The p.L302P mutation in the lysosomal enzyme gene *SMPD1* is a risk factor for Parkinson disease

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ABSTRACT

Objective: To study the possible association of founder mutations in the lysosomal storage disorder genes *HEXA*, *SMPD1*, and *MCOLN1* (causing Tay-Sachs, Niemann-Pick A, and mucolipidosis type IV diseases, respectively) with Parkinson disease (PD).

Methods: Two PD patient cohorts of Ashkenazi Jewish (AJ) ancestry, that included a total of 938 patients, were studied: a cohort of 654 patients from Tel Aviv, and a replication cohort of 284 patients from New York. Eight AJ founder mutations in the *HEXA*, *SMPD1*, and *MCOLN1* genes were analyzed. The frequencies of these mutations were compared to AJ control groups that included large published groups undergoing prenatal screening and 282 individuals matched for age and sex.

Results: Mutation frequencies were similar in the 2 groups of patients with PD. The *SMPD1* p.L302P was strongly associated with a highly increased risk for PD (odds ratio 9.4, 95% confidence interval 3.9–22.8, $p < 0.0001$), as 9/938 patients with PD were carriers of this mutation compared to only 11/10,709 controls.

Conclusions: The *SMPD1* p.L302P mutation is a novel risk factor for PD. Although it is rare on a population level, the identification of this mutation as a strong risk factor for PD may further elucidate PD pathogenesis and the role of lysosomal pathways in disease development.
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GLOSSARY

AJ = Ashkenazi Jewish; **ANOVA** = analysis of variance; **CI** = confidence interval; **GCase** = glucocerebrosidase; **OR** = odds ratio; **PD** = Parkinson disease; **SMase** = sphingomyelin phosphodiesterase.

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Gaucher disease is the most common lysosomal storage disease in the Ashkenazi Jewish (AJ) population.[1] It is an autosomal recessive disorder caused by mutations in the *GBA* gene that encodes the lysosomal enzyme glucocerebrosidase (GCase). Founder mutations in *GBA* can be detected in 1 out of 16 Ashkenazi Jews, and were shown to be important risk factors for Parkinson disease (PD) in this population[2,3] and in many other populations worldwide.[4–18]

Three other lysosomal storage diseases that are caused by founder mutations can be found in the AJ population: Tay-Sachs disease[19] (carrier frequency of 1:27[20]), Niemann-Pick disease type A[21] (1:115[20]), and mucolipidosis type IV[22] (1:89[20]). These 3 autosomal recessive diseases are caused by mutations in genes encoding lysosomal enzymes,[23] and their deficiency results in cellular accumulation of the enzymes' substrates.

In recent years, studies not related to *GBA* suggest that lysosomal dysfunction is an important mechanism involved in PD pathogenesis.[24] Genetic causes of PD including α-synuclein, *LRRK2*, Parkin, *PINK1*, *DJ1*, and *ATP13A2* encode proteins that reside in the lysosome or function in lysosomal-related pathways, such as autophagy and mitophagy.[25–32]

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Supplemental data at www.neurology.org

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We hypothesized that carriers of lysosomal storage diseases causing mutations may be at higher risk for PD. Eight founder mutations in the *HEXA*, *SMPD1*, and *MCOLN1* genes are common in Ashkenazi Jews, making this an ideal population for testing this hypothesis. Herein, we report for the first time on the association of these mutations in a cohort of 938 AJ patients with PD and in thousands of AJ controls from both Israel and the United States.

METHODS

Population. The patient population included 654 consecutively recruited patients with PD (2005–2009) from Tel Aviv Sourasky Medical Center in Israel and 284 patients (1999–2010) from Beth Israel Medical Center in New York, New York, which served as a replication set (table e-1 on the *Neurology*® Web site at www.neurology.org). Patients with PD from Tel Aviv and New York were diagnosed by a movement disorders specialist according to UK Parkinson's Disease Society Brain Bank criteria,[33] and underwent a detailed interview to ascertain ancestry, family history of PD and other movement disorders, presenting symptoms, and age at onset of motor symptoms. AJ ancestry was determined by self-report, and only patients reporting 2 AJ parents were included in Tel Aviv, while in New York all but 3 patients had 2 AJ parents. Familial PD was defined as having at least one first- or second-degree relative with a diagnosis of PD.

Two groups of controls were analyzed: 1) a group of 282 AJ elderly individuals matched by age and sex to the group of patients with PD from Tel Aviv (age 67.7 ± 10.2, 64.9% men); and 2) large groups of young AJ individuals who underwent routine genetic screening tests for the mutations analyzed here, which were previously published,[20] and detailed in table 1.

Standard protocol approvals, registrations, and patient consents. All patients and controls signed an informed consent before entering the study. The institutional review board (Tel Aviv, New York) and Helsinki Committee (Tel Aviv) approved the study protocols and the informed consents.

Mutation detection. Eight mutations in 3 genes, *HEXA* (c.1274_1277dupTATC, c.1421+1 G>C, and p.G269S), *SMPD1* (p.L302P, p.R496L, and c.996delC), and *MCOLN1* (c.406-2A>G and g.511_6943del), were analyzed. In Tel Aviv, 6 mutations were genotyped using Taqman assay in StepOnePlus RT-PCR system (Applied Biosystems, Foster City, CA; table e-2). The *SMPD1* c.996delC mutation was genotyped using the forward primer 5′–ACACCTGTCAATAGCTTCCCTGGCCC and the reverse primer 5′–TTCGGCAGGCAGCCAGGGCTC, followed by *Nla*IV restriction enzyme analysis. The *MCOLN1* g.511_6943del mutation was identified by using a 3-primer reaction. The forward primer 5′ CTGATATAAATGGCAGGCAGCTTTC was designed to target the point of deletion. The second forward primer was 5′ TGGTCAATGTCACCATCCAC, and the reverse primer was 5′ CTCACCGTGCTGGAAGACAC. All detected mutation carriers were genotyped again to validate the presence of a mutation, using a second method. The primers and methods used are detailed in table e-3. Mutation detection in the AJ patients with PD from New York, the confirmation cohort, was done using Tag-It Mutation Detection Kits (Luminex Corporation, Austin, TX) as previously described.[20]

Table 1 Frequency of 8 founder Ashkenazi mutations in the *HEXA*, *SMPD1*, and *MCOLN1* genes among patients with PD and controls[a]

Gene	Mutation	Patients with PD, Tel Aviv, n (%) (n = 654)	Patients with PD, New York (replication), n (%) (n = 284)	Total patients with PD, n (%) (n = 938)	Elderly controls, n (%) (n = 282)	Young controls, n (%)	*p* Value[b]	*p* Value[c]
HEXA	c.1274_1277dupTATC	20 (3.0)	8 (2.8)	28 (3.0)	6 (2.1)	32/1,015 (3.2)	1.0	0.9
	c.1421+1 G>C	2 (0.3)	2 (0.7)	4 (0.4)	4 (1.4)	5/1,015 (0.5)	0.7	0.7
	p.G269S	0	0	0	0	0/1,015 (0)	NA	NA
	Three *HEXA* mut.	22 (3.4)	10 (3.5)	32 (3.4)	10 (3.5)	37/1,015 (3.6)	0.8	0.8
SMPD1	p.L302P	7 (1.1)	2 (0.7)	9 (1.0)	0	11/10,709 (0.1)	<0.0001[d]	<0.0001[d]
	p.R496L	2 (0.3)	2 (0.7)	4 (0.4)	2 (0.7)	52/10,709 (0.5)	0.7	1.0
	c.996delC	4 (0.6)	1 (0.4)	5 (0.5)	2 (0.7)	29/10,709 (0.3)	0.2	0.3
	Three *SMPD1* mut.	13 (2.0)	5 (1.8)	18 (1.9)	4 (1.4)	92/10,709 (0.9)	0.007	0.002[d]
MCOLN1	c.406-2A>G	9 (1.4)	1 (0.4)	10 (1.1)	3 (1.1)	56/6,648 (0.8)	0.2	0.5
	g.511_6943del	3 (0.5)	3 (1.1)	6 (0.6)	1 (0.4)	19/6,648 (0.3)	0.3	0.06
	Two *MCOLN1* mut.	12 (1.8)	4 (1.4)	16 (1.7)	4 (1.4)	75/6,648 (1.1)	0.1	0.1

Abbreviations: mut. = mutations; NA = not applicable; PD = Parkinson disease.
[a] In parentheses, percentages of carriers.
[b] Patients with PD from Tel Aviv vs young controls, Fisher test.
[c] All patients with PD vs young controls, Fisher test.
[d] Significant *p* values after Bonferroni correction.

Statistical analysis. Data are presented in the text as mean (± SD) for continuous variables. Clinical and demographic categorical variables are presented in percentages whereas allele frequency is presented as a range of 0–1. Any differences among groups in continuous variables were tested using analysis of variance (ANOVA), and χ^2 or Fisher exact test was used for comparison of categorical variables. When comparing groups with small numbers of individuals, the nonparametric Kruskal-Wallis ANOVA was used. Goodness-of-fit test with 1 degree of freedom was applied to look for any deviation from the Hardy-Weinberg equilibrium among the young controls and among patients with PD who were screened for *HEXA*, *SMPD1*, and *MCOLN1* mutations. When comparing to the groups of young controls, an online calculator was used to determine the odds ratio (OR) and confidence interval (CI) (DJR Hutchon Calculator). SPSS software v. 17 (SPSS Inc., Chicago, IL) was used for all other data analysis.

RESULTS **The *SMPD1* p.L302P mutation is strongly associated with PD.** Table 1 details the frequencies of the 8 Ashkenazi founder mutations in the *HEXA*, *SMPD1*, and *MCOLN1* genes in patients with PD and controls. Bonferroni correction for multiple comparisons set the cutoff p value to 0.0063. The frequencies of all 8 mutations were similar in both PD patient populations from Tel Aviv and New York. There were no statistically significant differences in mutation frequencies between the elderly and young control groups, allowing us to compare the PD patient population to the young control groups, which represent an average-risk population. This approach was previously applied for the analysis of *GBA* mutations.[3] The combined analysis demonstrated that the frequency of the 3 *SMPD1* mutations that cause Niemann-Pick type A was significantly higher in patients with PD compared to young controls (1.9% vs 0.9%, $p = 0.002$, Fisher test). However, the analysis of each mutation separately demonstrated that only the *SMPD1* p.L302P mutation was significantly more frequent in patients with PD (1.1% vs 0.1%, $p < 0.0001$ in Tel Aviv, 0.7% vs 0.1%, $p = 0.04$ in the replication analysis, and 1.0% vs 0.1%, $p < 0.0001$ in the combined analysis, Fisher or χ^2 with Yates correction test). The OR to develop PD among carriers of this mutation was 9.4 (95% CI 3.9–22.8). The frequencies of the other mutations did not differ significantly between patients with PD and controls.

The effect of harboring one of the founder mutations in the *HEXA*, *SMPD1*, and *MCOLN1* genes on age at motor symptoms onset (AAO) was examined among patients with PD from Tel Aviv Sourasky Medical Center. The AAO was calculated for each gene and for each mutation and was compared to noncarriers of the same mutation using the Kruskal-Wallis nonparametric ANOVA, since the number of mutation carriers was too small to assume normal distribution of AAO. In addition, since carriers of the *LRRK2* p.G2019S mutation and carriers of Ashkenazi founder *GBA* mutations have an earlier AAO of PD,[34] and their inclusion in this analysis may bias the results, the comparison was done twice, before and after excluding these carriers from the analysis. No statistically significant differences were found. Table e-4 details the AAO of different mutation carriers after the exclusion of carriers of *LRRK2* and *GBA* mutations (data including these patients are not shown). Carriers of the *SMPD1* p.L302P mutation ($n = 7$) had an average AAO of 56.4 ± 16.2, more than 4 years younger than noncarriers, but due to the small number of patients with this mutation this difference was not statistically significant.

DISCUSSION The results presented here suggest that carrying the *SMPD1* p.L302P founder mutation is associated with PD in the AJ population, increasing the risk for developing PD by about ninefold. By studying this genetically homogeneous population, we demonstrated that statistically significant results could be obtained even for a rare mutation such as the *SMPD1* p.L302P, with a carrier frequency of about 1:1,000. Our results further illustrated the importance of the AJ population for genetic studies of PD and other diseases. Since the carrier frequency of *SMPD1* p.L302P is probably similar or lower in other populations,[20] it is currently not possible to estimate the role of *SMPD1* mutations in PD pathogenesis worldwide. Nevertheless, this specific finding is of importance for further understanding the mechanisms underlying PD pathogenesis.

SMPD1 encodes sphingomyelin phosphodiesterase 1 (acid-sphingomyelinase, SMase), a lysosomal enzyme that cleaves the phosphocholine head group of sphingomyelin to generate ceramide. The p.L302P amino acid change is a severe mutation that, when inherited from both parents, causes a fatal infantile type A Niemann-Pick disease. The residual activity of p.L302P mutated SMase is dramatically reduced,[35] resulting in substrate accumulation and loss of cellular function in the CNS and other organs.[36] Our results therefore strengthen accumulating data that emphasize the potential role of the lysosome in PD pathogenesis and the involvement of key PD-causing genes in lysosomal pathways. The lysosome is the main cellular organelle responsible for the degradation of α-synuclein,[26] the major protein aggregate in Lewy bodies, which is the pathologic hallmark of PD.[24]

Is it possible that both *GBA*- and *SMPD1*-encoded lysosomal enzymes, GCase and SMase, are involved in PD pathogenesis in a similar manner? Interestingly, both share a common feature: the end product of their enzymatic cleavage is ceramide. It was previously hypothesized[37] that a defect in the ceramide metabolism pathway may be involved in PD pathogenesis, perhaps by altering the properties and function of the lysosome,

which may result in α-synuclein accumulation and Lewy body formation. This hypothesis was supported by the fact that the *PANK2* and *PLA2G6* genes that are involved in ceramide metabolism cause neurodegenerative diseases (neurodegeneration with brain iron accumulation type 1 and 2, respectively), in which Lewy bodies also accumulate.[37]

One question that arises from our study originated from the isolated association of *SMPD1* p.L302P mutation, while the 2 other *SMPD1* mutations were not associated with PD. These findings raise the possibility that the p.L302P mutation might be in linkage disequilibrium with another alteration that increases the risk for PD. It is therefore important to note that in the original description of the p.L302P founder mutation in AJ patients, sequencing of the entire *SMPD1* cDNA was performed, and did not identify any additional mutations in this gene.[35] These data rule out the possibility of linkage disequilibrium between p.L302P and other pathogenic *SMPD1* coding mutations, but cannot exclude the possibility of a noncoding mutation in this gene or a distant mutation in another gene. However, none of the genes that reside in the 3 Mb region around this mutation is known to be associated with PD. Furthermore, the replication of p.L302P association with PD in 2 independent cohorts in our study demonstrates the importance of this mutation either as causative or as a marker for increased PD risk. Another explanation to consider is the possibility that the p.L302P mutation results in a toxic gain-of-function effect, as suggested for some of the *GBA* mutations associated with PD.[38] Of interest, although not statistically significant, the c.996delC mutation was also more frequent in patients with PD as compared to young controls (1.96-fold, 5/938 vs 29/10,709), suggesting that studies of *SMPD1* mutations in other populations are warranted to further determine the role of this gene in PD.

AUTHOR CONTRIBUTIONS

Dr. Gan-Or: design and conceptualization of the study, study coordination, acquisition of data, analysis and interpretation of the data, statistical analysis, drafting the manuscript, and revising the manuscript for intellectual content. Dr. Ozelius: design and conceptualization of the study, study coordination, acquisition of data, analysis and interpretation of the data, statistical analysis, supervision of the study, obtaining funding. and revising the manuscript for intellectual content. Dr. Bar-Shira: study coordination, acquisition of the data, analysis and interpretation of the data, and revising the manuscript for intellectual content. Dr. Saunders-Pullman: study coordination, acquisition of data, obtaining funding, and revising the manuscript for intellectual content. Dr. Mirelman: acquisition of data and revising the manuscript for intellectual content. Dr. Kornreich: acquisition of data, obtaining funding, and revising the manuscript for intellectual content. Dr. Gana-Weisz: acquisition of data and revising the manuscript for intellectual content. Ms. Raymond: acquisition of data and revising the manuscript for intellectual content. Ms. Rozenkrantz: acquisition of data and revising the manuscript for intellectual content. Dr. Deik: acquisition of data and revising the manuscript for intellectual content. Dr. Gurevich: acquisition of data and revising the manuscript for intellectual content. Dr. Gross: acquisition of data and revising the manuscript for intellectual content. Dr. Schreiber-Agus: acquisition of data and revising the manuscript for intellectual content. Dr. Giladi: design and conceptualization of the study, study coordination, acquisition of data, obtaining funding, and revising the manuscript for intellectual content. Dr. Bressman: study coordination, acquisition of data, supervision of the study, obtaining funding, and revising the manuscript for intellectual content. Dr. Orr-Urtreger: design and conceptualization of the study, study coordination, acquisition of data, analysis and interpretation of the data, drafting the manuscript, supervision of the study, obtaining funding, and revising the manuscript for intellectual content.

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DISCLOSURE

Z. Gan-Or reports no disclosures. L. Ozelius serves on scientific advisory boards for the Benign Essential Blepharospasm Research Foundation, the National Spasmodic Dysphonia Association, and the Tourette Syndrome Association Inc.; is listed as an author on patents re: Torsin, Torsin genes and methods of use, and Nucleic acids, methods and kits for the diagnosis of DYT6 primary torsion dystonia; receives research support from the NIH and the Bachmann Strauss Dystonia & Parkinson Foundation; and receives royalties from Athena Diagnostics, Inc. for a patent re: Torsin, Torsin genes and methods of use. A. Bar-Shira reports no disclosures. R. Saunders-Pullman serves on the Scientific Advisory Board of the Dystonia Medical Research Foundation; has received research support from NIH/NINDS (K23NS047256 and K02NS073836), the Michael J. Fox Foundation for Parkinson's Research, the Thomas Hartman Foundation for Parkinson's Research, the Bachmann-Strauss Dystonia & Parkinson Foundation, and the Marcled Foundation. A. Mirelman, R. Kornreich, and M. Gana-Weisz report no disclosures. D. Raymond receives research support from the Michael J. Fox Foundation for Parkinson's Research, the Thomas Hartman Foundation for Parkinson's Research, Inc., and the Marcled Foundation. L. Rozenkrantz and A. Deik report no disclosures. T. Gurevich receives research support from the Michael J. Fox Foundation for Parkinson's Research and from National Parkinson Foundation. S. Gross receives research grant support from PerkinElmer Inc. and the NIH and is listed as an inventor on a patent for a potential marker for fetal aneuploidy for which she has received no royalties. N. Schreiber-Agus reports no disclosures. N. Giladi provided consultancy to Teva-Lundbeck, IntecPharma, Neuroderm, and UCB, and receives research support from Michael J. Fox Foundation, National Parkinson Foundation, Israel Science Foundation, and FP7 European Commission. S. Bressman serves on scientific advisory boards for the Bachmann Strauss Dystonia & Parkinson Foundation, the Michael J. Fox Foundation for Parkinson's Research, and the Dystonia Medical Research Foundation; is listed as an author on a patent re: Methods and kits for the diagnosis of DYT6 primary torsion dystonia; and receives research support from the NIH and Michael J. Fox Foundation for Parkinson's Research. A. Orr-Urtreger receives research support from Tel Aviv Sourasky Medical Center, Kahn Foundation, Chief Scientist Israel Ministry of Health, Legacy Heritage Biomedical Science Partnership Program of the Israel Science Foundation, and Michael J. Fox Foundation for Parkinson's Research. Go to Neurology.org for full disclosures.

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