RESEARCH ARTICLE

GBA Variants in Parkinson's Disease: Clinical, Metabolomic, and Multimodal Neuroimaging Phenotypes

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ABSTRACT: Background: Alterations in the *GBA* gene (NM_000157.3) are the most important genetic risk factor for Parkinson's disease (PD). Biallelic *GBA* mutations cause the lysosomal storage disorder Gaucher's disease. The *GBA* variants p.E365K and p.T408M are associated with PD but not with Gaucher's disease. The pathophysiological role of these variants needs to be further explored.

Objective: This study analyzed clinical, neuropsychological, metabolic, and neuroimaging phenotypes of patients with PD carrying the *GBA* variants p.E365K and p.T408M.

Methods: *GBA* was sequenced in 56 patients with mid-stage PD. Carriers of *GBA* variants were compared with noncarriers regarding clinical history and symptoms, neuropsychological features, metabolomics, and multimodal neuroimaging. Blood plasma gas chromatography coupled to mass spectrometry, 6-[^{18}F]fluoro-L-Dopa positron emission tomography (PET), [^{18}F]fluorodeoxyglucose PET, and resting-state functional magnetic resonance imaging were performed.

Results: Sequence analysis detected 13 heterozygous *GBA* variant carriers (7 with p.E365K, 6 with p.T408M). One patient carried a *GBA* mutation (p.N409S) and was excluded. Clinical history and symptoms were not significantly different between groups. Global cognitive performance was lower in variant carriers. Metabolomic group differences were suggestive of more severe PD-related alterations in carriers versus noncarriers. Both PET scans showed signs of a more advanced disease; [^{18}F] fluorodeoxyglucose PET and functional magnetic resonance imaging showed similarities with Lewy body dementia and PD dementia in carriers.

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Conclusions: This is the first study to comprehensively assess (neuro-)biological phenotypes of *GBA* variants in PD. Metabolomics and neuroimaging detected more significant group differences than clinical and behavioral evaluation. These alterations could be promising to monitor effects of disease-modifying treatments targeting glucocerebrosidase metabolism.

Key Words: *GBA*; Parkinson's disease genetics; metabolomics; multimodal functional neuroimaging

Alterations in the *GBA* gene (NM_000157.3) represent the most common genetic risk factor for Parkinson's disease recognized to date.[1] *GBA* encodes glucocerebrosidase, a lysosomal enzyme involved in sphingolipid metabolism.[2] A number of known *GBA* mutations cause the autosomal-recessive lysosomal storage disorder Gaucher's disease in biallelic carriers.[3] It has been hypothesized that glucocerebrosidase plays a role in α-synuclein degradation and therefore aggregate formation may be facilitated when glucocerebrosidase function is impaired,[4,5] thereby increasing the risk to develop Parkinson's disease and dementia with Lewy bodies (DLB) in mono- and biallelic carriers.[4,6] Clinical presentation and long-term clinical course of patients with Parkinson's disease carrying *GBA* mutations is not overtly different from patients without known genetic risk factors; however, many studies have presented evidence for an earlier age at onset,[7,8] faster progression of motor symptoms and cognitive decline,[1,4,8–10] and more visual hallucinations or psychotic symptoms.[8,11–13]

Recently, more frequently occurring alterations in *GBA* that do not cause Gaucher's disease, termed *GBA* variants (rather than mutations), have also been recognized as genetic risk factors for Parkinson's disease: large multicenter studies and a meta-analysis have established significant associations between Parkinson's disease and the single nucleotide polymorphisms p.E365K and p.T408M (traditional nomenclature: p.E326K and p.T369M).[9,14,15] The 1000 Genomes Project reports p.E365K in 1% and p.T408M in about 0.4% of the world population, whereas they were found in up to 5% and 3.9% of patients with Parkinson's disease, respectively.[9,16] It has repeatedly been shown that carriers of p.E365K, similar to mutation carriers, suffer from a faster cognitive decline than noncarriers, which has not (yet) been demonstrated for p.T408M.[10,16,17] A meta-analysis of 13 Parkinson's disease cohorts suggested a faster disease progression in both variants.[16]

Metabolic consequences of glucocerebrosidase dysfunction in affected patients with Parkinson's disease have rarely been explored in vivo.[18] Mass spectrometry-based analysis of dried blood spots showed reduced glucocerebrosidase enzymatic activity[19] as well as increased levels of the lysosphingolipid hexosylsphingosine not only in Gaucher's disease-related mutations but also in p.E365K and p.T408M.[18]

Neuroimaging studies comparing patients with Parkinson's disease with and without *GBA* mutations reported reduced cerebral blood flow in the parieto-occipital cortex, which resembled the pattern typically seen in DLB.[8,20,21] To the best of our knowledge, no neuroimaging studies to date have focused on *GBA* variants.

In summary, current evidence suggests that the clinical and neurobiological phenotype of patients with Parkinson's disease carrying *GBA* alterations (mutations or variants) is not fundamentally different from *GBA* noncarrier patients, but may be more severe and/or progress slightly faster, especially with severe mutations,[8,9] whereas variants may have milder clinical effects.[9]

The current study aimed to comprehensively assess the phenotypes of patients with Parkinson's disease carrying the *GBA* variants p.E365K or p.T408M compared with patients carrying wildtype *GBA*. Carriers and noncarriers were compared regarding clinical and family history, motor and nonmotor symptom severity, cognitive function, metabolomics, and multimodal neuroimaging using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

Methods

Patients

From a larger, well-characterized cohort (KFO 219), DNA samples were available for 56 patients with Parkinson's disease. Inclusion criteria were Hoehn and Yahr stage[22] ≤ 3, age ≥ 40 years, and absence of dementia,[23] deep brain stimulation, or cerebral pathologies other than Parkinson's disease. All patients were recruited at the University Hospital of Cologne and diagnosed by a movement disorder specialist according to the UK Brain Bank criteria.[24] The study was approved by the local medical ethics committee (EK12-265) and registered with the German Clinical Trials Register (DRKS00005388); informed consent was obtained from each participant per the Declaration of Helsinki.

Patients in this cohort underwent an extensive study protocol with the assessment of motor, cognitive, neuropsychiatric, and other nonmotor symptoms; multimodal neuroimaging; and metabolomic and genetic analysis. Several of these procedures have been described in previous publications.[25–27]

Clinical and Behavioral Data

The motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III, including subscores for tremor and akinesia-rigidity to determine motor subtypes[28]), collection of blood samples, and functional neuroimaging were performed after antiparkinsonian medication was discontinued for a minimum of 12 hours (levodopa) and up to 3 days (dopamine agonists). Clinical history, neuropsychological and other nonmotor data were obtained on dopaminergic medication. A cognitive test battery covered the domains executive function, memory, attention, language, and visual–spatial abilities, from which a global cognition *z* score was computed using age and education-adjusted standard norms. Self-rated scales were applied to measure apathy, depression, (hypo-)mania, impulsivity, and other nonmotor symptoms.

Groups were compared using IBM SPSS statistics version 25 (IBM Corp., Armonk, NY). Categorical data were analyzed with Fisher's exact test, and Mann–Whitney *U* test was used for ordinal variables. For continuous variables, normal distribution was tested by Shapiro–Wilk test; groups were compared by *t* test or *U* test as appropriate. Cognitive scores were compared by analysis of covariance to adjust for points on the Beck Depression Inventory, version II (BDI-II), as depression is known to heavily influence test performance.[29]

Biospecimen Collection and Processing

Blood samples for metabolomic and genetic analyses were drawn after overnight fasting. A gene panel analysis was performed comprising 29 genes previously linked to parkinsonism or dystonia. Rare variants in Parkinson's disease genes (*GBA*, *LRRK2*, *PARK7*, *PRKN*, *PINK1*, *SNCA*, *VPS35*) were validated by Sanger sequencing, and confirmed alterations were registered.

Details of metabolomics processing and analysis in the KFO 219 cohort were previously published.[25] Plasma samples of 54 patients could be analyzed (Table 1). Gas chromatography coupled to mass spectrometry was applied to measure polar and nonpolar metabolite extracts. Metabolomic profiles were analyzed in an untargeted approach, comparing 71 metabolites between wildtype patients and *GBA* variant carriers using Welch's *t* test. In this exploratory analysis, suggestive group differences with uncorrected $P < 0.05$ are reported.

Neuroimaging Data Acquisition and Analysis

Image acquisition and preprocessing have previously been described in detail.[27] 6-[^{18}F]fluoro-L-Dopa ([^{18}F]FDopa) PET to estimate dopaminergic denervation and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET to quantify cerebral metabolic activity were performed under standard conditions with an average dose of 185 MBq on a high-resolution research tomograph (ECAT HRRT, Siemens, Erlangen, Germany) and processed in SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12). [^{18}F]FDopa scans were aligned with the more affected body side according to UPDRS-III. PET images were normalized to Montreal Neurological Institute (MNI) space (voxel size 1.22 mm) and spatially smoothed with a 3-dimensional Gaussian filter of 6 mm full width at half maximum (FWHM). Resting-state fMRI time series were acquired on a 3 T Siemens Magnetom Prisma (repetition time, 776 ms; echo time, 37.4 ms; 617 time points; 72 slices; voxel size, $2 \times 2 \times 2$ mm) and preprocessed using the SPM toolbox Conn[30] with default parameters: realignment, outlier detection for correction of motion artifacts, normalization to MNI space, 5 mm FWHM spatial smoothing, temporal band-pass filtering (0.01–0.1), linear detrending, and anatomical component-based noise correction. [^{18}F]FDopa PET was available for 39, [^{18}F]FDG for 47, and fMRI for 54 of the 56 patients who underwent genetic testing (Table 1).

[^{18}F]FDopa uptake was compared between patient groups in a voxel-wise 2-sample *t* test, restricting the

TABLE 1. Clinical and demographic data of the study cohort and subsamples

	All Patients	[^{18}F]FDopa PET	[^{18}F]FDG PET	fMRI	Metabolomics
n	56	39	47	54	54
Gender, M/F (%M)	39/17 (69.6)	24/15 (61.5)	31/16 (66.0)	37/17 (68.5)	37/17 (68.5)
Age, y	65.2 ± 9.9	67.6 ± 8.6	66.7 ± 8.6	65.2 ± 10.1	66.0 ± 9.2
Education, y	14.5 ± 2.8	14.2 ± 2.7	14.1 ± 2.7	14.6 ± 2.8	14.4 ± 2.8
Age at onset, y	60.2 ± 9.7	63.1 ± 8.2	62.1 ± 8.2	60.5 ± 9.5	60.9 ± 9.0
Disease duration, y	5.0 ± 3.9	4.5 ± 3.5	4.5 ± 3.4	4.7 ± 3.6	5.1 ± 4.0
H&Y stage	2 (1–3)	2 (2–3)	2 (2–3)	2 (1–3)	2 (1–3)
UPDRS-III	24.7 ± 9.5	24.7 ± 8.5	25.3 ± 9.8	24.2 ± 9.3	24.9 ± 9.5
LEDD (mg)	481.2 ± 279.9	451.6 ± 264.4	457.0 ± 243.4	477.2 ± 284.3	489.0 ± 277.1

Frequencies (categorical data), median and range (ordinal data), or means ± standard deviations (continuous data). All patients who underwent genetic testing are included.
Abbreviations: [^{18}F]FDopa, [^{18}F]fluoro-L-Dopa; PET, positron emission tomography; [^{18}F]FDG, [^{18}F]fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; M, male; F, female; H&Y, Hoehn and Yahr; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; LEDD, levodopa equivalent daily dose.

search volume to the bilateral striatum. An uncorrected threshold of $P < 0.05$ was defined as a suggestive group difference. [^{18}F]FDG PET scans were processed using the topographic rating algorithm implemented in ScAnVP (http://feinsteinneuroscience.org) to measure the expression of 2 distinct Parkinson's disease-related covariance patterns: the Parkinson's disease related pattern (PDRP), associated with disease progression and motor symptoms,[31,32] and the Parkinson's disease cognitive pattern (PDCP), associated with cognitive dysfunction.[33,34] A control sample of 11 healthy subjects with wildtype *GBA* and an identical [^{18}F]FDG PET scan was used to *z* transform raw subject scores. Regional metabolic changes were analyzed in a whole-brain voxel-wise 2-sample *t* test of normalized [^{18}F]FDG uptake, thresholded at $P < 0.05$ family-wise error (FWE-) corrected at the cluster level. Proportional scaling with default settings was applied in PET analyses ([^{18}F]FDopa and [^{18}F]FDG global signals were similar between groups).

Resting-state fMRI data were analyzed by seed-to-voxel functional connectivity (FC) analysis of each left and right putamen, caudate, and nucleus accumbens; second-level group comparisons were thresholded at $P < 0.05$, cluster-level FWE-corrected. In all neuroimaging analyses, anatomical regions were defined with the Harvard–Oxford cortical and subcortical atlas as implemented in Conn. For each modality, mean cluster values ([^{18}F]FDopa or [^{18}F]FDG uptake for PET, FC beta values for resting-state fMRI) were extracted from significant clusters found in the voxel-wise analyses.

Results

Genotyping Results

Gene panel analysis identified 7 patients (12.5%) who were heterozygous for the c.1093G>A (p.E365K (p.E326K)) variant and 6 patients (10.7%) heterozygous for c.1223C>T (p. T408M (p.T369M)), thus 23.2% of the cohort carried a *GBA* variant. One patient carried the Gaucher's-associated *GBA* mutation c.1226A>G (p.N409S (p. N370S)) and was excluded from further analysis. The remaining 42 patients had no variant in *GBA*.

In addition, 1 *GBA* wildtype patient was heterozygous for the likely benign variant c.1000C>T (p.R334C) in *PRKN*; 1 carrier of *GBA*:p.E365K was also heterozygous for the likely benign variant c.587C>T (p.P196L) in *PINK1* and the *PRKN* mutation c.823C>T (p.R275W). Although the *PRKN* mutation p.R275W in biallelic carriers is associated with autosomal-recessive Parkinson's disease,[35] only a heterozygous carrier was detected here. Group comparisons were repeated without the *PRKN* mutation carrier, and because the results were largely unaltered, the subject was not excluded from final analyses.

Because carriers of the 2 variants p.E365K and p. 408M were similar concerning all measures of interest in this study (see Fig. 1, Tables 2, 3, S1), variant carriers were combined into 1 group for all comparisons with noncarriers.

Demographic Data

The 42 patients with wildtype *GBA* were 65.0 ± 10.2 years old, and 27 (64.3%) of them were

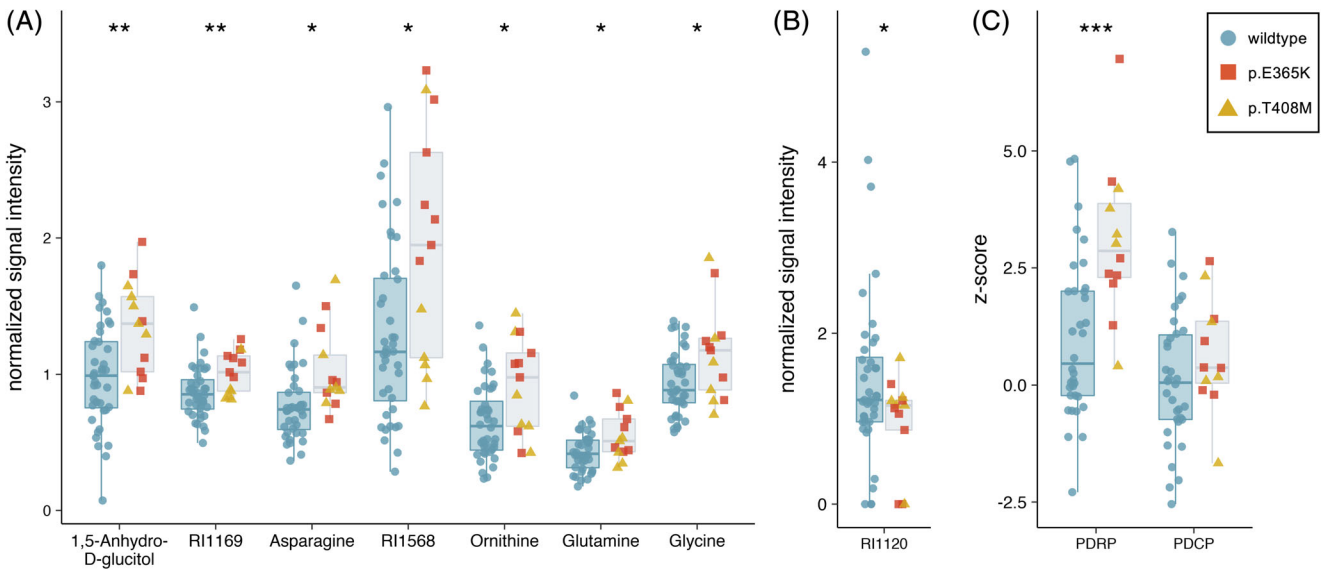

FIG. 1. Group comparison of metabolomics and [^{18}F]FDG PETcovariance patterns. Metabolites with significantly (**A**) increased and (**B**) decreased levels in *GBA* variant carriers. (**C**) PDRP and PDCP expression. The 2 variants are indicated by color and shape of dots but were combined for group comparisons. Significance levels: **P* < 0.05, ***P* < 0.01, ****P* < 0.001. [^{18}F]FDG PET, [^{18}F]fluorodeoxyglucose positron emission tomography; PDCP, Parkinson's disease cognitive pattern; PDRP, Parkinson's disease related pattern. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2. Demographic, clinical, and behavioral data compared between wildtype *GBA* and variant carriers (combined)

	Wildtype *GBA*	Variant Carrier	p.E365K	p.T408M	Test Statistic*	*P* Value*
n	42	13	7	6	–	–
Gender, M/F (%M)	27/15 (64.3)	11/2 (84.6)	6/1 (85.7)	5/1 (83.3)	–	0.303[a]
Age, y	65.0 ± 10.2	66.7 ± 8.9	68.9 ± 6.3	64.2 ± 11.2	$T = 0.52$	0.603[b]
Education, y	14.4 ± 2.8	14.9 ± 2.9	16.0 ± 2.5	13.5 ± 3.0	$T = 0.51$	0.610[b]
PD in 1st-degree relatives, n (%)	3 (7.1)	3 (23.1)	2 (28.6)	1 (16.7)	–	0.136[a]
Age at onset, y	60.1 ± 10.2	61.2 ± 8.1	62.7 ± 5.6	59.3 ± 10.7	$T = 0.33$	0.745[b]
Disease duration, y	4.9 ± 4.0	5.5 ± 3.9	6.1 ± 4.7	4.8 ± 2.9	$T = 0.50$	0.620[b]
H&Y stage	2.5 (1–3)	2 (2–3)	2 (2–3)	2 (2–2.5)	$U = 249$	0.595[c]
UPDRS-III	23.7 ± 9.1	27.5 ± 10.9	26.9 ± 10.9	28.2 ± 12.0	$T = 1.23$	0.225[b]
Motor subtype, A/M/T[d]	28/12/2	8/4/1	5/2/0	3/2/1	–	0.882[a]
LEDD, mg	455.8 ± 286.1	577.1 ± 253.9	617.5 ± 201.5	530.0 ± 317.9	$T = 1.37$	0.177[b]
LEDD, dopamine agonists, mg	148.2 ± 129.5	137.5 ± 91.5	122.5 ± 95.3	155.0 ± 92.2	$T = 0.28$	0.783[b]
Antidepressive medication, n (%)	10 (23.8)	2 (15.4)	2 (28.6)	0 (0.0)	–	0.709[a]
NMSS	53.5 ± 46.7	39.2 ± 44.4	47.1 ± 55.3	30.0 ± 29.7	$U = 193$	0.113[c]
Global cognition *z* score	−0.13 ± 0.53	−0.34 ± 0.36	−0.32 ± 0.30	−0.36 ± 0.45	$F = 4.51$	**0.039**[d]
Attention	−0.20 ± 0.82	−0.23 ± 1.03	0.09 ± 1.07	−0.62 ± 0.91	$F = 0.50$	0.482[d]
Executive functions	−0.07 ± 0.60	−0.44 ± 0.70	−0.55 ± 0.67	−0.31 ± 0.77	$F = 3.54$	0.066[d]
Language	0.22 ± 0.66	0.21 ± 0.53	0.22 ± 0.73	0.21 ± 0.17	$F = 0.19$	0.663[d]
Memory	−0.22 ± 1.12	−0.37 ± 0.78	−0.66 ± 0.78	−0.03 ± 0.69	$F = 0.78$	0.382[d]
Visual–spatial	−0.28 ± 1.06	−0.79 ± 1.34	−0.63 ± 1.28	−0.97 ± 1.51	$F = 2.99$	0.090[d]
BDI-II	11.6 ± 7.8	5.8 ± 6.4	6.0 ± 6.7	5.5 ± 6.7	$U = 143$	**0.012**[c]
AES	32.5 ± 8.5	31.8 ± 11.8	31.4 ± 12.5	32.2 ± 12.1	$U = 238$	0.564[c]
MSS	5.8 ± 5.8	4.2 ± 4.2	4.3 ± 5.4	4.0 ± 2.8	$U = 229$	0.444[c]
HPS	9.4 ± 5.8	10.1 ± 7.3	10.7 ± 8.8	9.3 ± 5.9	$U = 265$	0.968[c]
QUIP-RS	12.6 ± 14.0	8.1 ± 10.2	10.7 ± 12.9	5.5 ± 6.7	$U = 206$	0.388[c]

Frequencies (categorical data), median and range (ordinal data), or means ± standard deviations (continuous data).
P-values of significant group differences are shown in bold font.
Abbreviations: M, male; F, female; PD, Parkinson' disease; H&Y, Hoehn and Yahr; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; A, akinetic-rigid; M, mixed; T, tremor dominant; LEDD, levodopa equivalent daily dose; NMSS, Non-Motor Symptom Scale; BDI-II, Beck Depression Inventory version II; AES, Apathy Evaluation Scale; MSS, Mania Self-Rating Scale; HPS, Hypomanic Personality Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders In Parkinson's Disease.
[a]Groups were compared by Fisher's exact test.
[b]Groups were compared by independent-samples *t* test.
[c]Groups were compared by Mann–Whitney *U* test.
[d]Groups were compared by analysis of covariance with BDI-II as a covariate.
*Patients with wildtype *GBA* compared with variant carriers (combined); data for variant subgroups is included to demonstrate similarity between both variants.

men. The 13 variant carriers were 66.7 ± 8.9 years old, and 11 (84.6%) were men. In each group, 3 patients had a first-degree relative with Parkinson's disease, corresponding to 7.1% of wildtype and 23.1% of variant carriers. These differences were not statistically significant; details are presented in Table 2.

Clinical History and Symptoms

Clinical history, symptom severity, and motor subtypes were not significantly different between genotypes and are detailed in Table 2. Wildtype patients had an average age at onset of 60.1 ± 10.2 years compared with 61.2 ± 8.1 years in the variant group, disease duration was 4.9 ± 4.0 (wildtype) versus 5.5 ± 3.9 (variant carriers) years. Median Hoehn and Yahr stages were similar between groups with 2.5 (range 1–3) for patients with the *GBA* wildtype sequence and 2 (2–3) for variant carriers. Total UPDRS-III scores were 23.7 ± 9.1 in patients with wildtype *GBA* and 16% higher (27.5 ± 10.9) in variant carriers; levodopa equivalent daily dose (LEDD)[36] was 455.8 ± 286.1 mg in noncarriers and 26% higher (577.1 ± 253.9 mg) in carriers; these group differences were not statistically significant. Likewise, no significant differences were detected with the nonmotor symptom scale.

Variant carriers scored lower in all 5 cognitive domains. The global cognition *z* score was significantly lower when BDI-II was included as a covariate ($P = 0.039$). Among the cognitive domains, executive and visual–spatial functions were the most affected, although group differences were narrowly not significant. BDI-II scores were significantly lower in carriers (5.8 ± 6.4) than in noncarriers (11.6 ± 7.8; $P = 0.012$), whereas groups were similar concerning apathy, (hypo-)mania, and impulsivity. Clinical and behavioral data are summarized in Table 2.

Metabolomics

Abundance of 1,5-anhydro-D-glucitol, asparagine, ornithine, glutamine, and glycine as well as the unknown metabolites with retention indices (RI) RI1169 and RI1568 was increased in *GBA* variant

TABLE 3. Results of voxel-wise *t* tests between wildtype *GBA* and variant carriers (combined)

Modality	Region	MNI Coordinates	Statistic		Mean Cluster Value (Normalized Uptake/FC Beta Value)			
		x/y/z	*T*	*P*	Wildtype *GBA*	Variant Carriers	p.E365K	p.T408M
[^{18}F]FDopa PET					n = 31	n = 7	n = 5	n = 2
	Caudate (IL)	−12/6/8	2.38	**0.011**[a]	93.2 ± 20.9	76.2 ± 12.3	73.1 ± 12.0	83.9 ± 13.0
	Accumbens (CL)	5/9/−5	2.15	**0.019**[a]	106.8 ± 16.1	94.4 ± 5.5	93.3 ± 6.3	97.2 ± 1.6
	Putamen (IL)	−18/8/4	1.91	**0.032**[a]	123.5 ± 11.5	113.2 ± 18.1	107.5 ± 15.3	127.6 ± 21.1
	Caudate (CL)	11/9/7	1.85	**0.036**[a]	89.8 ± 27.3	70.5 ± 13.0	69.5 ± 12.8	73.0 ± 18.4
[^{18}F]FDG PET					n = 34	n = 12	n = 7	n = 5
	sLOC, angular gyrus (L)	−51/−69/25	6.91	**<0.001**[b]	106.6 ± 7.6	92.3 ± 6.4	92.6 ± 6.9	91.8 ± 6.5
	sLOC, angular gyrus (R)	60/−53/35	5.65	**<0.001**[b]	109.9 ± 8.2	95.4 ± 5.2	94.8 ± 4.8	96.3 ± 6.1
	Precuneus, ICC (L, R)	−5/−68/40	4.92	**<0.001**[b]	118.4 ± 10.1	102.1 ± 7.4	104.4 ± 7.6	98.9 ± 6.5
Functional connectivity					n = 41	n = 12	n = 7	n = 5
Seed: caudate (L)	iLOC (L)	44/−50/6	4.90	**0.002**[b]	0.03 ± 0.06	−0.11 ± 0.07	−0.11 ± 0.09	−0.10 ± 0.04
	Occipital pole, sLOC (L)	−42/−88/10	4.89	**0.004**[b]	−0.01 ± 0.09	−0.15 ± 0.08	−0.13 ± 0.09	−0.18 ± 0.05
	Occipital pole, sLOC (R)	20/−88/22	4.66	**0.035**[b]	0.00 ± 0.09	−0.14 ± 0.13	−0.11 ± 0.14	−0.19 ± 0.11
Seed: caudate (R)	iLOC, sLOC (L)	−38/−84/8	4.57	**<0.001**[b]	−0.01 ± 0.10	−0.16 ± 0.10	−0.15 ± 0.07	−0.18 ± 0.13
	Occipital pole (R)	16/−94/26	4.11	**0.008**[b]	0.01 ± 0.08	−0.13 ± 0.11	−0.11 ± 0.07	−0.15 ± 0.15
Seed: accumbens (R)	SPL (L)	−34/−40/54	4.22	**0.013**[b]	0.02 ± 0.08	−0.12 ± 0.09	−0.14 ± 0.09	−0.09 ± 0.07
	iLOC, oFusG (R)	46/−66/−14	4.04	**0.008**[b]	0.03 ± 0.08	−0.11 ± 0.07	−0.13 ± 0.07	−0.10 ± 0.07

Statistics are for wildtype vs. variant carriers (combined), group means of both variants are separately included to demonstrate their similarity. Cluster values are means ± standard deviations.
P-values of significant group differences are shown in bold font.
Abbreviations: MNI, Montreal Neurological Institute; FC, functional connectivity; PET, positron emission tomography; [^{18}F]FDG, [^{18}F]fluorodeoxyglucose; L, left; R, right; IL, ipsilateral; CL, contralateral; sLOC, superior lateral occipital cortex; ICC, intracalcarine cortex; iLOC, inferior lateral occipital cortex; SPL, superior parietal lobule; oFusG, occipital fusiform gyrus.
[a]*P* values are uncorrected.
[b]*P* values are cluster-level family-wise error corrected.

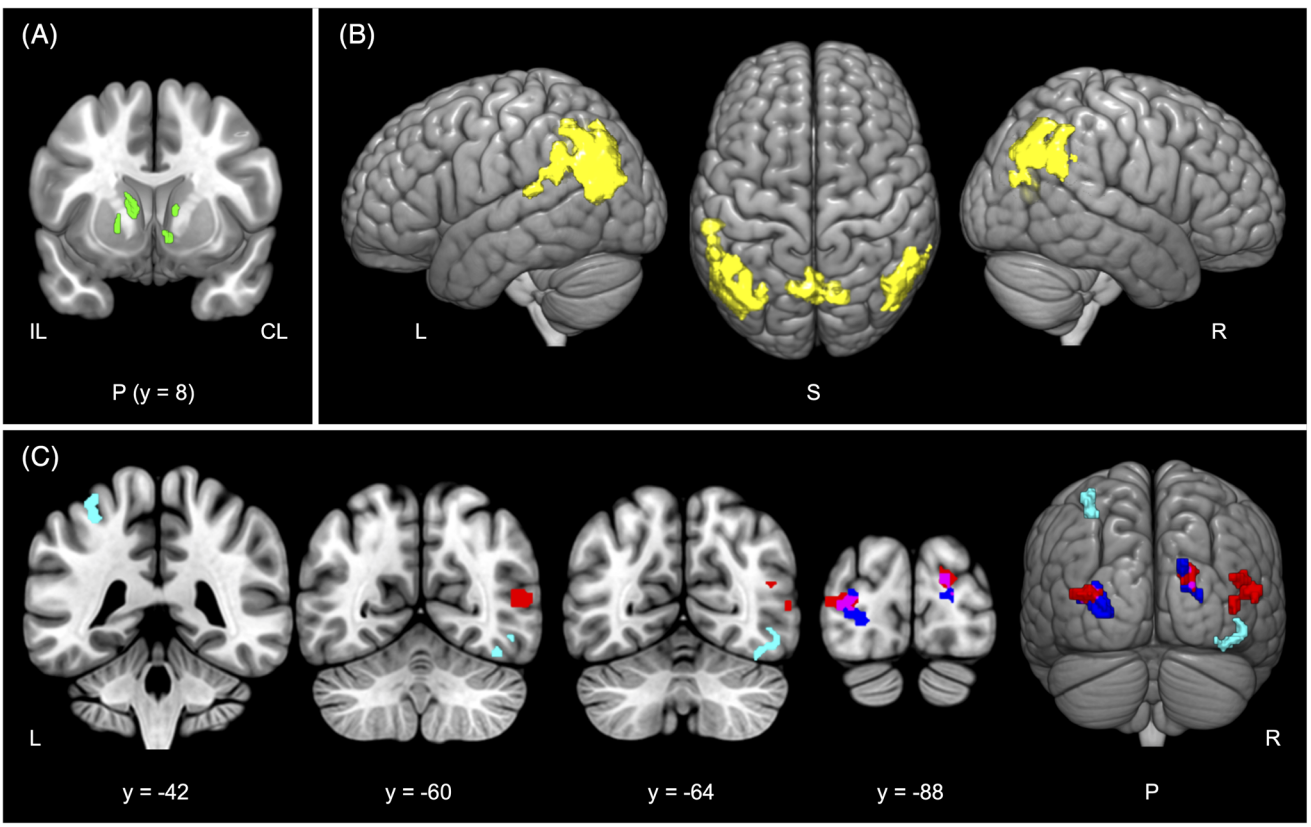

FIG. 2. Reduced metabolism and functional connectivity in *GBA* variant carriers. Clusters found in voxel-wise group comparisons of (**A**) [^{18}F]FDopa uptake (3-dimensional view, template cut at y = 8), (**B**) [^{18}F]fluorodeoxyglucose uptake, and (**C**) functional connectivity analysis (red = seed in left caudate, dark blue = seed in right caudate, purple = overlap, light blue = seed in right accumbens). CL, contralateral; IL, ipsilateral; L, left; P, posterior; R, right; S, superior. [Color figure can be viewed at wileyonlinelibrary.com]

carriers compared with noncarriers, whereas an unknown metabolite RI1120 showed decreased levels in carriers. All variant carriers were included in the metabolomics analysis. Results are presented in Figure 1 and Table S1.

Neuroimaging

Genotyping results in imaging subsamples can be found in Table 3. [^{18}F]FDopa uptake was reduced in the bilateral caudate nuclei, the antero-medial putamen ipsilateral, and nucleus accumbens contralateral to the more affected body side in variant carriers compared with noncarriers. PDRP expression was significantly higher in patients with *GBA* variants (3.07 ± 1.67) than in patients with wildtype *GBA* (0.99 ± 1.71, $P = 0.0007$), with similar scores in both variants (see Fig. 1C). PDCP expression was higher in carriers (0.64 ± 1.18) than in noncarriers (0.11 ± 1.41), but not significantly different between groups ($P = 0.250$). *GBA* variant carriers showed significantly reduced [^{18}F]FDG PET activity in the bilateral medial and lateral parietal lobe. FC was significantly reduced between the left and right caudate nuclei and the bilateral occipital cortex in carriers; the right nucleus accumbens showed reduced connectivity with the left superior parietal and right occipital fusiform cortex. More precisely, FC values were near zero in wildtype and negative in variant carriers, showing anticorrelations between activity fluctuations of the seed regions and the occipital/parietal cortex. FC of the left nucleus accumbens and left and right putamen was not different between groups. The results of voxel-wise group comparisons are detailed in Table 3 and depicted in Figure 2.

Further Analyses

Group characteristics in the subsamples for each analysis were similar to the whole sample (see Tables S2a–d). In patients with [^{18}F]FDG PET, the higher LEDD in carriers reached statistical significance ($P = 0.017$; Table S2b). To control for a potential influence of disease duration or antiparkinsonian medication, clinical, metabolomic, and imaging data were additionally compared with correction for disease duration and LEDD, which had only minimal effects on group differences; PDRP results remained significant with UPDRS-III as a covariate ($P = 0.0015$). The difference in BDI-II scores could not be explained by antidepressive medication or dopamine agonists, which were similar between groups (Tables 2, S2a–d). When Apathy Evaluation Scale scores were corrected for BDI-II, a trend for more apathy in variant carriers was observed ($P = 0.083$).

Discussion

This is the first study to date that provides detailed phenotypical data about the 2 main *GBA* variants that do not cause Gaucher's disease but are associated with Parkinson's disease, p.E365K and p.T408M. The results point to similarities with Gaucher's disease–related *GBA* mutations and are suggestive of a more severe course of the disease.

The present cohort had a relatively high proportion of *GBA* variant carriers (23.2%) compared with less than 10% reported in previous studies, whereas the rate of *GBA* mutations (1/56) was comparably low.[9,16] The total frequency of *GBA* alterations was not significantly higher than in the Dutch PROPARK cohort[9] and considering the sample size is probably coincidental. Mutations are much rarer than variants, most of them occurring far less frequently than p.N409S,[9] so they may be missed in a small cohort. The high proportion of variant carriers makes it extremely unlikely that exclusion criteria (eg, dementia) were biased against them. Carriers had a trend for more first-degree relatives with Parkinson's disease than noncarriers (23.1% vs. 7.1%); similar rates of a positive family history are regularly reported in *GBA* mutations.[1,7] A meta-analysis has not found higher UPDRS-III scores in variant carriers,[16] whereas LEDD may be increased[11] and should be investigated longitudinally in larger cohorts. Surprisingly, *GBA* carriers showed less symptoms of depression than wildtype patients. More depression in mutation carriers has been reported,[37] but often no effect was found.[11,12,38] In non-Gaucher's-related variants, no change in depression has been described.[11,16,39] When BDI-II was taken into account, significantly reduced global cognition was detected. However, cognition z scores in both groups indicated function within the normal range (−0.13 in wildtypes vs. −0.34 in carriers). An increased risk for cognitive deficits has previously only been demonstrated for p. E365K. In this study, both variants scored similarly in global cognition and BDI-II, thus contributing equally to the group difference.

Although carriers and noncarriers presented only minor clinical differences, metabolomics and neuroimaging highlighted interesting effects of *GBA* variants. Levels of 8 metabolites were suggestively altered in *GBA* variant carriers compared with noncarriers, that is, 1,5-anhydro-D-glucitol, asparagine, ornithine, glutamine, glycine, and 2 unidentified metabolites (RI1169 and RI1568) being increased, and the unknown metabolite RI1120 being decreased. Further elucidation is required for the identification and validation of the unknown metabolites. These preliminary results provide new hints to which pathways may be altered in *GBA*-related Parkinson's disease.

Increases of anhydroglucitol and other polyol pathway metabolites have been shown in the brain tissue of a *DJ-1* knockout Parkinson's disease mouse model, together with decreased levels of glycolysis intermediates.[40] Therefore, the polyol pathway might be dysregulated in *GBA* variant carriers. Ornithine has been reported to be higher in the cerebrospinal fluid of patients with Parkinson's disease than in healthy controls,[41] whereas blood plasma levels were increased in a rotenone-lesioned rat model.[42] The authors suspected a link to impairments in mitochondrial transport and the urea cycle. Asparagine, glutamine, and glycine have all been found to be significantly increased in blood plasma of patients with Parkinson's disease compared with healthy controls.[43] Higher levels in *GBA* variant carriers may indicate that changes observed in Parkinson's disease are more severe in patients with genetically determined glucocerebrosidase dysfunction. The results of this untargeted, hypothesis-generating approach are preliminary but can help focus future investigations on certain pathways or metabolites.

Neuroimaging studies of *GBA*-related Parkinson's disease so far have almost exclusively examined Gaucher's disease–causing mutations, and no publications could be found that applied imaging techniques specifically in the p.E365K and p.T408M variants. Recently, metabolic networks have been investigated in patients with Parkinson's disease carrying Gaucher's-related *GBA* mutations, showing similar results of significantly increased PDRP scores and slightly, not significantly increased PDCP expression values.[44] Increased PDRP scores are in line with a more severe course of the disease and suggest that subclinical neurobiological changes are present in *GBA* variant carriers even when clinical differences are not (yet) significant. The PDRP is already expressed in very early stages of the disease, even before the onset of motor symptoms in hemiparkinsonism[32] and prodromal Parkinson's disease.[45] Conversely, increased PDCP expression values may only reach significance with more advanced impairment: they steadily increase with disease progression and cognitive decline, but a significant group difference was described only between patients with multidomain cognitive impairment and healthy controls.[34]

Integrity of the dopaminergic system has not previously been examined in carriers of *GBA* variants. In mutation carriers, results were variable: [^{18}F]FDopa uptake was reduced in patients with Gaucher's disease with and without Parkinson's disease compared with healthy controls[20]; compared with noncarriers, [^{123}I] FP-CIT binding was lower in patients with more advanced stage Parkinson's disease carrying severe but not mild mutations,[8] whereas a recent study reported higher dopamine transporter density in carriers' more affected striatum at an early stage.[46] Discrepancies between these and our results may be attributed to different methodologies (ie, higher statistical threshold, region-of-interest based approach, radiotracer and target), and group differences may evolve with progression. Here, reduced uptake was detected at a low threshold, possibly because of the small number of variant carriers with [^{18}F]FDopa PET (n = 7). Striatal dopaminergic loss progresses from posterior to anterior in Parkinson's disease,[47] and the caudate nucleus is involved in cognition, particularly executive functions.[48]

Interestingly, variant carriers displayed FC anticorrelations between the caudate nuclei and the occipital cortex, whereas noncarriers' FC values were near zero. An almost identical pattern of caudate-occipital anticorrelations was previously reported in Parkinson's disease dementia (PDD) compared with positive correlations in healthy controls.[49] The striking similarity between these findings strongly suggests a link to more cognitive deficits in patients with Parkinson's disease with *GBA* alterations. In addition, altered connectivity patterns detected here could relate to *GBA* mutation carrier's susceptibility to psychotic symptoms: in Parkinson's disease with hallucinations, occipital and striatal regions show reduced connectivity,[50] and visual areas are deactivated during the hallucinatory experience.[51] In schizophrenia with visual hallucinations, abnormal FC was described between the nucleus accumbens and higher visual areas.[52] Functional MRI has, to our knowledge, never before been applied in *GBA*-related Parkinson's disease.

Parieto-occipital cortex hypoactivity in our cohort was very similar to previous findings in Parkinson's disease with *GBA* mutations[20] and in DLB[8] as well as in Parkinson's disease with visual hallucinations.[53] In line with this, cortical Lewy body load has been shown to be higher in patients with Parkinson's disease carrying *GBA* mutations.[54] In our cross-sectional study of mid-stage and early-stage patients, hallucinations or psychotic symptoms were not observed, but imaging findings indicate an increased susceptibility to these symptoms in variant carriers, which has repeatedly been described in *GBA* mutation carriers.[1] It has been shown that hallucinations and temporo-parieto-occipital hypometabolism precede PDD,[53] but to date no imaging predictors of hallucinations in Parkinson's disease have been described.

Despite a high degree of similarity between the 2 variants investigated here (Tables 1–3, S1-S2, Fig. 1), future studies with more participants should address potential differences between them. To date, most neuroimaging studies are performed without genetic testing. The unexpectedly high number of carriers found here is a reminder that, especially in smaller cohorts, the rate at which certain genetic risk variants occur is somewhat random. Depending on the methods used, results could potentially be confounded by the genetic risk profile of included patients. The results of previous studies in the

same cohort investigated here are unrelated to the differences detected between carriers and noncarriers of *GBA* variants.[25–27]

One reason why *GBA* has lately been drawing attention among researchers and clinicians is the hope for an—at least partially—causative therapy targeting glucocerebrosidase metabolism. Ambroxol, for example, enhances glucocerebrosidase activity in the cerebrospinal fluid of patients with Parkinson's disease,[55] and a randomized controlled trial in patients with PDD with and without *GBA* mutations or variants is currently recruiting.[56]

In conclusion, metabolomic and neuroimaging findings are suggestive of a more severe Parkinson's disease pathology and demonstrate similarities with PDD and DLB even in carriers with only minimal cognitive decline. Group differences were apparent at the (neuro-)biological level, but not significant at the clinical level. The lack of clinical differences is congruent with the hypothesis that more severe mutations have a more profound effect on the clinical course,[8] and evidence suggesting that patients with non-Gaucher's-related variants fall in between carriers of mild mutations and noncarriers.[9,16] Similarities with DLB are thought to be most apparent with severe mutations,[1] but here were also seen in patterns of cortical hypoactivity. We demonstrate for the first time that even in the absence of a significantly more severe clinical syndrome, subclinical findings are present in "mild" *GBA* variants. To the best of our knowledge, this is the most in-depth description to date of clinical and biological phenotypes of patients with Parkinson's disease carrying the *GBA* variants p.E365K and p.T408M. Metabolomic changes have to be validated, and longitudinal studies are needed to investigate whether the observed neuroimaging changes progress or if they are followed by significantly more severe motor symptoms, clinical dementia, and psychotic symptoms. Similar approaches could be applied to other genetic variants associated with Parkinson's disease, and the observed alterations could be promising to monitor effects of targeted disease-modifying treatments. ●

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

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