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Morbus Fabry and Parkinson's Disease—More Evidence for a Possible Genetic Link

Although investigation of the potential role of lysosomal storage disorders in Parkinson's disease (PD) has been ongoing since reports highlighted that Gaucher disease can be accompanied by parkinsonism,[1] for Fabry disease (FD), an X-linked recessive multisystem disorder caused by *Galactosidase* gene (*GLA*) mutations, the potential relationship to PD has not been studied until more recently[2] and literature cited therein. Here, we report the frequency of *GLA* variants in 252 PD patients retrospectively selected from our database (mean age, 68.6 years; range, 33–93 years; 59.9% male). With the systematic sequence strategy applied, we found a mean α-galactosidase-A (GAL)-activity of 3.4 μM/h ± 1.44 μM/h (cutoff, <2,8 μM/h) and mean Lyso-globotriaosylsphingosine (Lyso-Gb3) levels of 3.6 ng/mL ±1.30 ng/mL (cutoff, >3.5 ng/mL). By bidirectional Sanger sequencing of all seven exons and flanking 5′untranslated region with at least 20 base pairs of flanking intronic sequences, we detected a total of 96 *GLA* variants in 57 individuals. None of these variants were classified as pathogenic/likely pathogenic for FD according to the American College of Medical Genetics and Genomics, inasmuch as most variants were intronic or in non-coding part of the gene.[3] Most had similar mean allele frequencies (MAF), as reported in major genetic databases gnomAD.[4] Nevertheless, two variants predicted to alter the *GLA* protein were detected in four patients (p.Asp182Asn and p.Asp313Tyr, both of uncertain significance). Of these, p.Asp313Tyr (MAF, 0.85%; MAF in general world population [GWP], 0.30%; $P = 0.094$; MAF in European Non-Finnish Population [ENFP], 0.45%; $P = 0.209$) drew our attention (Table 1). All three patients displayed clinical FD features predominantly involving the central nervous system and heart (Table 1), showing a lower mean GAL-activity of 2.3 μM/h ± 0.19 μM/h than cutoff ($P = 0.001$) and normal mean Lyso-Gb3 level of 3.0 ng/mL ±0.33 ng/mL ($P = 0.197$). Because p.Asp313Tyr formerly was considered to result in a "pseudodeficient allele" with a pH-dependent enzyme activity, it failed to be classified as clinically relevant or pathogenetic for FD. In recent literature, however, this opinion has shifted, as p.Asp313Tyr may cause predominantly FD nervous system manifestations associated with a milder phenotype and later disease onset—a hypothesis that our data support.[5,6] We performed a meta-analysis with a similarly-sized previous study,[7] which screened 236 PD patients in a multistep approach, including *GLA* next generation sequencing in females and all males with abnormal GAL levels, thereby identifying four women with a p.Asp313Tyr variant. By merging the data, MAF of the *GLA* p.Asp313Tyr variant in PD patients clearly reached statistical significance ($P = 0.006$ compared to MAF of the GWP/alone $P = 0.021$; and $P = 0.038$ to ENFP/alone $P = 0.068$).[7]

In closing, ours is the first biochemically and genetically systematic study of FD in patients with PD. The limited sample size and the lack of a control group make it challenging to draw firm conclusions; nevertheless, we believe our study is meaningful because it highlights anew the possible link between the *GLA* p.Asp313Tyr variant and PD. Further studies involving larger cohorts are required because the possible pathogenetic role might influence monitoring of p.Asp313Tyr variant carriers and decisions involving potential enzyme replacement therapy.

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Data Availability Statement

Data are available from the corresponding author upon individual request.

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TABLE 1 *Characteristics of four PD patients with* GLA *variants predicted to alter the* GLA *protein*

Patient	P1	P2	P3	P4
Gender	M	F	M	F
GLA variant	c.937G>T;pAsp313Tyr, hemizygous	c.937G>T;pAsp313Tyr, heterozygous	c.937G>T;pAsp313Tyr, hemizygous	c.544G>A;p.Asp182Asn, heterozygous
MAF of the *GLA* variant in general world population	0.003040	0.003040	0.003040	5.45e−6
MAF of the *GLA* variant in European non Finnish population	0.004456	0.004456	0.004456	0.00001222
MAF of the *GLA* variant in our study population	0.00849858	0.00849858	0.00849858	0.00283286
PD family history	No	Yes	No	Yes
PD subtype	Hypokinetic-rigid type, right side emphasized	Mixed-type, right side emphasized	Hypokinetic-rigid type, right side emphasized	Hypokinetic-rigid type, left side emphasized
Age (y) at sample storage	73	61	73	66
Age (y) at diagnosis	69	56	62	60
DaTSAN	Positive	Positive	Positive	Not performed
cMRI	Falxmeningeoma, moderate cerebral microangiopathy and global cerebral atrophy	Moderate internal cerebral atrophy, isolated periventricular microangiopathic lesions	Moderate cerebral microangiopathy, with beginning status lacunaris of basalganglia, global cerebral atrophy emphasized temporal on the right side without temporo mesial atrophy	Lowgrade cerebral microangiopathy, mesiotemporal atrophy
Neurological/psychiatric symptoms*	TIA, dementia	Depression	Stroke, dementia, polyneuropathy	Polyneuropathy
Cardiac symptoms*	Atrial fibrillation		Coronary heart disease with myocardial infarction, low grade concentric hypertrophy of the left ventricular, diastolic dysfunction I°	Diastolic dysfunction
Other diseases	Hypertension, hypercholesterolemia, chronic lumboischalgia, bilateral total hip replacement	Camptocormia, scoliosis since birth, beginning renal insufficiency, suspected congenital macular degeneration, hysterectomy, hallux valgus operation, spinal canal stenosis lumbar vertebrae 3/4 and neuroforaminal stenosis lumbar vertebrae 5/sacral vertebrae 1 right side	Hypertension, prostate cancer 2010, cataract operation, obstipation	Osteopenia, camptocormia with myositic infiltrates of the paravertebral muscles, postural instability, hypothyreosis, cholecystectomy, varicose vein operation, obesity, bilateral knee replacement, appendectomy, cataract-operation, obstructive sleep apnea syndrome, stenosis of the vertebral artery right side
Vital status at time of sample examination	Alive	Deceased	Deceased	Alive
aGAL-A activity [μM/h], cutoff <2,8	2,4	2,5	2,1	4,6

(Continues)

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TABLE 1 *Continued*

Patient	P1	P2	P3	P4
Lyso-Gb3 [ng/mL], cutoff: >3,5	2,6	3,4	2,9	4,1
Reexamination, aGAL-A activity [μM/h]	2,6			6,3
Reexamination Lyso- Gb3 [ng/mL]	1,43			1,21

Note: Characteristics of PD patients with *α-Galactosidase* (*GLA*) p.Asp313Tyr variant (P1–P3; yellow) and p.Asp182Asn variant (P4; grey).
*Symptoms marked in blue correspond to FD symptoms.
Abbreviations: aGAL-A activity, a-Galactosidase-A activity; F, female; FD, Fabry Disease; GLA, α-Galactosidase; Lyso-Gb3, Lyso-Globotriaosylsphingosine; M, male; MAF, mean allele frequencies; P, Patient; PD, Parkinson's disease.

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Supporting Data

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