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Association of Glucocerebrosidase Mutations With Dementia With Lewy Bodies

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Abstract

Background—Mutations in the glucocerebrosidase (*GBA*) gene are associated with Lewy body (LB) disorders.

Objective—To determine the relationship of *GBA* mutations and *APOE4* genotype to LB and Alzheimer disease (AD) pathological findings.

Design—Case-control study.

Setting—Academic research.

Participants—The 187 subjects included patients with primary neuropathological diagnoses of LB disorders with or without AD changes (95 cases), randomly selected patients with AD (without significant LB pathological findings; 60 cases), and controls with neither LB nor AD pathological findings (32 cases).

Main Outcome Measures—*GBA* mutation status, *APOE4* genotype, LB pathological findings (assessed according to the third report of the Dementia With Lewy Body Consortium), and Alzheimer plaque and tangle pathological findings (rated by criteria of Braak and Braak, the Consortium to Establish a Registry for Alzheimer Disease, and the National Institute on Aging–Reagan Institute).

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Results—*GBA* mutations were found in 18% (34 of 187) of all subjects, including 28% (27 of 95) of those with primary LB pathological findings compared with 10% (6 of 60) of those with AD pathological findings and 3% (1 of 32) of those without AD or LB pathological findings (*P*=.001). *GBA* mutation status was significantly associated with the presence of cortical LBs (odds ratio, 6.48; 95% confidence interval, 2.45–17.16; *P*<.001), after adjusting for sex, age at death, and presence of *APOE4*. *GBA* mutation carriers were significantly less likely to meet AD pathological diagnostic (National Institute on Aging–Reagan Institute intermediate or high likelihood) criteria (odds ratio, 0.35; 95% confidence interval, 0.15–0.79; *P*=.01) after adjustment for sex, age at death, and *APOE4*.

Conclusion—*GBA* mutations may be associated with pathologically "purer" LB disorders, characterized by more extensive (cortical) LB, and less severe AD pathological findings and may be a useful marker for LB disorders.

Lewy body (LB) disorders include Parkinson disease (PD), dementia with LBs (DLB), and LB variant of Alzheimer disease (LBV-AD). They have in common pathologically the presence of aberrant intracellular α-synuclein aggregates (LBs and Lewy neurites). Clinically, these disorders tend to have symptoms of parkinsonism and dementia.[1,2] It is common for Alzheimer disease (AD) and LB disorders to overlap; both may occur in the same brain (eg, LBV-AD).

We and others have shown that mutations in the glucocerebrosidase gene (*GBA*; OMIM 606463) are a risk factor for PD[3–16] and neuropathologically confirmed DLB.[17,18] In the present study, we have sequenced the *GBA* gene and performed *APOE* (OMIM 107741) genotype in 187 brains without and with LB and AD pathological findings. We report the clinical and pathological characteristics of *GBA* mutation carriers and the relation of mutation status to pathological changes.

METHODS

BRAIN MATERIAL

Brain tissue samples were obtained from the Columbia University New York Brain Bank, including samples from patients seen at the Alzheimer Disease Research Center and the Center for Parkinson Disease and Other Movement Disorders. The 187 patients included all cases with frozen brain tissue between 2001 and 2007 with primary neuropathological diagnoses of LB disorders with or without AD changes (95 cases), randomly selected cases of AD (without significant LB pathological findings; 60 cases), and controls with neither LB nor AD pathological findings (32 cases). Lewy body pathological findings were assessed according to the third report of the DLB consortium and used α-synuclein immunohistochemistry, with LBs characterized as being brainstem-predominant or "cortical" (limbic or neocortical).[19] Alzheimer plaque and tangle pathological features were detected by means of hematoxylin-eosin and Bielschowsky stains and β-amyloid and AT-8 immunohistochemistry, and were rated by means of Braak and Braak, Consortium to Establish a Registry for Alzheimer Disease, and National Institute on Aging–Reagan Institute (NIA-RI) criteria.20 All cases with either Braak and Braak stage III or greater neurofibrillary pathological findings and/or plaque-based possible, probable, or definite AD by the Consortium to Establish a Registry for Alzheimer Disease criteria were rated as having "any Alzheimer pathological findings." Neuropathological findings were described as per the National Alzheimer Coordinating Center Neuropathology Manual Version 9.1.21 Only cases that met NIA-RI criteria for intermediate or high likelihood of AD were deemed to have an "AD pathological diagnosis." Cases with cortical LB by consortium criteria were considered DLB if they did not have a concomitant AD pathological diagnosis and LBV-AD if they did. Clinical information on dementia was available in 85 of 95 brains with primary

pathological diagnoses of LB disorders, in 60 of 60 cases with AD, and in only 9 of 32 cases with neither AD nor LB pathological findings.

MOLECULAR GENETIC ANALYSIS

Frozen cerebellar tissue was used to extract DNA by means of a kit (Gentra Puregene; Qiagen, Valencia, California) following the manufacturer's instructions. All *GBA* exons were sequenced by means of polymerase chain reaction and sequencing primers described previously.[22] Cycle sequencing in forward and reverse directions was performed on purified polymerase chain reaction products and run on a genetic analyzer (ABI 3700; Applied Biosystems, Foster City, California). Sequence chromatograms were viewed and genotypes determined by means of Sequencher (Gene Codes Corp, Ann Arbor, Michigan). *APOE4* genotyping was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on the Sequenom, Inc (San Diego, California) platform as described previously.[23]

STATISTICAL ANALYSIS

Continuous and categorical variables were compared by *t* tests and χ^2 tests, respectively. Logistic regression models were constructed to examine the association of *GBA* mutation carrier status with the presence of each pathological diagnosis adjusting for sex, age at death, and the presence of *APOE4*.

RESULTS

GBA MUTATIONS

Table 1 lists all cases with mutations, together with age at onset of cognitive or extrapyramidal motor disorder, initial clinical presentation, and pathological diagnosis. *GBA* mutations were found in 34 of the 187 subjects (18%). We classified mutation types in Table 1 as having null, severe, mild, or unknown phenotypic effect according to previously published studies.[16,24] Overall, 5 of 34 subjects with a *GBA* mutation (15%) had a null or severe mutation, although none of these was homozygous. Among the 17 different *GBA* mutations found in 34 individuals, 14 were missense mutations, 1 was an insertion mutation, 1 was a silent mutation (synonymous substitution), and 1 was a nucleotide substitution located in the noncoding region of exon 1 (g.1444A>G; −15 of the ATG start codon). With the exception of 5 variants (g.1444 A>G, E388K, G389V, P171P, and N188R), all mutations have been reported previously.[25] These 5 variants were not found in the 32 control brains reported on herein nor in an additional 179 controls described previously.10 Table 2 shows basic demographic and neuropathological information on carriers and noncarriers of *GBA* mutations. There was no difference in age at death or duration of symptoms in the carriers compared with noncarriers. Carriers were younger at diagnosis of dementia (63.2 vs 69.1 years; P=.01). There was no difference in ethnicity between carriers and noncarriers.

RELATIONSHIP OF *GBA* TO PATHOLOGICAL DIAGNOSES

GBA mutations were found in 28% (27 of 95) of those with primary pathological diagnoses of LB disorders, compared with 10% (6 of 60) of cases with primary AD and 3% (1 of 32) of control cases containing neither AD nor LB pathological findings (P<.001). *GBA* mutations were not significantly more frequent among primary AD cases than among controls. *GBA* mutation carriers were significantly more likely to have cortical LBs (28 of 34 [82%]) than were nonmutation carriers (66 of 153 [43%]; P<.001). Presence of a *GBA* mutation appeared to relate more to the presence of cortical LBs than to LBs confined to the subcortical regions, but there were only 14 cases of the latter (Table 2).

In contrast to the greater likelihood of *GBA* mutation carriers to have LBs, these carriers were significantly less likely to meet NIA-RI pathological criteria for AD (13 of 34 [38%]) than were *GBA* mutation noncarriers (96 of 153 [63%]; *P*=.01) (Table 2). No significant difference was seen among carriers and noncarriers of *APOE4* among cases with any LB pathological findings, cortical LB pathological findings, or presence of *any* AD pathological changes. There were significantly more *APOE4* carriers who had AD pathological findings; more *APOE4* carriers met NIA-RI criteria for AD (59 of 79 [75%]) than did non–*APOE4* carriers (50 of 107 [47%]; *P*< .001). Examining both *APOE4* and *GBA* mutation status conjointly among the 109 cases with pathological diagnosis of AD, the least frequent category was that of persons who were *GBA* carriers and *APOE4* noncarriers (6 of 109 [6%]; Table 3).

RELATIONSHIP OF *GBA* MUTATION STATUS TO CORTICAL LB AND AD PATHOLOGICAL FINDINGS

In separate logistic models, *GBA* mutation carrier status was significantly associated with the presence of cortical LBs, not only adjusting for sex and age at death but also in models additionally including the presence of AD pathological findings, presence of *APOE4*, and a clinical diagnosis of dementia (Table 4). *APOE4* was not independently associated with the presence of cortical LBs in any of the models. Analyses in which the dependent variable was the presence of any LB pathological finding, rather than just the presence of cortical LBs, gave similar results (because there were only 14 cases in which LB pathological findings were confined to the brainstem). As shown in Table 4, the presence of the *GBA* mutation was inversely associated with the presence of a pathological diagnosis of AD, even after adjustment for age at death, sex, and the presence of *APOE4* (odds ratio, 0.35; 95% confidence interval, 0.15–0.79; *P*=.01), although *APOE4* was significantly associated with AD pathological diagnosis in this model (3.97, 1.97–8.04; *P*< .001).

COMMENT

We have shown that carriers of *GBA* mutations are significantly more likely than noncarriers to have cortical LB pathological findings. This is true when adjusting for sex, age at death, the presence of AD pathological findings, *APOE4*, and clinical diagnosis of dementia. The presence of a *GBA* mutation is not associated with AD pathological findings, whereas *APOE4* is independently associated with AD diagnostic pathological findings in the same model, suggesting that *GBA* mutation status may be a useful clinical marker in the accurate diagnosis of LB disorders.

GBA mutations are not exclusively present in cases with LBs, even in this autopsy series of elderly persons. One case with no significant AD or LB pathological findings and 10 cases with autopsy-proved primary AD (4 of which lacked any LB pathological findings) nonetheless had *GBA* mutations. A previous report analyzing *GBA* status in a clinic-based series of 74 Ashkenazi patients with AD geno-typed for only 6 mutations (N370S, L444P, 84GG, IVS+1, V394L, and R496H) found that 4% (3 of 74) carried a *GBA* mutation. This is not dissimilar from our observed mutation frequency of 10% (6 of 60) in cases with primary pathological diagnoses of AD; 2 of these cases had rare LBs, but 4 had complete absence of any discernible LBs. The mutations in these 6 cases were all of the mild or unknown function type.

Two previously published studies have examined *GBA* genotype in neuropathologically confirmed DLB cases from autopsy series.[17,18] Mata et al[18] examined 57 cases with DLB (54 had autopsies) and found a mutation frequency of only 3.5%, but they sequenced for only 2 *GBA* mutations (N370S and L444P). Goker-Alpan et al[17] did perform full genotyping of *GBA* in 63 cases with LB pathological findings including 35 with cortical LBs (DLB or

LBV-AD) and 28 with pure PD. They found an overall *GBA* mutation frequency of 14% (9 of 63) among the LB cases but 29% (8 of 28) among the cases with cortical LB.[17] Thus, the frequency of *GBA* mutations of 28% that we found in a set of LB cases (of which few had pure PD pathological findings) is similar to that observed in the previous studies. Our study, which examined not only individuals with LB pathological findings but also those with AD and some with neither AD nor LB pathological findings and included genotyping for *APOE*, shows that *GBA* is a marker for cortical LB pathological findings, independent of AD pathological features, and is unrelated to *APOE* genotype.

We, like Goker-Alpan et al,[17] observed a higher frequency of *GBA* mutation carriers among those with cortical LBs than among those with only brainstem LBs (pure PD), although we had proportionately few cases with pure PD. If this finding should be further confirmed, there are several possible explanations, including that *GBA* relates specifically to cortical LB degeneration, as differentiated from pure PD, or that *GBA* relates to some combination of age at onset, rapidity of disease progression, and mortality. We are currently expanding our studies to distinguish between these possibilities.

It is unclear whether specific mutations in the *GBA* gene are more likely to be associated with specific phenotypic responses. In the study of Goker-Alpan et al, 9 of 63 subjects with LBs (14%) carried a *GBA* mutation including N370S (n = 5), R120W (n = 1), A359X (n = 1), T267I (n=1), and I161N (n=1).[17] We also found that N370S was the most frequent mutation in subjects with LBs; this mutation was found in 29% (10 of 34) of our *GBA* mutation carriers. We also observed additional mutations that have been previously reported in PD cases and that are reported to be pathogenic in cases of Gaucher disease.[25] Five mutations identified in our study are novel. Three of these are missense mutations, 1 is a silent mutation (synonymous substitution), and 1 nucleotide substitution is located in the noncoding promoter region of exon 1. Currently, the pathogenicity of these mutations is unknown, and functional studies will be needed to determine their effects on the *GBA* protein. The mechanism by which *GBA* mutations might increase the likelihood of LB disease, such as DLB, is unclear. The mutations are nearly exclusively heterozygous and many are deemed “mild” for Gaucher disease even if homozygous, so it is unlikely but possible that gene product insufficiency might be the predisposing factor. More likely, alterations in *GBA* might affect lysosomal protein degradational processes, increasing the likelihood of aberrant α-synuclein processing, and LB neurodegeneration.

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Table 1

Characteristics of Autopsy Cases With Identified *GBA* Mutations

GBA Mutation/ Severity[a]	cDNA Nucleotide Substitution[b]	Exon	Zygosity	Initial Clinical Presentation		Primary Pathological Diagnosis
				Age, y	Symptom	
Null						
84insGG	c.84dupG	2	Heterozygous	66	Memory problems	DLB
Severe						
H255Q	c.882T>G	7	Heterozygous	55	Behavior change	DLB
D409H	c.1342G>C	9	Heterozygous	71	Memory problems	DLB
L444P	c.1448T>C	10	Heterozygous	55	Parkinsonism	DLB
R463C	c.1504C>T	10	Heterozygous	NA	Memory problems	DLB
Mild						
N370S	c.1226A>G	9	Heterozygous	68	Memory problems	LBV-AD
N370S	c.1226A>G	9	Heterozygous	62	Parkinsonism	DLB
N370S	c.1226A>G	9	Heterozygous	58	Parkinsonism	DLB
N370S	c.1226A>G	9	Heterozygous	74	Parkinsonism	DLB
N370S	c.1226A>G	9	Heterozygous	69	Parkinsonism	DLB
N370S	c.1226A>G	9	Heterozygous	NA	NA	DLB
N370S	c.1226A>G	9	Heterozygous	54	Parkinsonism	DLB
N370S	c.1226A>G	9	Heterozygous	55	Memory problems	DLB
N370S	c.1226A>G	9	Heterozygous	69	Memory problems	LBV-AD
N370S	c.1226A>G	9	Homozygous	NA	Memory problems	AD
R496H	c.1604G>A	11	Heterozygous	74	Parkinsonism	DLB
Unknown						
g.1444 A>G	g.1444 A>G	−15 of ATG start codon	Heterozygous	74	Memory problems	AD
P171P	c.630C>T	6	Heterozygous	57	Language problems	AD
W184R	c.667T>C	6	Heterozygous	53	Parkinsonism	DLB
E326K	c.1093G>A	8	Heterozygous	41	Parkinsonism	DLB
E326K	c.1093G>A	8	Heterozygous	58	Parkinsonism	DLB
E326K	c.1093G>A	8	Heterozygous	58	Parkinsonism	PD
E326K	c.1093G>A	8	Heterozygous	67	Parkinsonism	LBV-AD

GBA Mutation/ Severity[a]	cDNA Nucleotide Substitution[b]	Exon	Zygosity	Initial Clinical Presentation		Primary Pathological Diagnosis
				Age, y	Symptom	
E326K + N188R + S196P +V191G	c.1093G>A, c.680A>G + c.681T>G, C.703T>C, c.689T>G	8, 6, 6, 6	Compound heterozygous	65	Hallucinations	DLB
T369M	c.1223C>T	8	Heterozygous	69	Parkinsonism	DLB
T369M	c.1223C>T	8	Heterozygous	72	Memory problems	LBV-AD
T369M	c.1223C>T	8	Heterozygous	NA	NA	Normal brain
T369M	c.1223C>T	8	Heterozygous	53	Memory problems	AD
T369M	c.1223C>T	8	Heterozygous	70	Depression	AD
T369M	c.1223C>T	8	Heterozygous	69	Personality change	DLB
T369M	c.1223C>T	8	Homozygous	67	Performance change	DLB
T369M	c.1223C>T	8	Heterozygous	NA	Memory problems	DLB
E388K	c.1279G>A	9	Heterozygous	55	Memory problems	LBV-AD
G389V	c.1283G>T	9	Heterozygous	58	Performance change	AD

Abbreviations: AD, Alzheimer disease; cDNA, complementary DNA; DLB, dementia with Lewy bodies; LBV-AD, Lewy body variant of Alzheimer disease; NA, not available; PD, Parkinson disease.

[a] Mutations are classified as having null, severe, mild, and unknown effect on the expected clinical phenotype according to Beutler et al.[24]

[b] Genomic nucleotide position is based on the accession file GenBank J03059.1, and *GBA* cDNA nucleotides are numbered according to the GenBank sequence NM_000157.2.

Table 2

Demographic and Neuropathological Characteristics of Subjects Examined at Autopsy

Characteristic	No *GBA* Mutation (n=153)	*GBA* Mutation (n=34)	*P* Value
Sex, No. (%) male	79 (52)	21 (62)	.34
Ethnicity, No. (%)			.26
White	123(80)	32 (94)	
Black	7(5)	0	
Asian	2(1)	0	
Hispanic	21 (14)	2(6)	
Age at death, mean (SD),y (n = 187)	77.8(11)	76.0(6.7)	.21
Age at dementia (total), mean (SD),y (n = 113)	69.1 (10)	63.2 (6.7)	.01
Duration from onset of dementia or parkinsonism to death, mean (SD), y (n = 113)	10.0(6)	12.6(5.8)	.07
No. (%) with Lewy bodies			
Any	79 (52)	29(85)	<.001
Cortical	66 (43)	28(82)	<.001
Subcortical	13(8)	1(3)	.24
No. (%) with pathological findings of AD			
Any	123(80)	29(85)	.35
Diagnosis (NIA-RI)	96 (63)	13(38)	.01

Abbreviations: AD, Alzheimer disease; NIA-RI, National Institute on Aging–Reagan Institute.

Table 3

Distribution of *GBA* and *AP0E4* by Pathological Diagnosis

		Pathological Findings, No. (%)			
		Lewy Body		Alzheimer Disease	
	No. of Cases[a]	Brainstem Only (n=13)	Cortical (n=85)	Any (n=152)	Diagnosis (n=109)
GBA+	34				
APOE4−	19	1(8)	14(16)	14(9)	6(6)
APOE4+	15	0	12(14)	15(10)	7(6)
GBA−	153				
APOE4−	88	11 (85)	37 (44)	66 (43)	44 (40)
APOE4+	64	1(8)	22 (26)	57 (38)	52 (48)

[a]One subject did not have an *APOE* genotype.

Table 4

Association of *GBA* Mutation With the Presence of Cortical Lewy Bodies or AD Pathological Diagnosis

OR (95% CI)	*P* Value	Covariates in Model
		Cortical Lewy Bodies
7.24(2.69–19.48)	<.001	Age at death, sex, AD pathological diagnosis
6.62(2.41–18.27)	<.001	Age at death, sex, any AD pathological findings
6.48(2.45–17.16)	<.001	Age at death, sex, *APOE4*
5.91 (2.14–16.33)	<.001	Age at death, sex, *APOE4*, dementia
		AD Pathological Diagnosis
0.40(0.18–0.89)	.03	Age at death, sex
0.35(0.15–0.79)	.01	Age at death, sex, *APOE4* (for *AP0E4* OR, 3.97; 95% CI, 1.97–8.04; *P*< .001)

Abbreviations: AD, Alzheimer disease; CI, confidence interval; OR, odds ratio.