Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease

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Abstract

Objective—To evaluate the frequency of glucocerebrosidase (*GBA*) mutations in cases and controls enrolled in the Genetic Epidemiology of Parkinson's Disease (GEPD) study.

Methods—We sequenced all exons of the *GBA* gene in 278 Parkinson disease (PD) cases and 179 controls enrolled in GEPD, with a wide range of age at onset (AAO), and that included a subset of 178 Jewish cases and 85 Jewish controls. Cases and controls were recruited without knowledge of family history of PD, and cases were oversampled in the AAO < 50 years category.

Results—13.7% of PD cases (38/278) carried *GBA* mutations, compared with 4.5% of controls (8/179) (odds ratio [OR] 3.4, 95% CI 1.5 to 7.4). The frequency of *GBA* mutations was 22.2% in 90 cases with AAO ≤ 50 years, compared with 9.7% in 185 cases with AAO > 50 years (OR 2.7, 95% CI 1.3 to 5.3). Adjusting for age at the time of evaluation, sex, family history of PD, and Jewish ancestry, *GBA* carriers had a 1.7-year-earlier AAO of PD (95% CI 0.5 to 3.3, $p < 0.04$) than noncarriers. The average AAO of PD was 2.5 years earlier in carriers with an AAO ≤ 50 years compared with noncarriers (95% CI 0.6 to 4.5, $p < 0.01$) and this was not seen in the AAO > 50 years group. The frequency of *GBA* mutations was higher in a subset of 178 cases that reported four Jewish grandparents (16.9%) than in cases who did not report Jewish ancestry (8.0%) ($p < 0.01$). Nine different *GBA* mutations were identified in PD cases, including 84insGG, E326K, T369M, N370S, D409H, R496H, L444P, Rec*NciI*, and a novel mutation, P175P.

Conclusions—This study suggests that the *Glucocerebrosidase* gene may be a susceptibility gene for Parkinson disease and that *Glucocerebrosidase* mutations may modify age at onset.

Gaucher disease (GD; MIM 230800), a lysosomal lipid storage disease, is one of the most common genetic diseases reported in the Ashkenazi Jewish population and is caused by mutations in the β-glucocerebrosidase (*GBA*) gene (reviewed in reference 1). In adult-onset "nonneuronopathic" GD (Type 1), a range of neurologic manifestations can occur, which

can include parkinsonism.[2–8] A family history of parkinsonism has been reported in patients with GD.[7] An association of the *GBA* N370S mutation was recently reported in Ashkenazi Jews,[9] and four studies report an increased frequency of different *GBA* mutations (84insGG, N370S, L444P, Rec*Nci*I, K198T, T369M, E326K, IVS1 + 1, V394L, and R496H) in Parkinson disease (PD) cases compared with controls,[10–13] and in pathologically confirmed dementia with Lewy bodies.[14] The *GBA* mutations, L444P and N370S, were found at a similar frequency in Norwegian PD cases (2.3%, 7/311) and controls (1.7%, 8/474), suggesting that these disease alleles are not risk factors for parkinsonism in this population.[15] In the present study, we explored the contribution of the *GBA* locus to PD by sequencing the *GBA* gene in PD cases and controls enrolled in a study of the genetic epidemiology of PD[16] (GEPD), that included a subset (cases n = 178, controls n = 85) who reported that all four grandparents were Jewish.

METHODS

Subjects

PD cases and controls were a subset of participants in the GEPD study.[16] We included all 178 cases and 85 controls who reported that all four grandparents were Jewish. One hundred PD cases who reported that all four grandparents were not Jewish were frequency matched to PD cases of Jewish ancestry by age at onset (AAO) of PD and sex. Ninety-four randomly chosen controls who were previously sequenced for mutations in the parkin gene and did not report Jewish ancestry were also included.[17] All cases were recruited from the Center for Parkinson's Disease and Other Movement Disorders at Columbia University. All met research criteria for PD.[18] The majority of controls were recruited by random digit dialing and were frequency matched by age, sex, ethnicity, and area code/exchange. The remaining controls were recruited from a 50% sample of Medicare recipients aged 65 years who resided in the Washington Heights community.[16] All controls underwent the same evaluation as cases, which included a medical history, Unified Parkinson's Disease Rating Scale (UPDRS),[19] and modified Mini-Mental State Examination (MMSE).[20] Family history of PD and related disorders in first-degree relatives was obtained using a structured interview that has been shown to be reliable and valid.[16,21] Information on Jewish ancestry in each of the grandparents was obtained during that interview. Information about Ashkenazi origin was not specifically obtained; however, approximately 90% of Jews in the United States are Ashkenazi.[22]

Molecular genetic analysis

Sequencing—PCR and amplification of the *GBA* gene was performed. The PCR and sequencing primers used for amplification of *GBA* have been described previously.[23] Cycle sequencing in forward and reverse directions was performed on purified PCR products and run on an ABI 3700 genetic analyser (Applied Biosystems, Foster City, CA). Sequence chromatograms were viewed and genotypes determined using Sequencher (Genecodes).

Statistical analysis

Demographic and clinical characteristics of PD cases compared with controls and mutation carriers compared with noncarriers were analyzed using χ^2 tests or Fisher exact tests for categorical data and Student's *t* tests for continuous data. Logistic regression was used to calculate the log odds and 95% CIs for being a *GBA* mutation carrier in the entire sample, and stratified by Jewish and non-Jewish ancestry. Separate analyses were performed for carriers and noncarriers of the NS370S mutation. Multiple logistic regression was used to examine the effect of *GBA* mutation carrier status on AAO of PD adjusting for age at the time of the evaluation, sex, family history of PD, and Jewish ancestry. Separate analyses were performed for cases recruited with AAO 50 years and AAO > 50 years because the

original sample was enriched for cases with AAO 50 years, and slightly different inclusion criteria were used.[16] Empirical distributions of AAO in PD carriers and noncarriers were plotted to examine the difference in AAO.

RESULTS

Mutations identified in the *GBA* gene

GEPD—We sequenced all exons of the *GBA* gene in a total of 278 cases and 179 controls enrolled in GEPD. Overall, nine different mutations were identified in PD cases, including the frameshift mutation 84*insGG*; six missense mutations, N370S, D409H, R496H, L444P, E326K, and T369M; the recombinant mutation Rec*NciI* (L444P + A456P + V460V); and the synonymous substitution P175P (table 1 and figure 1). Eight of the mutations, 84*insGG*, N370S, D409H, R496H, L444P, E326K, T369M, and Rec*NciI*, have been reported previously. The synonymous substitution P175P is novel and was absent in 358 control chromosomes. We identified a total of 3 homozygous (Jewish), 34 heterozygous (Jewish and non-Jewish), and 1 compound heterozygous (non-Jewish) PD case that carried *GBA* mutations (table 1).

All PD cases included in the current study have been analyzed for parkin mutations and genotyped for the LRRK2 mutations G2019S, L1114L, I1122V, R1441C, and Y1699C. None of the *GBA* mutation carriers had *parkin* mutations. However, one Jewish PD case heterozygous for N370S also carried the LRRK2 G2019S mutation.

Jewish PD cases and controls—16.9% (30/178) of Jewish PD cases carried GBA mutations, compared with 7.1% (6/85) of Jewish controls (odds ratio [OR] 2.7, 95% CI 1.1 to 6.7). Six different mutations were identified in Jewish PD cases, including the frameshift mutation 84*insGG*; four missense mutations, N370S, R496H, E326K, and T369M; and the synonymous substitution P175P (table 1 and figure 1). Five of the mutations, 84*insGG*, N370S, R496H, E326K, and T369M, have been reported previously and are common in the Jewish population.[24] The synonymous substitution P175P is novel and was absent in 358 control chromosomes, which included 178 Jewish control chromosomes. We identified a total of 3 homozygous and 28 heterozygous Jewish PD cases that carried *GBA* mutations (table 1). The following mutations were also observed in controls: N370S, T369M, and E326K (table 1). The N370S allele frequency observed in Jewish controls is consistent with our previously published study, which included only Jewish PD cases and Jewish controls genotyped for the *GBA* N370S mutation from GEPD.[12] An allele frequency of approximately 1% was observed for T369M in Jewish controls,[2] and one Jewish control carried E326K.

Non-Jewish PD cases and controls—Eight percent (8/100) of non-Jewish PD cases carried GBA mutations, compared with 2.1% (2/94) of non-Jewish controls (OR 4.0, 95% CI 0.8 to 19.3). Four different missense mutations were identified in non-Jewish PD cases, including N370S, T369M, D409H, and L444P, and one non-Jewish PD case carried the Rec*NciI* mutation (table 1 and figure 1). Four non-Jewish mutation carriers were heterozygous, and one carrier was compound heterozygous (table 1). One non-Jewish control carried the T369M mutation. None of the non-Jewish controls carried the N370S mutation or any of the other mutations identified in non-Jewish PD cases (table 1).

Frequency and clinical characteristics of mutation carriers

GEPD—The demographic characteristics of sequenced cases and controls are shown in table 2. Compared with GEPD subjects who were not sequenced, cases and controls were older, were more likely to be white, and had more years of education ($p < 0.01$; data not

shown). Sequenced cases also had a later AAO compared with all cases in GEPD ($p < 0.01$; data not shown). Controls were more likely to be non-white compared with cases ($p < 0.01$) because of the inclusion of a group of non-Jewish controls.[17] There were more Jewish cases than Jewish controls in the GEPD study, as reflected in this analysis ($p < 0.01$; table 2). Thirty-eight PD cases (13.7%) and 8 controls (4.5%) carried *GBA* mutations, including 30 Jewish PD cases and 6 Jewish controls. Seventy percent of the Jewish carriers had the N370S mutation, compared with 25% of non-Jewish carriers.

The odds of being a carrier of a *GBA* mutation based on specific demographic and clinical characteristics are shown in table 3. Overall, PD cases were 3.4 times as likely as controls (95% CI 1.5 to 7.4) to carry a *GBA* mutation. Individuals of Jewish ancestry were significantly more likely to carry a mutation than non-Jews (in both cases and controls), and this was also true for Jewish PD cases compared with non Jewish PD cases (OR 2.3, 95% CI 1.02 to 5.30, $p = 0.045$). Of note, family history of PD in a first-degree relative did not influence the log odds of carrying a mutation in the entire group or when stratified by Jewish ancestry. We also analyzed carriers and noncarriers of N370S mutations separately. PD cases were 5.6 times (95% CI 1.3 to 24.3) as likely as controls to carry N370S mutations, and early-onset cases were 3.4 times as likely (95% CI 1.2 to 7.5) as late-onset cases to carry this specific mutation. Family history of PD in a first-degree relative had no influence on the presence of the N370S mutation.

We also compared the clinical characteristics of PD cases who carried *GBA* mutations with PD cases who did not carry mutations. Mutation carriers report an earlier AAO and current age at evaluation compared with noncarriers ($p < 0.01$). Carriers did not differ from noncarriers in the presence of the cardinal features of PD, UPDRS Part III score, modified MMSE score, or Hoehn and Yahr score. However, carriers were more likely to report tremor as a first symptom compared with noncarriers ($p < 0.01$). They also were more likely to report the presence of dyskinesias; however, the dose of levodopa was significantly higher among carriers (687.0 mg, SD 396.5 mg) than among noncarriers (493.4 mg, SD 343.5 mg, n = 155, $p = 0.02$). The demographic and clinical characteristics of Jewish mutation carriers did not differ from those of non-Jewish mutation carriers (table E-1 on the *Neurology*® Web site at www.neurology.org).

Jewish mutation carriers—Jewish PD cases with AAO 50 years were significantly more likely than those with AAO > 50 years to carry *GBA* mutations (OR 2.4, 95% CI 1.1 to 5.4). Family history of PD in a first-degree relative did not influence the log odds of carrying a GBA mutation in Jewish cases (OR 1.4, 95% CI 0.5 to 4.0).

Non-Jewish mutation carriers—*GBA* mutations were not associated with PD among non-Jewish PD cases compared with controls (OR 4.0, 95% CI 0.8 to 19.3). When non-Jewish PD cases were stratified by AAO, a total of 16.2% of PD cases had early-onset PD (AAO 50 years), compared with 3.3% of PD cases with late-onset PD (AAO > 50 years). As observed in PD cases with Jewish ancestry, non-Jewish PD cases with AAO 50 years were significantly more likely than those with AAO > 50 years to carry *GBA* mutations (OR 5.7, 95% CI 1.1 to 30.0). Family history of PD in a first-degree relative did not influence the log odds of carrying a GBA mutation in non-Jewish cases (OR 0.3, 95% CI 0.04 to 2.9).

GBA mutations modify age at onset of PD

We constructed a model to predict AAO of PD, adjusting for the independent effects of age at evaluation, sex, whether the individual had an AAO 50 or > 50 years (since we oversampled for AAO 50 years), and whether the individual carried a *GBA* mutation. Carriers of *GBA* mutations had an AAO 1.7 years earlier than noncarriers (95% CI 0.04 to

3.3, $p < 0.04$). Among cases with AAO 50 years, the average AAO of PD was 2.5 years younger in GBA carriers than in noncarriers (95% CI 0.6 to 4.5 years, $p < 0.01$). However, AAO did not differ between carriers and noncarriers among cases with AAO > 50 years (95% CI −0.1 to 8.0 years, $p = 0.06$). When restricted to carriers and noncarriers of N370S, using the same model, carriers had a 2.0-year-earlier onset (95% CI 0.03 to 4.09 years, $p < 0.04$), and this difference was also confined to those who had an AAO < 50 years (3.0 years, 95% CI 0.45 to 5.70 years, $p < 0.02$). The cumulative incidence of PD in carriers and noncarriers is displayed graphically in the entire sample and in early-onset (50 years) and late-onset (>50 years) cases in figure 2. Significant differences in AAO are seen for the entire sample (figure 2A) and in the early-onset group (figure 2C).

DISCUSSION

This is the first study to sequence the *GBA* gene in both PD cases and matched controls. We have demonstrated that mutations in the *GBA* gene are associated with PD, are more frequent in Jewish PD cases than non-Jewish PD cases, and are more frequent in cases with AAO 50 years compared with AAO > 50 years in both Jewish and non-Jewish cases. Two other studies have also observed *GBA* mutations in early-onset PD cases.[10,13] We also showed that among cases with AAO 50 years, the presence of a *GBA* mutation decreased AAO by almost 2 years compared with noncarriers. We did not demonstrate familial aggregation in Jewish or non-Jewish cases, suggesting that the mutations, the majority of which were heterozygous, have reduced penetrance in first-degree relatives. Reduced penetrance has also been observed for other PD susceptibility genes, particularly when heterozygous mutations are observed in PD cases. For example, in a case–control study of the parkin gene, family history of PD in a first-degree relative did not differ significantly between mutation carriers and noncarriers ($p = 0.35$).[17] To date, there have been numerous reports of heterozygous mutations in PD cases in familial PD genes, including Parkin,[17,25–36] DJ-1,[31,37] and PINK1.[38–40] It is still unclear whether a single heterozygous mutation in these genes is the causative factor or merely a risk allele. However, some studies indicate that heterozygous parkin mutation carriers may have an increased susceptibility to PD.[41–45] The low penetrance observed for several PD susceptibility genes suggests that disease expression may be modified by additional genetic and environmental factors which may account for an "observed" decreased family history in mutation carriers.

In this study, the frequency of *GBA* mutations in cases with PD was 13.7% and was higher in PD cases with Jewish ancestry (16.9%) than in non-Jews (8%). Only one previously published study has sequenced the *GBA* gene in PD cases, and a carrier frequency of 21% (12/57) was observed.[10] All other studies have assessed the frequency of "common" *GBA* mutations, and mutation frequencies ranging from 2.3% (7/311) in a Norwegian population[15] to 5.7% (5/88)[11] in a North American population and 31.3% (31/99)[9] in an Ashkenazi Jewish population from Israel have been reported. Our results confirm that *GBA* mutations are risk factors in both sporadic and familial PD and modify AAO.

The frameshift mutation 84insGG; the missense mutations N370S, L444P, R496H, and D409H; and the recombinant mutation Rec*Nci*I (L444P + A456P + V460V) are predicted to result in decreased catalytic activity or result in conformational changes in the β-glucocerebrosidase protein and have been previously reported in PD cases. We identified one novel mutation, P175P, in the homozygous state. Four PD cases carried either T369M[3] or E326K.[1] We consider these variants to be polymorphisms because we also identified them in controls at a similar frequency. This is consistent with a previous publication that analyzed the *GBA* gene in PD cases.[10] In GD, both T369M and E326K have been described as "mild" mutations or modifier alleles and are always observed with pathogenic mutations on the same allele. In our study, we did not observe a "second" mutation that co-occurred

with either T369M or E326K, suggesting that they are unlikely to be pathogenic. However, the E326K variant has been observed together with a novel mutation T267I in a PD case who presented initially with parkinsonism and had a neuropathologic diagnosis of dementia with Lewy bodies (DLB).[14]

Although further studies will be required to determine the pathogenic role of different GBA variants identified in PD cases, two studies suggest that the N370S and L444P variants are pathogenic in the heterozygous state.[10,46] In PD subjects heterozygous for the N370S variant, GBA enzyme activity in brain tissue is reduced (50% to 84%) compared with controls.[10] PET studies in two GBA mutation carriers, a father (heterozygous for L444P) and his son (compound heterozygous for L444P and F213I), both of whom exhibited a parkinsonism phenotype, demonstrated that there is presynaptic dopaminergic neuronal dysfunction of the type normally seen in PD patients.[46] A striatal dopaminergic deficit has also been observed in PD patients heterozygous for a *parkin* mutation.[43]

The identification of mutations in the *GBA* gene in PD and DLB cases and the associated neuropathologic findings suggest that the *GBA* gene may by a susceptibility gene for synucleopathies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

GLOSSARY

AAO	age at onset
cDNA	complementary DNA
GBA	glucocerebrosidase
GD	Gaucher disease
GEPD	Genetic Epidemiology of Parkinson's Disease
MMSE	Mini-Mental State Examination
NA	not applicable
DLB	dementia with Lewy bodies
OR	odds ratio
PD	Parkinson disease
SNP	single nucleotide polymorphism
UPDRS	Unified Parkinson's Disease Rating Scale

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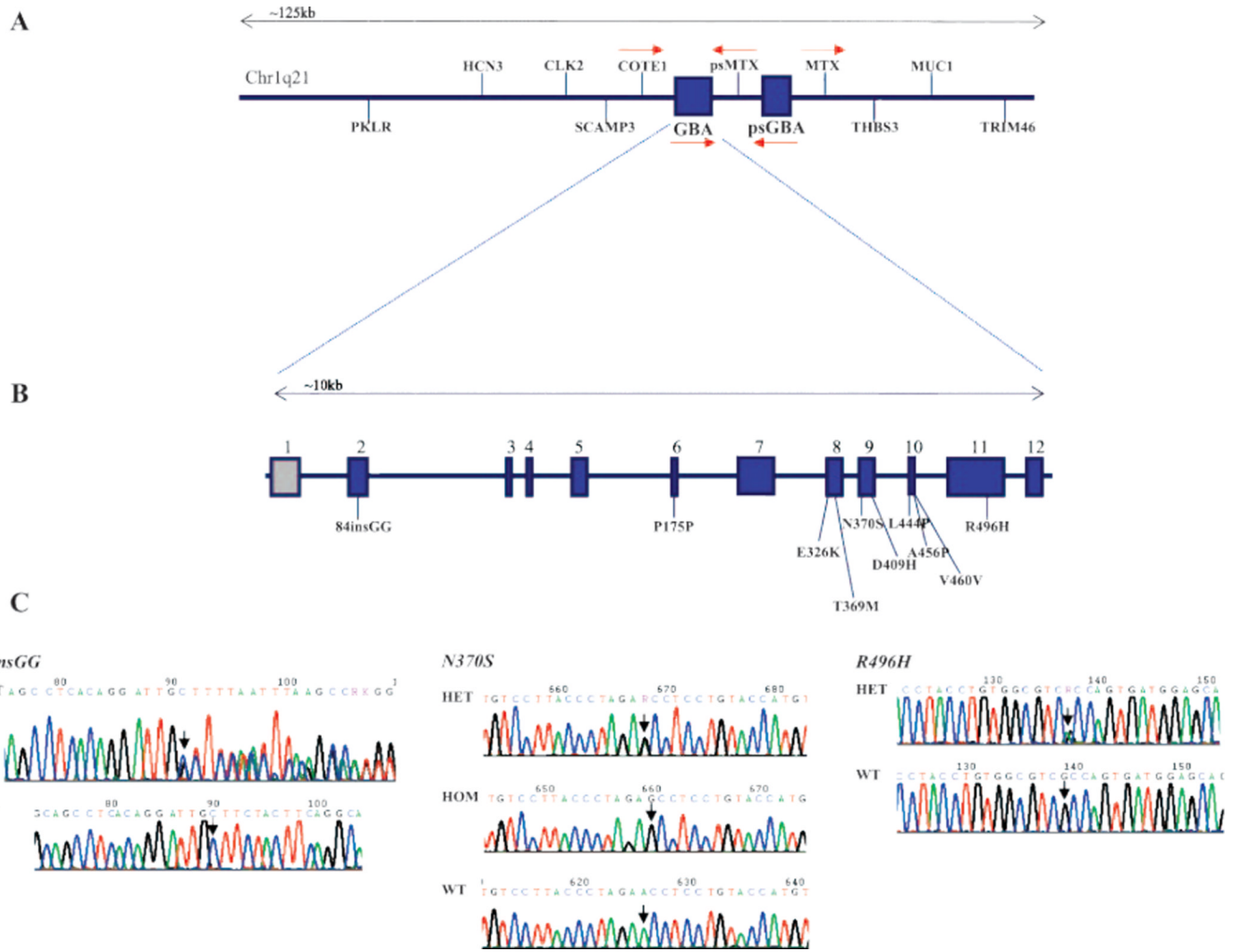
Figure 1.
Schematic of genes located at the chr1q21 locus that includes *GBA* (A); a schematic of the *GBA* gene showing the location of mutations identified in Parkinson disease (PD) cases (B); and sequence chromatograms showing the location of the N370S, 84insGG, and R496H mutations in PD cases (C)
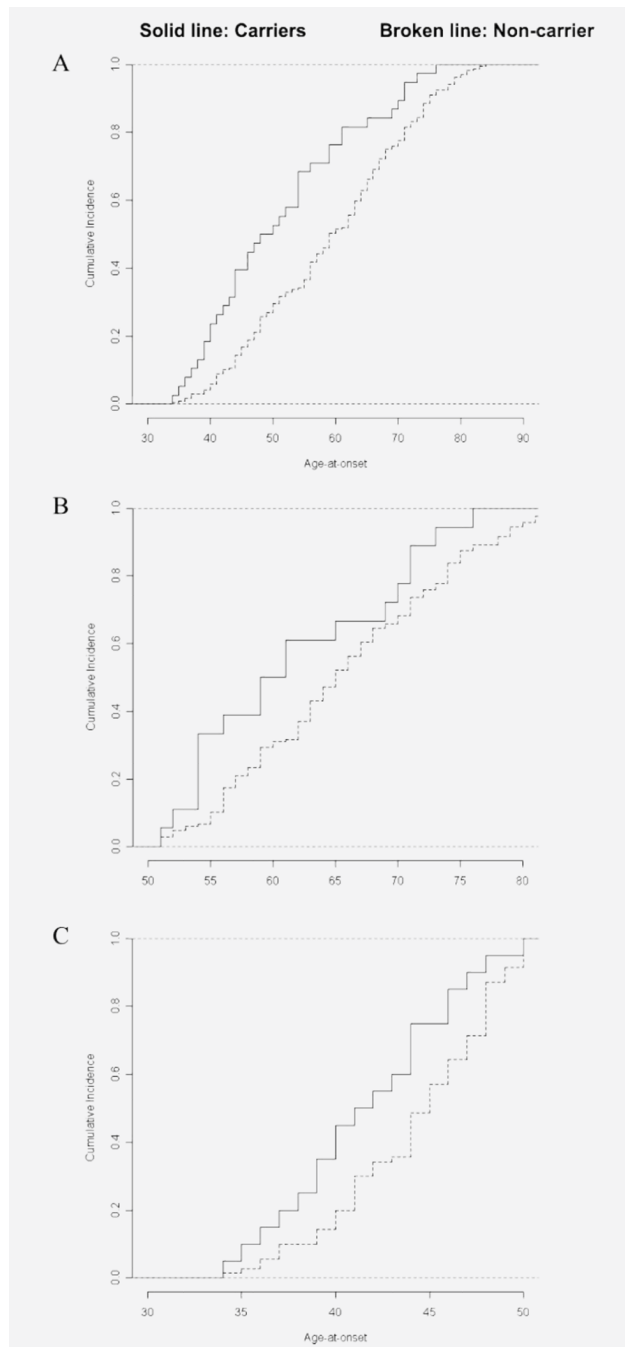
Figure 2.
Cumulative incidence rates of Parkinson disease in carriers and noncarriers
(A) Entire sample, (B) late onset, (C) early onset.

Table 1

GBA mutations identified in cases and controls and allele frequencies

Mutation/SNP, cDNA Acc#, M16328	No. of cases	Jewish ancestry	Exon	Amino acid change	Predicted effect on protein function	Zygosity	Allele frequency, non-Jewish controls, n = 188 chr	Allele frequency, Jewish controls, n = 170 chr
Nt.84insGG	5	Jewish	2	NA	Frameshift/Null	Het	0	0
Nt.1226 A>G	23	21 Jewish + 2 non-Jewish	9	N370S	Missense/Mild	21 Het, 2 Hom	0	0.02
Nt.1604G>A	1	Jewish	11	R496H	Missense/Mild	Het	0	0
Nt.1223C>T	3	1 Jewish, 2 non-Jewish	8	T369M	Unknown/Modifier allele?	Het	0.005	0.01
Nt.1093 G>A	1	Jewish	8	E326K	Unknown/Modifier allele?	Het	0	0.005
Nt.1067 C>T	1	Jewish	7	P175P	Unknown	Hom	0	0
Nt.1448T>C + nt.1483G>C + nt.1497G>C	1	Non-Jewish	10	RecNciI (L444P + A456P + V460V)	Missense/Severe	Comp. het	0	0
Nt.1343 A>T	1	Non-Jewish	9	D409H	Missense/Severe	Het	0	0
Nt.1448T>C	2	Non-Jewish	10	L444P	Missense/Severe	Het	0	0

SNP = single nucleotide polymorphism; cDNA = complementary DNA; NA = not applicable.

Table 2

Demographic characteristics of sequenced cases and controls

	Total, n = 457	Cases, n = 278	Controls, n = 179	Significance, cases vs controls
% Male (n)	60.2 (275)	62.6 (174)	56.4 (101)	0.20
Age (SD), y	65.3 (11.3)	65.6 (11.3)	64.9 (11.3)	0.57
Race				<0.01
% White (n)	98.0 (448)	100.0 (278)	95.0 (170)	
% African American (n)	0.7 (3)	0	1.7 (3)	
% Hispanic (n)	0.9 (4)	0	2.2 (4)	
% Other (n)	0.4 (2)	0	1.1 (2)	
Years of education (SD)	15.9 (3.0)	16.0 (3.0)	15.8 (2.9)	0.64
% Jewish (n)	57.6 (263)	64.0 (178)	47.5 (85)	<0.01
% with mutation (n)	10.1 (46)	13.7 (38)	4.5 (8)	<0.01
% with family history of PD (n)	13.8 (63/456)	18.8 (52)	6.2 (11)	<0.01

PD = Parkinson disease.

Table 3

Proportions of cases and controls with the mutation and odds ratios

	Total	No. with mutation	%	Odds ratio (95% CI)
All subjects				
Controls	179	8	4.5	
All PD cases	278	38	13.7	3.4 (1.5–7.4)
Late-onset PD cases	185	18	9.7	
Early-onset PD cases*	90	20	22.2	2.7 (1.3–5.3)
Cases without a family history of PD	226	32	14.2	
Cases with a family history of PD	52	6	11.5	0.8 (0.3–2.0)
Non-Jewish	194	10	5.2	
Jewish	263	36	13.7	2.9 (1.4–6.0)
Non-Jewish cases	100	8	8.0	
Jewish cases	178	30	16.9	2.3 (1.0–5.3)
Jewish subjects				
Controls	85	6	7.1	
All PD cases	178	30	16.9	2.7 (1.1–6.7)
Late-onset PD cases	124	16	12.9	
Early-onset PD cases*	53	14	26.4	2.4 (1.1–5.4)
Cases without a family history of PD	154	25	16.2	
Cases with a family history of PD	24	5	20.8	1.4 (0.5–4.0)
Non-Jewish subjects				
Controls	94	2	2.1	
All PD cases	100	8	8.0	4.0 (0.8–19.3)
Late-onset PD cases	61	2	3.3	
Early-onset PD cases*	37	6	16.2	5.7 (1.1–30.0)
Cases without a family history of PD	72	7	9.7	
Cases with a family history of PD	28	1	3.6	0.3 (0.04–2.9)

*
Early-onset Parkinson disease (PD) defined as age at onset   50 years.