form of disease.[1,2]

Parkinsonian manifestations reported in genotypically heterogeneous patients with GD,[3-11] together with family studies revealing a significant frequency of parkinsonian symptoms in obligate or confirmed *GBA* mutation carrier relatives of patients with GD,[6,9,12] suggested an association between GD and PD. Moreover, brain samples from autopsy-confirmed PD cases revealed significantly higher carrier frequencies than the estimated *GBA* mutation carrier frequency in the general population,[13,14] supporting an

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Supported by grants from M.K. Humanitarian Fund, National Parkinson Foundation, Miami, FL, Tel Aviv Sourasky Medical Center Grant of Excellence, and Wolfson and Kahn Foundations.

Disclosure: The authors report no disclosures.

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association between *GBA* mutations, in both homozygotes and heterozygotes, and PD susceptibility.

The high carrier frequency of *GBA* mutations in Ashkenazi Jews compared to the population at large suggests the importance of this population for the study of the relationship between *GBA* mutations and PD. Previous publications reported *GBA* mutation carrier frequencies of 31.3% and 10.6% in 99 and 150 Israeli Ashkenazi patients with PD,[15,16] and a carrier frequency for N370S of 10.7% in 160 Jewish American patients with PD,[17] two- to fivefold greater than frequencies observed in their ethnically matched controls. Subsequent independent studies in various ethnic populations also supported the association between *GBA* mutations and increased PD risk.[18-21] Two additional studies found no such association.[22,23]

Herein, using the largest cohort of Jewish Ashkenazi patients with PD analyzed to date, we aimed to validate the association between *GBA* mutations and PD, and explore the effects of mild and severe *GBA* mutations on PD risk and phenotype. Additionally, we explored the potential relationship between *GBA* mutations and the *LRRK2* G2019S mutation in patients with PD of Ashkenazi origin.

METHODS

Patient population. The study population included 420 unrelated patients with PD of Jewish Ashkenazi ancestry, 62.4% men (n = 262) and 37.6% women (n = 158), treated at the Movement Disorders Unit, Tel-Aviv Sourasky Medical Center. All patients were diagnosed by a movement disorder specialist, according to UK PD Society Brain Bank criteria.[24] Patients were enrolled consecutively between September 2005 and January 2007. The mean age at enrollment was 67.96 years (SD ± 10.2, range 41–96), with an average age at enrollment of 67.7 (±10.3) and 68.4 (±10.0) years for men and women.

All patients underwent a detailed interview to ascertain ancestry, family history of PD or other movement disorders, presenting symptoms, and age at onset of motor symptoms that retrospectively could be associated with PD onset. The mean age at onset (AAO) of patients was 59.4 (±11.3; range 21–94) years. Eighty patients (19.3%) had symptoms of PD before the age of 50 and are considered as having early onset PD. The mean AAO for men and women did not differ: 59.3 (±11.4) and 59.6 (±11.3) years. The mean age at PD diagnosis was 60.7 years (±10.9; range 26–94).

Family pedigrees were constructed for all patients. None were from consanguineous families. Familial PD, defined as having at least one first- or second-degree relative with a diagnosis of PD, was noted in 26.7% (111/416) of patients with information regarding family history, 16.8% of which had an affected first-degree relative.

Our cohort was also tested for the *LRRK2* G2019S (6055G>A) mutation but not for mutations in the recessively inherited *Parkin*, *PINK1*, or *DJ1* genes. The status of *LRRK2* G2019S in part of this cohort was previously reported.[25]

Control population. A total of 4,138 Ashkenazi control individuals were analyzed. These included 3,805 anonymous young individuals, aged 20–45, mostly women, who underwent routine genetic screening tests for GD at the Genetic Institute, Tel-Aviv Sourasky Medical Center, between January 2000 and January 2007. These individuals represent an average risk population for carrying *GBA* mutant alleles in Israel.

An additional 333 older Ashkenazi controls were tested (mean age at enrollment 65.3 years [±10.2], range 38–89 years, data were not available for one individual), including 173 who were interviewed, mostly spouses of patients with PD, and 160 anonymous healthy controls, whose DNA samples were purchased from the National Laboratory for the Genetics of Israeli Populations (described in detail in the NLGIP Web site). Neurologic examinations were not performed on control individuals; however, controls reporting tremor, balance problems, or movement and gait disturbances were excluded. Of the 333 older Ashkenazi controls, 204 were randomly selected to match in sex and age to the PD group. This age- and sex-matched control group included 58.3% men and 41.7% women with an average age of 66.8 years (±10.6) at study enrollment.

All patients and spouse controls signed an informed consent before entering the study. Patients and elderly controls with clinically significant dementia who could not sign an informed consent were excluded from our study. All DNA samples were coded and tested in an anonymous manner. The Institutional and National Supreme Helsinki Committees for Genetic Studies approved the study protocols and the informed consents.

***GBA* and *LRRK2* mutation analyses.** Genomic DNA was isolated from peripheral blood using standard protocols, or from saliva according to manufacturer's instruction (Oragene, Ottawa, Canada). Patients and controls were tested for the 84GG, IVS2 + 1, N370S, D409H, L444P, V394L, and RecTL *GBA* mutations, using PRONTO Gaucher kit (Pronto Diagnostics, Rehovot, Israel,[26]) and for the R496H mutation, using PRONTO Gaucher 496 MUT-only kit. The 3,805 anonymous young controls were not tested for the R496H mutation, which is not included in the *GBA*-mutation screening panel recommended by the Israeli Society of Medical Geneticists.

Alleles separation in RecTL carriers was performed using specific primers (primers p1 and 271, supplied by Dr. Nir Navot, Pronto Diagnostics, Rehovot, Israel), in order to delineate whether the N370S mutation is in cis (RecTL,N370S/+) or trans (N370S/RecTL) with D409H and L444P.

All samples carrying *GBA* mutations were tested by another method to confirm the results of the analysis above. Validations of the 84GG, IVS2 + 1, L444P, V394L, and R496H mutations were performed by sequence analysis (Applied Biosystems, Foster City, CA). Validation of the N370S mutation was performed using *Xho*I restriction enzyme

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Table 1 Frequencies of *GBA* gene mutations and alleles among Ashkenazi patients with Parkinson disease (PD) and control populations

	Patients with PD, n = 420		Elderly controls, n = 333		Young controls, n = 3,805	
	Individuals, n (%)	Alleles, n (Freq)	Individuals, n (%)	Alleles, n (Freq)	Individuals, n (%)	Alleles, n (Freq)
GBA mutation						
N370S/+	46* (10.95)	54 (0.064)	11 (3.3)	13 (0.0195)	224 (5.89)	226 (0.0297)
R496H/+	7 (1.67)	9 (0.011)	1 (0.3)	1 (0.0015)	NT	
84GG/+	8 (1.90)	8 (0.010)	1 (0.3)	1 (0.0015)	6 (0.16)	6 (0.0008)
IVS2+1/+	4 (0.95)	4 (0.005)			1 (0.03)	1 (0.0001)
V394L/+	3 (0.71)	4 (0.005)			4 (0.11)	4 (0.0005)
D409H/+						
L444P/+	2 (0.48)	2 (0.002)			4 (0.11)	4 (0.0005)
RecTL, N370S/+	5 (1.19)	6† (0.007)	1 (0.3)	1 (0.0015)	2 (0.05)	2 (0.0003)
Total carriers	75* (17.9)	87 (0.104)	14 (4.2)	16 (0.024)	241 (6.35)	243 (0.032)
N370S/N370S	2 (0.48)		1 (0.3)		1 (0.03)	
N370S/RecTL	1 (0.24)					
N370S/V394L	1 (0.24)					
N370S/R496H	2 (0.48)					
Total homozygotes and compound heterozygotes	6 (1.4)		1 (0.3)		1 (0.03)	
Total carriers, homozygotes, and compound heterozygotes	81* (19.3)		15 (4.5)		242 (6.4)	
Total individuals/alleles tested	420	840	333	666	3805	7610

*Including four carriers of *LRRK2* G2019S mutation.
†Including one RecTL allele.
Freq = allele frequency; NT = not tested.

analysis (New England Biolabs, Beverly, MA). All PCR reactions for validation were performed using Sigma Taq Polymerase (Sigma Aldrich, St. Louis, MO) and Biometra PCR systems (Biometra GmbH, Gottingen, Germany). All specific primer pairs used are detailed in table e-1 on the *Neurology*® Web site at www.neurology.org.

All patients with PD were screened for the *LRRK2* 6055G>A (G2019S) mutation as described previously.[25]

Statistical analysis. Data are presented as mean (±SD) for continuous variables. Clinical and demographic categorical variables are presented in percentage whereas allele frequency is presented on a range of 0–1. Any differences among groups in continuous variables were tested using analysis of variance (ANOVA) and chi square or Fisher exact test were used for comparison of categorical variables. Goodness of fit test with one degree of freedom was applied to look for any deviation from the Hardy-Weinberg equilibrium (HWE) among the 3,805 young controls and among patients with PD who were screened for *GBA* mutations. Logistic regression model was applied with the mutation status of the individual as the predictive variable and the disease status (PD/non PD) as the dependent variable. With this model, the Exp(β) was used to determine the calculated OR and the 95% CI around it. When comparing to the group of 3,805 young controls, an online calculator was used to determine the OR and CI (DJR Hutchon Calculator). SPSS software V. 15 (SPSS Inc., Chicago, IL) was used for all data analysis unless otherwise mentioned.

RESULTS ***GBA* mutations are more frequent in Ashkenazi patients with PD, with an overrepresentation of severe *GBA* mutations.** Of the 420 Jewish Ashkenazi patients with PD, 75 (17.9%) were carriers of one of the *GBA* mutations tested compared to 4.2% and 6.35% carriers among the elderly and young control populations (table 1, $p < 0.0001$). Six patients (1.4%) were either homozygous or compound heterozygous for *GBA* mutations. Sixty patients carried the *LRRK2* G2019S mutation (14.3%), four of whom also carried the *GBA* N370S mutation. These four patients were excluded from additional statistical analyses to enable direct comparison among the three groups of patients with PD: those who carried either *GBA* (n = 71) or *LRRK2* G2019S (n = 56) mutations and patients who were not detected as mutation carriers (n = 283, table 2).

GBA mutations tested here are classified as mild (N370S and R496H) or severe (84GG, IVS2 + 1, V394L, D409H, L444P, and RecTL), depending on their expected and observed phenotypic effects in GD.[1,2] The frequency of N370S carriers among patients with PD was higher than among the elderly

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Table 2 Comparison between Ashkenazi patients with Parkinson disease (PD) who are carriers of either *GBA* mutations or *LRRK2* G2019S mutation and noncarrier patients*

	Carriers of GBA mutation	Carriers of *LRRK2* G2019S mutation	*GBA* homozygous and compound heterozygous	Noncarriers	Total
No. of patients	71*	56*	6	283	416*
Average age at motor symptoms onset, y (SD)	57.2 (10.3); $p = 0.021$#	56.9 (11.4); $p = 0.027$#	51.2 (9.7); $p = 0.042$#	60.7† (11.5)	59.4† (11.4)
Early onset PD <50 y (%)	17 (23.9); $p = 0.09$	15‡ (27.8); $p = 0.036$#	3 (50.0); $p = 0.06$	45† (16.1)	80§ (19.5)
No. of women (%)	30 (42.3); $p = 0.21$	28 (50.0); $p = 0.03$#	2 (33.0); $p = 1.0$	96 (33.9)	156 (37.6)
First-degree relatives with PD (%)	11¶ (15.7); $p = 0.35$	19 (33.9); $p < 0.001$#	2 (33.3); $p = 0.19$	37‡ (13.2)	69‖ (16.7)
First- or second-degree relatives with PD (%)	18¶ (25.7); $p = 0.35$	24¶ (43.6); $p = 0.002$#	2 (33.3); $p = 0.42$	64‡ (22.8)	108† (26.2)

*Not including four patients who carried both *GBA* N370S and *LRRK2* G2019S mutations.
Data not available for †4, ‡2, §6, ¶1, and ‖3 patients.
#Significant *p* values.

and young control populations (10.95%, 3.30%, and 5.89%, $p < 0.001$). However, the frequency of severe *GBA* mutation carriers among patients with PD was much higher than the frequency of these mutation carriers among the elderly and young control populations (5.24%, 0.6%, and 0.45%, $p < 0.001$). Furthermore, while N370S carriers accounted for 93% of all *GBA* mutation carriers detected among the 3,804 young control individuals, they accounted for only 61% of patient with PD mutation carriers (table 1, $p < 0.001$), demonstrating an over-representation of severe *GBA* mutations among the patients with PD. No deviation from HWE was found regarding the number of homozygous and compound heterozygous individuals among patients with PD and the young controls.

Carriers of severe *GBA* mutations have a particularly increased risk for developing PD. The risk of heterozygous *GBA* mutation carriers to develop PD was calculated relative to an elderly control group (age 38–89 years) and a young control group (age 20–45 years). When patient with PD carriers of *GBA* mutations were compared to the elderly controls using a logistic regression model (not including the *LRRK2* G2019S carriers and individuals homozygous or compound heterozygous for *GBA* mutations), the Exp(β) was 5.6 (CI 3.1–10.1) when comparing the 354 patients with PD to 324 elderly controls, and 8.1 (CI 3.4–18.9) when comparing these patients to the 199 age- and sex-matched controls only. For an additional estimation of this risk, we calculated an OR of 3.7 (CI 2.8–5.0, table 3) for a mutation carrier to develop PD using the young control population as a reference, possibly reflecting the influence of aging.

Since only about 1/250 Ashkenazis carry a severe *GBA* mutation, the number of mutation carriers among the 330 elderly controls would not have been sufficient for estimating the OR of a specific *GBA* mutation carrier to develop PD. Therefore, we performed this analysis relative to the 3,804 young controls (table 3). The OR for carriers of all five severe *GBA* mutations tested was more than sixfold higher compared to the OR of N370S carriers (13.6 [CI 7.2–25.9] and 2.2 [CI 1.5–3.1]).

Table 3 The average age at Parkinson disease motor symptoms onset and the OR depend on the type of GBA mutation

Carrier genotype	No. of carriers	Average age at onset, y	SD	OR*	95% CI
All *GBA* carriers	71†	57.2	10.3	3.7	2.8-5.0
Mild mutations					
N370S/+	42†	57.9	11.1	2.2	1.5-3.1
R496H/+	7	57.6	10.5	NT	NT
Severe mutations					
84GG/+	8	58.5	9.8	14.0	4.8-40.6
IVS2+1/+	4	55.8	11.2	42.0	4.7-377.2
V394L/+	3	52.7	12.4	7.9	1.8-35.4
L444P/+	2	55.0	7.1	5.3	0.96-28.8
RecTL, N370S/+	5	53.2	5.9	26.3	5.1-135.9

*OR was calculated relative to the young control population.
†Not including four patients who carried both *GBA* N370S and *LRRK2* G2019S mutations. Similar results were obtained with these four patients included in this analysis.

Earlier age at PD onset in *GBA* mutation and *LRRK2* G2019S carriers. The age at PD motor symptoms onset (AAO) differed among the four groups presented in table 2 [one-way ANOVA, $F(3,406) = 3.99$, $p = 0.008$]. Post hoc analysis revealed that the source of significance was the younger AAO in the three groups of patients with mutations compared to patients without mutations ($p = 0.021$, $p = 0.027$, and $p = 0.042$). While the mean AAO of noncarriers was 60.7 years, it

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Table 4 Presenting symptoms of Parkinson disease in patient carriers of *GBA* mutations and noncarrier patients

Presenting symptom	Percentage among 71 *GBA* mutation carriers	Percentage among 280* noncarriers	χ^2	*p* Value
Tremor	50.70	57.86	1.18	0.278
Bradykinesia	25.35	17.14	2.50	0.114
Rigidity	16.90	28.57	3.99	0.046
Gait and balance disturbances	23.94	24.29	0.004	0.952
Weakness	16.90	7.14	6.51	0.011
Micrographia	9.86	7.86	0.30	0.584
Pain	9.86	6.07	1.28	0.259
Depression	8.45	10.00	0.16	0.693

*Data available for 280 of 283 noncarrier patients.

was 3.5, 3.7, and 9.5 years younger in these three groups of patients with PD with mutations.

Furthermore, while the AAO in patients with PD carrying mild *GBA* mutations (n = 49) was 57.9 years (±10.9), it was 55.7 years (±8.9) in patients with severe *GBA* mutations [one-way ANOVA, F (2,347) = 2.97, $p = 0.05$]. Post hoc analysis revealed that the source of significance was the earlier age at PD onset (5.0 years younger) in the 22 patient carriers of severe *GBA* mutations compared to the 279 patients who did not carry *GBA* or *LRRK2* mutations ($p = 0.047$). Table 3 further details the different AAOs of PD according to the specific *GBA* mutation.

Are there distinctive clinical characteristics for patient with PD carriers of *GBA* mutations? The predictive value of a family history (first- or second-degree relative with PD) for the development of PD was calculated using a binary regression model with the status of the subject (patient or control) as the dependent variable. When comparing all Ashkenazi patients with PD to elderly controls (data were available for 416 and 169 individuals), the OR for a family history was 4.8 (CI 2.5–8.9). Additionally, the frequency of a family history of first- or second-degree relatives with PD in the three groups of patients with mutations differed (25.7%, 43.6%, and 22.8%, $\chi^2 = 15.216$, $df = 4$, $p = 0.004$, table 2) when compared to noncarrier patients, similar to the proportions of patients with PD with only first-degree relatives (15.7%, 33.9%, and 13.2%, $\chi^2 = 15.842$, $df = 4$, $p = 0.003$, table 2). While the ratio of first- or second-degree relatives among patients who carried the *LRRK2* G2019S mutation was higher, as previously reported,[25] there was no difference in the frequency of a family history of PD between patients with *GBA* mutations and patients who did not carry mutations.

When analyzing the presenting symptoms of PD (table 4), a tendency toward a higher frequency of weakness ($\chi^2 = 6.51$, $df = 1$, $p = 0.01$) and a lower frequency of rigidity ($\chi^2 = 3.99$, $df = 1$, $p = 0.046$) was noted in *GBA* mutation carriers. However, these results should be interpreted with caution, as applying Bonferroni correction for multiple comparison sets the cutoff *p* value from the a priori $p = 0.05$ to $p = 0.006$. Therefore, the over-representation of weakness and under-representation of rigidity as presenting symptoms in *GBA* mutation carriers is only of borderline significance.

DISCUSSION The well-defined Ashkenazi population, which carries a significantly high frequency of mutant *GBA* alleles, is extremely valuable for validation and further elucidation of the relationship between *GBA* mutations and PD risk. The first association study, reporting a 31.3% *GBA* carrier frequency in Jewish Ashkenazi patients with PD compared to 4–6% in ethnically matched controls,[15] generated considerable interest. However, the discrepancy between these results and threefold lower frequencies in two ethnically similar cohorts, 10.6% in a multicenter Israeli study of 150 Jewish Ashkenazi patients with PD[16] and 10.7% in a Jewish American cohort of 160 patients with PD,[17] raised a number of questions regarding the validity of the association. Our study resolves this discrepancy, confirming that genetic variance in *GBA* is a risk factor for PD.

Our cohort afforded a sufficient frequency of variant *GBA* alleles to permit the comparison of carriers of mild vs severe *GBA* mutations. Due to the increased representation of severe mutations in the PD group, the proportion of mild vs severe mutations varied significantly between *GBA* carriers in the young control and patient populations. We suggest that the reduced proportion of N370S among patient with PD *GBA* carriers might explain the 10.7% *GBA* carrier frequency reported previously in a Jewish PD cohort screened only for the N370S mutation.[17]

The marked overrepresentation of severe *GBA* mutations among patients with PD detected here allowed us to examine the possible clinical implications of carrying mild vs severe mutations. Carriers of severe mutations had a substantially increased disease risk and decreased AAO, compared to carriers of mild mutations, while patients homozygous or compound heterozygous for *GBA* mutations had the earliest AAO. Of note, previous studies in Ashkenazi patients,[15] ethnic Chinese patients,[21] and autopsy samples

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from American patients with PD[13] reported the influence of *GBA* carriage on early age at onset, and the development of parkinsonian symptoms in patients with GD has been reported mainly in patients' fourth and fifth decades.[3-11] Moreover, when calculating the average AAO of all homozygous and compound heterozygous *GBA* carriers published in these studies, together with the six patients from our cohort (a total of 37 patients), the average age at PD onset was 49.0 years, approximately 10 years earlier than the average onset of PD.

The high frequency of *GBA* mutant alleles in the Ashkenazi population together with observations of increased PD risk and early AAO among Ashkenazi carriers suggest that *GBA*-associated PD might represent a significant health risk in this population. Interestingly, while epidemiologic research has confirmed that PD occurs worldwide, with a higher prevalence rate among Caucasian populations, individuals of Jewish Ashkenazi ancestry have not been defined as a particularly high risk group for disease.[27] While our observations suggest that carriers of severe mutations have a significantly increased risk for disease, only about 1/250 Ashkenazis carry these mutations, therefore challenging their impact on PD frequency at the population level. On the other hand, carriers of the mild *GBA* mutations are more common, about 1/17, but have only a twofold increased disease risk. Furthermore, since PD is a disease of advanced age, carriers might have other lethal diseases prior to the onset of PD. Additionally, since the vast majority of *GBA* carriers and individuals with homozygous or compound heterozygous *GBA* mutations never develop PD,[28-30] it is likely that disease risk is influenced by additional genetic modifiers and environmental factors. These issues must be carefully considered, together with the absence of proven presymptomatic medical or behavioral interventions that can modify the natural history of PD, before meaningful genetic counseling can be offered to thousands of young Jewish individuals who perform genetic screening tests for *GBA* mutations.

Mutations in the *LRRK2* gene are the most common genetic determinant of PD identified to date.[31] The significant frequency of the common *LRRK2* G2019S mutation in Ashkenazi Jewish patients with PD[25,32,33] suggests a possible relationship between *LRRK2* G2019S and *GBA* variants in PD risk in Ashkenazi Jews. Given the frequency of *LRRK2* G2019S in our patient population,[25] 12 of the 81 *GBA* mutation carriers detected herein were also expected to harbor *LRRK2* G2019S. The detection of only four such patients (two tailed $\chi^2 = 5.49$, $df = 1$, $p = 0.04$), who lacked remarkable clinical symptoms or an earlier AAO, may suggest that these founder mutations occurred in distinct Ashkenazi Jewish subpopulations, who due to sociogeographic factors have not been fully mixed. Interestingly, the separate analysis of *LRRK2* G2019S carrier, *GBA* carrier, and noncarrier patients with PD in our cohort revealed an earlier age at disease onset in *LRRK2* G2019S carriers, compared to noncarriers, a finding that was masked in our previous analysis.[25]

Our data demonstrate that more than one third of our Ashkenazi patients with PD carried a mutation in genes that are associated with or contribute to the development of PD, *GBA* or *LRRK2*. However, since a substantial percentage of our cohort reporting a familial history of PD did not carry these mutations, it is likely that additional genetic factors influence PD susceptibility in this population. Genetic studies have provided tremendous insight into the molecular mechanisms underlying PD pathogenesis, suggesting roles for genes involved in putative pathogenic pathways including lipid and vesicle dynamics, the accumulation of aberrant or misfolded protein, impaired ubiquitin-proteosomal system, mitochondrial dysfunction, and the impairment of mechanisms protecting from oxidative stress and apoptosis.[31,34-37] We therefore suggest that additional studies of patients with PD of Ashkenazi origin could be of great importance for further understanding of the proposed PD-causing and PD-risk genes, and the genetic contribution to PD.

ACKNOWLEDGMENT

The authors thank the patients and their spouses for their participation in this study. The assistance of Dr. Helena Yagev-More, Ilana Elroi, Drs. Balash, Merims, and Shabtai, and Orna Moore is acknowledged.

Received August 15, 2007. Accepted in final form October 22, 2007.

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