Differential effects of severe vs mild *GBA* mutations on Parkinson disease

Ziv Gan-Or, MD, PhD*
Idan Amshalom, BMedSci*
Laura L. Kilarski, PhD
Anat Bar-Shira, PhD
Mali Gana-Weisz, PhD
Anat Mirelman, PhD
Karen Marder, MD
Susan Bressman, MD
Nir Giladi, MD
Avi Orr-Urtreger, MD, PhD

Correspondence to Dr. Orr-Urtreger: aviorr@tasmc.health.gov.il or Dr. Gan-Or: ziv.gan-or@mail.mcgill.ca

ABSTRACT

Objective: To better define the genotype-phenotype correlations between the type of *GBA* (glucosidase, beta, acid) mutation, severe or mild, and the risk and age at onset (AAO), and potential mechanism of Parkinson disease (PD).

Methods: We analyzed 1,000 patients of Ashkenazi-Jewish descent with PD for 7 founder *GBA* mutations, and conducted a meta-analysis of risk and AAO according to *GBA* genotype (severe or mild mutation). The meta-analysis included 11,453 patients with PD and 14,565 controls from worldwide populations. The statistical analysis was done with and without continuity correction (constant or empirical), considering biases that could potentially affect the results.

Results: Among Ashkenazi-Jewish patients with PD, the odds ratios for PD were 2.2 and 10.3 for mild and severe *GBA* mutation carriers, respectively. The observed frequency of severe *GBA* mutation carriers among patients with PD was more than 4-fold than expected (4.4% vs 0.9%, respectively, $p < 0.0001$, Fisher exact test). In the different models of the meta-analysis, the odds ratios for PD ranged between 2.84 and 4.94 for mild *GBA* mutation carriers and 9.92 and 21.29 for severe *GBA* mutation carriers ($p < 1 \times 10^{-6}$ for all analyses). Pooled analysis demonstrated AAO of 53.1 (±11.2) and 58.1 (±10.6) years for severe and mild *GBA* mutation carriers, respectively ($p = 4.3 \times 10^{-5}$).

Conclusions: These data demonstrate that mild and severe heterozygous *GBA* mutations differentially affect the risk and the AAO of PD. Our results have important implications for genetic counseling and clinical follow-up. ***Neurology*® 2015;84:880–887**

GLOSSARY

AAO = age at onset; **CI** = confidence interval; ***GBA*** = glucosidase, beta, acid; **GD** = Gaucher disease; **OR** = odds ratio; **PD** = Parkinson disease.

Mutations in *GBA* (glucosidase, beta, acid), encoding the lysosomal enzyme glucocerebrosidase, are important risk factors for Parkinson disease (PD) worldwide.[1] Positive association between *GBA* mutations and PD was demonstrated in various populations, including Asians,[2–6] Europeans,[7–12] North Africans,[13] North Americans[14–16] and South Americans,[17–20] but most frequently among Jews of Ashkenazi origin.[21,22]

When inherited from both parents, *GBA* mutations cause Gaucher disease (GD), a lysosomal storage disorder with 3 clinical types: nonneuropathic (type I), acute neuropathic (type II), and chronic neuropathic (type III). Accordingly, *GBA* mutations can be categorized as mild or severe: mild mutations are those that cause GD type I, and severe mutations are those that cause GD types II and III.[23] Approximately 300 *GBA* mutations have been described in GD, many of which are also found in PD. We previously reported genotype-phenotype correlations between *GBA* mutation severity and PD in a cohort of 420 Ashkenazi patients with PD.[22] Only a few case-control studies confirmed this observation,[7,24] while most studies did not examine it.

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Supplemental data at Neurology.org

*These authors contributed equally to this work.

From The Genetic Institute (Z.G.-O., I.A., A.B.-S., M.G.-W., A.O.-R.) and Movement Disorders Unit, Parkinson Center, and Department of Neurology (A.M., N.G.), Tel Aviv Sourasky Medical Center; The Sackler Faculty of Medicine (N.G., A.O.-U.), Tel Aviv University, Israel; Stroke and Dementia Research Centre (L.L.K.), St. George's, University of London, UK; Columbia University (K.M.), Columbia Presbyterian Medical Center, New York; and Beth Israel Medical Center (S.B.), New York, NY. Z.G.-O. is currently affiliated with the Department of Human Genetics and Montreal Neurological Institute, McGill University, Montreal, Canada.

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If this genotype-phenotype correlation is confirmed worldwide, it could be important for genetic counseling and clinical follow-up of *GBA* mutation carriers, and may also aid in understanding the pathophysiology of PD. The mechanism by which *GBA* mutations cause or increase the susceptibility for PD is not fully understood, and both gain- or

Table 1 Studies included in the meta-analysis

			Patients with PD		Controls		
Reference	Population	Mutations tested	Total	*GBA* mutation carriers, n (%)	Total	*GBA* mutation carriers, n (%)	Inclusion
21	Ashkenazi-Jewish	N370S, L444P, 84GG, IVS2+1, V394L, R496H	99	31 (31.3)	1,543	95 (6.2)	R[a]
33	Caucasian	N370S, K178T, 84GG, R329C, RecNcil, IVS2+1, L444P	88	5 (5.7)	122	1 (0.8)	R + A
17	Venezuelan	Whole-gene sequencing	33	4 (12.1)	31	1 (3.2)	R + A
34	Norwegian	N370S, L444P	311	7 (2.3)	474	8 (1.7)	R + A
6	Chinese	Whole-gene sequencing	92	4 (4.3)	92	1 (1.1)	R + A
4	Chinese	N370S, L444P	331	8 (2.4)	347	0 (0)	R + A
5	Taiwanese	L444P, RecNcil, R120W	518	16 (3.1)	339	4 (1.2)	R + A
20	Brazilian	N370S, L444P, G377S	65	2 (3.1)	267	0 (0)	R + A
14	Jewish	Whole-gene sequencing	178	30 (16.9)	85	6 (7.1)	R[a]
	Non-Jewish	Whole-gene sequencing	100	8 (8.0)	94	2 (2.1)	R[a]
35	Italian	N370S, L444P	395	11 (2.8)	483	1 (0.2)	R[a]
15	North American	N370S, L444P	721	21 (2.9)	554	2 (0.4)	R + A
7	Portuguese	Whole-gene sequencing	230	14 (6.1)	430	3 (0.7)	R[a]
11	British	Whole-gene sequencing	790	33 (4.2)	257	3 (1.2)	R + A
9	Greek	Whole-gene sequencing	172	11 (6.4)	132	4 (3.0)	R[a]
3	Japanese	Whole-gene sequencing	534	50 (9.4)	544	2 (0.4)	R[b]
36	Chinese	L444P	616	20 (3.2)	411	1 (0.2)	R[b]
37	Chinese	L444P	402	11 (2.7)	413	0 (0)	R + A
13	North African	Whole-gene sequencing	194	9 (4.6)	177	1 (0.5)	R + A
24	European	Whole-gene sequencing	1,130	76 (6.7)	391	4 (1.0)	R[a]
38	Taiwanese	L444P, D409H, R120W, L174P, Q497R	967	36 (3.7)	780	2 (0.3)	R[b]
16	French-Canadian	Whole-gene sequencing	212	22 (10.4)	189	11 (5.8)	R[a]
10	Greek	N370S, D409H, L444P, IVS10-1, H255Q, R120W, Y108C, IVS6-2	205	21 (10.2)	206	7 (3.4)	R + A
12	Spanish	Whole-gene sequencing	225	22 (9.8)	186	1 (0.5)	R + A
8	Russian	N370S, L444P	330	9 (2.7)	240	1 (0.4)	R[a]
19	Brazilian	N370S, L444P	347	13 (3.7)	341	0 (0)	R[a]
29	Serbian	Sequence of exons 8–11	360	21 (5.8)	348	5 (1.4)	R[a]
2	Korean	Whole-gene sequencing	277	9 (3.2)	291	0 (0)	R + A
39	Chinese	L444P, N370S, R120W	208	7 (3.4)	298	1 (0.3)	R[b]
40	Chinese	L444P, N370S, R120W	195	6 (3.1)	443	0 (0)	R + A
18	Mexican	L444P, N370S	128	7 (5.5)	252	0 (0)	R[c]
Current study	Ashkenazi-Jewish	N370S, R496H, 84GG, IVS2+1, V394L, D409H, L444P, RecTL	1,000	192 (19.2)	3,805	242 (6.4)	R + A

Abbreviations: A = included in meta-analysis of age at onset; PD = Parkinson disease; R = included in meta-analysis of risk.
[a] Excluded from age-at-onset (AAO) analysis because data not available.
[b] Excluded from AAO analysis because there were no data per mutation carrier, only average AAO.
[c] Excluded from AAO analysis because of preselected patients with PD with AAO younger than 45 years.

loss-of-function mechanisms have been suggested.[25]

Herein, we examined whether severe and mild *GBA* mutations differentially affect PD susceptibility or age at onset (AAO) by studying the largest Ashkenazi PD cohort investigated to date and by conducting a meta-analysis of all relevant published case-control studies.

METHODS

Population. The patient population in Tel Aviv included 1,000 consecutively recruited patients with PD, all unrelated, of full Ashkenazi-Jewish descent, who were examined at the Movement Disorders Unit at the Tel Aviv Sourasky Medical Center between July 2005 and August 2013. Details regarding their recruitment, diagnostic criteria, and interview procedure were previously described, including data for the first 420 patients recruited.[22] In this cohort, 61% of the patients with PD are men, the average age at symptom onset is 60.1 ± 11.2 years, and the average age at enrollment is 67.4 ± 10.5 years. The control population included 3,805 individuals who have been previously described.[22]

Standard protocol approvals, registrations, and patient consents. All participants provided informed consent before entering the study. The Institutional and National Supreme Helsinki (Institutional Review Board) Committees for Genetic Studies approved the study protocols and the informed consent.

Selection of studies for meta-analysis. To identify all studies that analyzed *GBA* mutations in PD populations, we searched PubMed using all combinations of the following search terms: "*GBA*," "glucocerebrosidase," "Parkinson," "Parkinson's," and "parkinsonism." The search was performed in May 2014. All studies that reported the genotypes of *GBA* mutations in patients with PD and controls (n = 31 including the current study; table 1) were included in the analysis of risk, and all studies that reported the AAO of the different *GBA* mutation carriers were included in the analysis of AAO (n = 16 including the current study; table 1). Studies were excluded from the analysis of AAO for one of the following reasons: (1) there were no data on the mutations or AAO (11 studies were excluded based on this criterion; table 1); (2) there were no data on AAO per carrier (4 studies were excluded based on this criterion; table 1); or (3) if early-onset cases were preselected (one study was excluded, defined as AAO <45 years[18]).

Classification of mutations in meta-analysis. Mutations were defined as mild or severe according to a previously published classification that inferred the definition of the mutation as mild or severe based on the resulting GD. Mutations that caused the nonneuropathic type I GD were classified as mild, and mutations that caused the neuropathic types II and III were classified as severe.[23] Because this classification was published in 2005, we searched for new information regarding mutations that were found in the studies analyzed here and were classified as unknown in the reference.[23] The p.I260T mutation (described in a patient with PD in reference 12) is now classified as severe based on a report of a patient with type II GD with this mutation,[26] the p.S271G mutation (described in a patient with PD in reference 2) is now classified as mild based on a report of a patient with type I GD with this mutation,[27] and the p.R277C mutation (described in a patient with PD in reference 2) is now classified as mild based on a report of a patient with type I GD with this mutation.[28] The classification of all the mutations is detailed in table e-1 on the *Neurology*® Web site at Neurology.org.

Genotyping in the Tel Aviv sample. DNA was extracted from white blood cells by using a standard salting-out protocol, and the genotyping of founder *GBA* mutations and the *LRRK2* p.G2019S mutation was performed as previously described.[22] In brief, patients and controls were tested for the 84GG, IVS2+1, p.N370S, p.L444P, p.V394L, p.R496H, and 370Rec (previously referred to as RecTL[23]) *GBA* mutations using PRONTO Gaucher kits (Pronto Diagnostics, Rehovot, Israel). The 3,805 controls were not tested for the p.R496H mutation, because it was not recommended by the Israeli Society of Medical Geneticists to be included in the *GBA* mutation screening panel. The *LRRK2* p.G2019S mutation (rs34637584) was also detected using TaqMan assay ID C_63498123_10 in the StepOnePlus Real-Time PCR System (Applied Biosystems, Foster City, CA).

Statistical analysis. ***Analysis of 1,000 Ashkenazi-Jewish patients with PD.*** Differences in continuous variables were tested using analysis of variance, Mann–Whitney, or Kruskal-Wallis tests, and χ^2 or Fisher exact test was used for comparison of categorical variables. To test for any deviation from Hardy-Weinberg equilibrium among patients with PD and controls, a goodness-of-fit test with 1 degree of freedom was applied. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using an online calculator (DJR Hutchon Calculator). There are 2 mild founder mutations in the Ashkenazi population: p.R496H and p.N370S. Because the p.R496H mutation was not tested among the young Ashkenazi controls, the calculated OR of mild mutation carriers in the Ashkenazi population refers only to p.N370S mutation carriers. For the analysis of risk and AAO, carriers of the *LRRK2* p.G2019S mutation were excluded. SPSS software version 17 (SPSS Inc., Chicago, IL) was used for all other data analyses.

Meta-analysis. Cochran-Mantel-Haenszel test was used for pooling study outcomes, and the Tarone test was used for determining heterogeneity. The analysis was conducted using the "metafor" package in R. Because some of the studies included in the meta-analysis had no (zero) severe or mild *GBA* mutation carriers in either patients with PD or controls, not allowing for calculation of ORs, the meta-analysis was done both with and without a continuity correction. AAO of severe or mild *GBA* mutation carriers were pooled together, and Student *t* test was used for statistical analysis. To avoid bias regarding the analysis of AAO, studies that included only patients with early-onset PD were excluded. In addition, all individuals with available data on mutations other than *GBA*, which may affect the AAO of PD, such as *LRRK2*, *Parkin*, and *PINK1* mutations, were excluded.

RESULTS

PD risk in mild vs severe *GBA* mutation carriers among 1,000 patients of Ashkenazi origin. Table 2 details the frequencies of *GBA* mutations that were identified among 1,000 patients with PD and 3,805 controls of full Ashkenazi-Jewish origin. The OR for PD among mild *GBA* mutation carriers was 2.2 (95% CI 1.7–2.8, including only the p.N370S mutation, because the p.R496H mutation was not tested in controls; see the methods section), compared with 10.3 (95% CI 5.8–18.0) among severe *GBA* mutation carriers. To examine whether these ORs were significantly different, the expected vs

Table 2 *GBA* mutations in 1,000 patients with PD and 3,805 controls of full Ashkenazi ancestry

GBA mutation	Patients with PD[a] (n = 1,000), % (n)	Controls[a] (n = 3,805), % (n)	OR (95% CI)	p Value
Heterozygous carriers				
p.N370S/+	12.0 (120)	5.89 (224)	2.2 (1.7–2.8)	<0.0001
p.R496H/+[b]	1.6 (16)	NT	NA	NA
84GG/+	2.1 (21)	0.16 (6)	13.6 (5.5–33.7)	<0.0001
IVS2+1G>A/+	0.5 (5)	0.03 (1)	19.1 (2.2–163.8)	0.002
p.V394L/+	0.7 (7)	0.11 (4)	6.7 (2.0–22.9)	0.003
p.L444P/+	0.3 (3)	0.11 (4)	2.9 (0.6–12.8)	0.16
370Rec/+	0.8 (8)	0.05 (2)	15.3 (3.3–72.3)	<0.0001
Total mild *GBA* mutation carriers	13.6 (136)	5.89 (224)	2.2 (1.7–2.8)	<0.0001
Total severe *GBA* mutation carriers	4.4 (44)	0.45 (17)	10.3 (5.8–18.0)	<0.0001
Total heterozygous carriers	18.0 (180)	6.35 (241)	3.2 (2.6–4.0)	<0.0001
Homozygous/compound heterozygous				
p.N370S/p.N370S	0.3 (3)	0.03 (1)	11.4 (1.2–110.2)	0.03
p.N370S/p.R496H	0.3 (3)	0 (0)	NA	NA
p.N370S/370Rec	0.2 (2)	0 (0)	NA	NA
p.N370S/p.V394L	0.3 (3)	0 (0)	NA	NA
p.V394L/p.R44C[b]	0.1 (1)	0 (0)	NA	NA
Total homozygous and compound heterozygous carriers	1.2 (12)	0.03 (1)	42.3 (5.4–328.1)	<0.0001
Total heterozygous, homozygous, and compound heterozygous carriers	19.2 (192)	6.4 (242)	3.5 (2.9–4.3)	<0.0001

Abbreviations: CI = confidence interval; NA = not applicable; NT = not tested; OR = odds ratio; PD = Parkinson disease.
[a] Including 420 patients and controls that were previously published.[22]
[b] The p.R496H and p.R44C mutations were not included in the OR calculation because they were not tested in the control group.

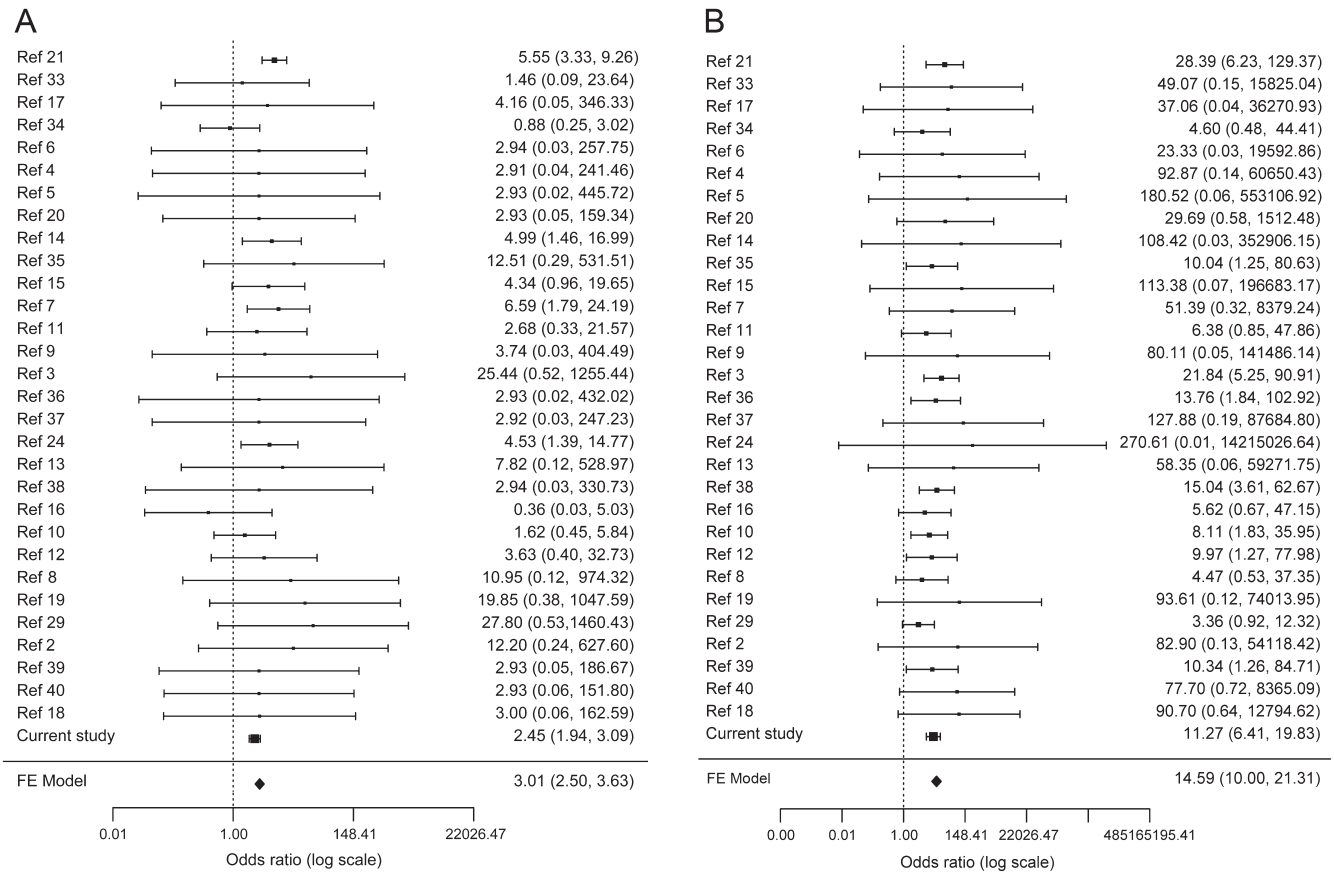
observed frequency of severe *GBA* mutations among patients was analyzed. Based on the frequencies of mild *GBA* mutations, which are 2.04 more frequent in patients than in controls, the expected frequency of carriers of a severe *GBA* mutation among 1,000 patients with PD was 0.92%, while the observed frequency was significantly higher, at 4.4% ($p < 0.0001$, Fisher exact test).

Differential effects of severe vs mild *GBA* mutations: A meta-analysis. To further determine whether the effects of severe vs mild *GBA* mutations on risk and AAO of PD are a common phenomenon worldwide, we conducted a meta-analysis that included all studies published until May 2014. We found 31 peer-reviewed publications with data on *GBA* mutation types, including our current study, with a total of 11,453 patients with PD and 14,565 controls, and 16 studies with data on AAO per individual with a *GBA* mutation.

When including studies that identified severe and mild *GBA* mutation carriers among both patients and controls, the pooled ORs for PD in mild and severe *GBA* mutation carrier groups were 2.84 (95% CI 2.34–3.45; 11 studies were included; figure e-1A) and 10.28 (95% CI 6.95–15.20; 14 studies were included; figure e-1B), respectively ($p < 1 \times 10^{-20}$ for both). Using a constant continuity correction of 0.5 for studies with no (zero) severe or mild *GBA* mutation carriers among either patients or controls, the ORs for PD in mild and severe *GBA* mutation carrier groups were 3.07 (95% CI 2.53–3.71) and 15.49 (95% CI 10.50–22.86), respectively ($p < 1 \times 10^{-20}$ for both; figures e-1C and e-1D). Using empirical continuity correction based on case/control ratio and estimated prior OR (see methods), the ORs for PD among mild and severe *GBA* mutation carriers were 3.01 (95% CI 2.50–3.63) and 14.59 (95% CI 10.00–21.31), respectively ($p < 1 \times 10^{-20}$ for both; figure 1).

The same analysis was conducted excluding our current data for 1,000 Ashkenazi patients and 3,805 controls to avoid the possibility of bias of the results (figure e-2, A–F). When excluding studies with no (zero) severe or mild *GBA* mutation carriers in either patients or controls, the pooled ORs for PD among mild and severe *GBA* mutation carriers were 3.78 (95% CI 2.62–5.46) and 9.92 (95% CI 6.05–16.25), respectively ($p < 1 \times 10^{-13}$ for both; figures e-2A and e-2B). Using a constant continuity correction of 0.5, the ORs for PD among mild and severe

Figure 1 Meta-analysis of severe and mild *GBA* mutations and Parkinson disease risk



(A) Forest plot of studies with data on mild *GBA* mutations, using an empirical continuity correction (see methods) for studies with zero cases with mild *GBA* mutations. The analysis included data from 31 studies with a total of 11,453 cases and 14,565 controls. The *p* value for heterogeneity was 0.62. (B) Forest plot of studies with data on severe *GBA* mutations, using an empirical continuity correction (see methods) for studies with zero cases with severe *GBA* mutations. The analysis included data from 31 studies with a total of 11,453 cases and 14,565 controls. The *p* value for heterogeneity was 0.94. FE = fixed effect; Ref = reference number.

GBA mutation carriers were 4.47 (95% CI 3.14–6.35) and 17.03 (95% CI 10.49–27.64), respectively ($p < 1 \times 10^{-18}$ for both; figures e-2C and e-2D). Using empirical continuity correction, the ORs for PD among mild and severe *GBA* mutation carriers were 4.25 (95% CI 3.03–5.95) and 15.67 (95% CI 9.84–24.94), respectively ($p < 1 \times 10^{-19}$ for both; figures e-2E and e-2F).

Because 12 studies used a whole *GBA* gene sequencing approach instead of only analyzing specific mutations, it was possible to conduct a meta-analysis for these studies separately (table 1, figure e-3, A–F). When excluding studies with no severe or mild *GBA* mutation carriers in either patients or controls, the pooled ORs for PD among mild and severe *GBA* mutation carriers were 4.69 (95% CI 2.44–9.01, $p < 1 \times 10^{-6}$; figure e-3A) and 12.2 (95% CI 4.92–30.24, $p < 1 \times 10^{-11}$; figure e-3B), respectively. Using a constant continuity correction of 0.5, the ORs for PD among mild and severe *GBA* mutation carriers were 4.94 (95% CI 2.72–8.98, $p < 1 \times 10^{-8}$; figure e-3C) and 21.29 (95% CI 8.65–52.42, $p < 1 \times 10^{-20}$; figure e-3D), respectively. Using empirical continuity correction, the ORs for PD among mild and severe *GBA* mutation carriers were 4.73 (95% CI 2.65–8.43, $p < 1 \times 10^{-8}$; figure e-3E) and 19.34 (95% CI 8.19–45.63, $p < 1 \times 10^{-20}$; figure e-3F), respectively.

Calculations of *p* values for data heterogeneity were performed for all 3 meta-analyses presented above: all studies included, all studies excluding the Tel Aviv Ashkenazi cohort, and only studies in which the entire *GBA* gene had been sequenced. Because the best *p* values were obtained for the empirical continuity correction model ($p = 0.62$–0.95), this model is thought to be most accurately estimating the ORs for mild and severe *GBA* mutation carriers. It is important to emphasize, however, that both with or without continuity correction, the effects remained the same, demonstrating differential effects of severe and mild *GBA* mutations.

To analyze the effects of severe vs mild *GBA* mutation on AAO, we pooled the results from 16 studies that included data on AAO of specific *GBA* mutation

carriers (table 1). The AAO was 53.1 (±11.2) years among severe *GBA* mutation carriers (n = 166), and 58.1 (±10.6) years among mild *GBA* mutation carriers (n = 162, $p = 4.3 \times 10^{-5}$). After excluding our current study, the AAO was 52.0 (±11.5) years among severe *GBA* mutation carriers (n = 122), and 56.1 (±10.6) years among mild *GBA* mutation carriers (n = 40, $p < 0.05$). Of note, in both analyses, with and without the current study, the AAO of severe *GBA* mutation carriers was 4 to 5 years younger than the AAO of mild *GBA* mutation carriers. In our population alone, although not statistically significant, the AAO were 56.2 ± 9.9 and 58.5 ± 10.6 years among severe and mild *GBA* mutation carriers, respectively, which is comparable to our previous report from 420 patients.[22]

DISCUSSION The meta-analysis study presented here included data from a large variety of populations around the world, including from North, Central, and South America, Western and Eastern Europe, Asia, North Africa, and Ashkenazi Jews (table 1). While a previous meta-analysis examined whether *GBA* mutations are associated with PD, it did not determine the role of severe vs mild mutations in PD risk and onset.[1] In the current study, we demonstrated that there is a clear, significant differential effect of severe vs mild *GBA* mutations on the risk and AAO of PD, not only in Ashkenazi patients, where founder *GBA* mutations are common (approximately 20%), but also worldwide. Carriers of severe *GBA* mutations have about 3- to 4-fold higher risk and about 5 years younger AAO than carriers of mild *GBA* mutations. These results were demonstrated in all the models used for the analysis, with and without continuity correction.

Additional published studies that support our findings were not included in our meta-analysis of AAO because they did not contain per-individual AAO information[19,29]: in 347 Brazilian patients with PD, 5 patients with the mild *GBA* mutation p.N370S had an average AAO of 54.6 years, and 8 patients with the severe *GBA* mutation p.L444P had an average AAO of 47.0 years.[19] In a Serbian population of 360 patients with PD, the average AAO for mild *GBA* mutation carriers (n = 7) was 56.2 years, and 45.1 years among severe *GBA* mutation carriers (n = 10).[29] It is possible that other disease phenotypes may also be differentially presented among severe vs mild *GBA* mutation carriers. Because recent studies reported that carriers of *GBA* mutations may be at higher risk of cognitive impairment,[30] it could be of interest to study large cohorts of patients to determine whether this phenotype may be associated with severe vs mild *GBA* genotype as well. While in the current study there were no available data on the subtypes of PD (tremor-dominant or akinetic-rigid), it would be of interest to examine these phenotypes and their association with *GBA* genotypes.

Based on the meta-analysis results, the estimated risk of PD (OR) among mild *GBA* mutation carriers ranged from 3.0 to 4.7, and from 14.6 to 19.3 among severe *GBA* mutation carriers. These estimates suggest that known healthy carriers of severe *GBA* mutations should undergo genetic counseling regarding the increased risk of PD. In addition, they suggest that the approach described for the *LRRK2* p.G2019S mutation carriers[31] might be adopted, i.e., a closer clinical follow-up, to identify early symptoms of PD among carriers of severe *GBA* mutations. Such follow-up will be particularly important when preventive treatment for PD becomes available.

Although the role of *GBA* mutations as risk factors for PD is clearly established, the mechanism underlying *GBA*-associated PD is still not clear. Several suggestions have been made, including loss-of-function mechanisms or toxic gain-of-function mechanisms.[25] Our findings may support the loss-of-function hypothesis. This could be further exemplified by the 2 founder null mutations that have been identified in the Ashkenazi population, 84GG and IVS2+1. These 2 mutations are found in 26 of 1,000 patients (2.6%) compared with only 7 of 3,805 controls (0.19%), with ORs of 13.6 and 19.1, respectively. These null mutations result in significantly reduced production of the glucocerebrosidase protein, and a possible loss-of-function mechanism was already suggested[32]: depletion of glucocerebrosidase results in the accumulation of α-synuclein, subsequently leading to inhibition of trafficking of glucocerebrosidase into the lysosome, thus creating a pathogenic positive feedback loop.[32] However, more studies are required to identify the specific mechanism by which *GBA* mutations cause α-synuclein accumulation and predispose to PD.

AUTHOR CONTRIBUTIONS

Ziv Gan-Or: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Idan Amshalom: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Laura L. Kilarski: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. Anat Bar-Shira: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Mali Gana-Weisz: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Anat Mirelman: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Karen Marder: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Susan Bressman: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval,

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DISCLOSURE

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