Movement Disorders
CLINICAL PRACTICE

CASE REPORT

GM1-Gangliosidosis Type III Associated Parkinsonism

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GLB1 encodes beta-galactosidase-1, a lysosomal hydrolase that cleaves the terminal beta-galactose from ganglioside substrates. Biallelic variants in *GLB1* cause beta-galactosidase deficiency leading to GM1 gangliosidosis.[1] Type III GM1 gangliosidosis shows extreme clinical variability and is less severe than GM1-gangliosidosis types I and II.[2] Here we describe a new family with GM1-gangliosidosis type III extending the geographic range of reported cases to Transcaucasia and expanding the disease phenotype.

Case Report

The index case (II-5) is a 20-year-old female born full-term after uneventful pregnancy and delivery to neurologically healthy parents of Azerbaijani origin. No consanguinity was reported in the family but the parents are from the same village. The proband had a similarly affected older brother and three unaffected adult siblings (Fig. 1A). She had normal early development and was healthy until the age of 12 years. At this age, the gradual onset of muscular stiffness and slowness of movements were noticed. This progressed to speech and swallowing impairment, walking difficulties, cognitive deterioration, and urinary frequency. Her past medical history was remarkable for nocturnal hypoventilation and the family history was positive for parkinsonism and unspecified movement disorders in the paternal relatives. Upon examination, she was cognitively impaired and anarthric with risus sardonicus, orolingual dystonia, and impaired saccades with a reduced range of vertical eye movements. Her body movements were slow and rigid, and her gait was stiff and shuffling with postural instability. There were axial dystonia leading to stooped posture and the lateral flexion of the body, bilateral asymmetric parkinsonism, limb dystonia and spasticity, and brisk tendon reflexes (Video 1). The proband's affected older brother (II-2), currently aged 31 years old, presented with a similar but significantly milder phenotype. He manifested at age 12 years old and displayed minimal upper limb dystonia upon walking but asymmetric parkinsonism (Video 1). Both affected siblings were short-statured with kyphoscoliosis and had no organomegaly, cerebellar ataxia, corneal opacity, or Kayser-Fleischer ring. Serum ceruloplasmin and 24-hour urinary copper levels were unremarkable. Brain MRI in both affected siblings revealed well-defined symmetrical high signal intensities in the posterior part of the putamina on T2-weighted images (Fig. 1G). Neither susceptibility-weighted MRI images, nor DATscan, nor leukocyte beta-galactosidase activity levels were available. Bone radiography excluded skeletal dysplasia.

To identify the genetic cause of the disease in the affected individuals, exome sequencing (ES) on DNA extracted from probands' leucocytes and variant filtering were performed as previously described.[3] An ultra-rare homozygous missense variant in exon 3 of *GLB1* c.319 T > C, p.(Phe107Leu) (NM_000404.4) residing within a 9.9 Mb region of homozygosity was identified. This variant resides in a highly conserved region of the catalytic TIM-barrel domain of beta-galactosidase[1] (Fig. 1B,C) and destabilizes the neighboring residues that flank the active ligand-binding site[4] (Fig. 1E). The variant has one allele count in a heterozygous state in gnomAD and is predicted to be deleterious/damaging by various in-silico prediction tools (Fig. 1D). Sanger sequencing confirmed the homozygous and the heterozygous carrier status for p. (Phe107Leu) in the affected siblings and their parents respectively (Fig. 1A). ES data was negative for all other disease-causing genes.

Discussion

Half of the reported families with GM1-gangliosidosis type III come from Japan with almost all harboring a homozygous pathogenic founder p. (Ile51Thr) variant.[2] The majority of non-Japanese cases harbor compound heterozygous *GLB1* variants;[2] therefore,

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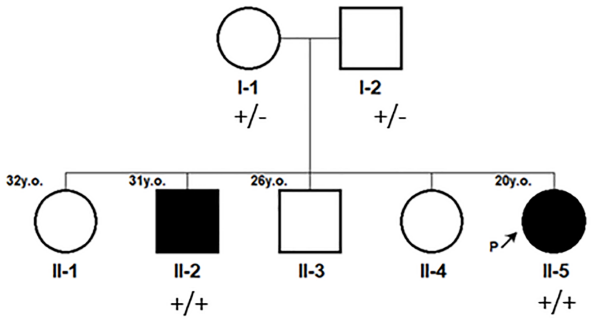
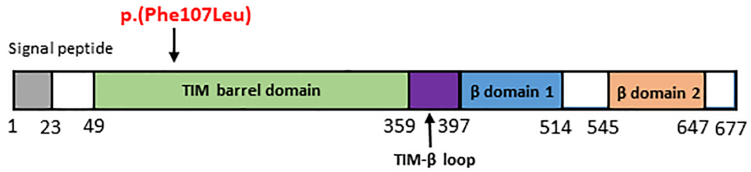
A



B



C

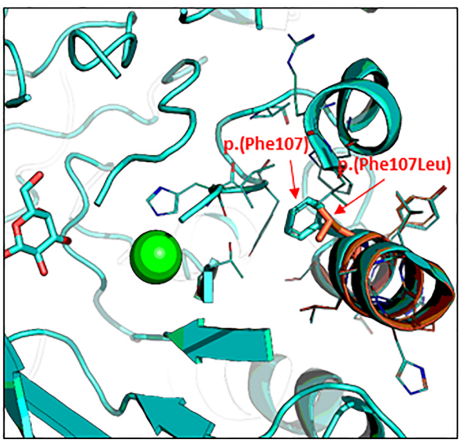
GLB1 p.(Phe107)

Frog	NGDRDLSHFLDLTNELGLLVIIRPGPYICAEWDMGGLPAWL
Zebrafish	SGDRDLEQFLQLCQDIGLLVIMRPGPYICAEWDMGGLPAWL
Mouse	SGDRDVEHFIQLAHELGLLVILRPGPYICAEWDMGGLPAWL
Human	SEDHDVEYFLRLAHELGLLVILRPGPYICAEWEMGGLPAWL
Chimpanzee	SEDHDVEYFLRLAHELGLLVILRPGPYICAEWEMGGLPAWL
Dog	SGEQDVEYFIKLAHELGLLVILRPGPYICAEWDMGGLPAWL
Horse	SEDHDVEYFIQLAHELGLLVILRPGPYICAEWDMGGLPAWL

D

GLB1 variant c.319T>C, p.(Phe107Leu) (NM_000404.4)	SIFT score	PolyPhen score	CADD PHRED	GERP	PROVEAN	REVEL score
	0 (deleterious)	0.999 (probably damaging)	28.6	4.1	-5.58 (damaging)	0.9 (damaging)

E



F

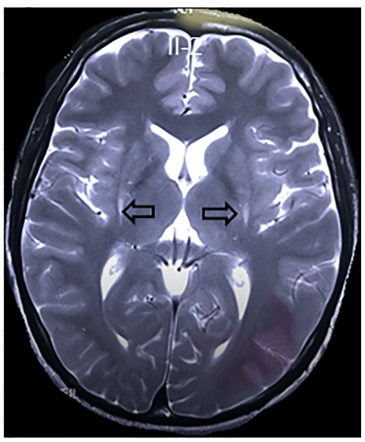


FIG. 1. Genetic and clinical summary of the investigated family. (**A**) Family tree of the presented cases. Square: Male, circle: Female, black symbols: Affected individuals, white symbols: Unaffected carriers. "+"–*GLB1* p.(Phe107Leu) variant, "-"–wild type. (**B**) A schematic organization of β-galactosidase domains with the position of p.(Phe107Leu) variant. TIM barrel domain is responsible for catalysis. (**C**) Protein multiple sequence alignment showing that p.(Phe107Leu) is located in the highly-conserved β-galactosidase protein region. (**D**) In silico pathogenicity predictions for the *GLB1* variant found in this study. (**E**) The structural effect of p.(Phe107Leu) on β-galactosidase protein. Wild type in turquoise and mutant in coral. The variant changes a buried residue to one with a different shape destabilizing the neighborhood (+20 kcal/mol). The residue is 14 Å away from the galactose substrate but is in contact with residues flanking the active site. (https://venus.sgc.ox.ac.uk/data/34353e6a-ca22-482e-b746-e594fca4a180). (**F**) Brain MRI of II-2. MRI findings are provided in the manuscript text.

Video 1. The part of the video between 00 minute:01 second–01 minute:10 seconds shows the proband (II-5). The rest of the video starting from 01 minute:11 seconds displays the affected brother (II-2).
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13289

the present family with the homozygous *GLB1* variant expands the genotypic spectrum of the non-Japanese cases and extends their geographic range to Transcaucasia.

Over 90% of GM1-gangliosidosis type III cases present with progressive dystonia, which is usually moderate-to-severe and generalized.[2,5] In our report, the affected brother (II-2) presented with minimal dystonia if any but parkinsonism over the disease course of 19 years. No impaired saccades and limited vertical gaze, seen in our cases, have previously been reported in GM1-gangliosidosis type III.[2,4] The presented MRI finding is typical of GM1-gangliosidosis type III and Glutaric aciduria type 1.[6] The discussed features seem to expand the clinico-genetic phenotype of the disease.

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Author Roles

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

R.K.: 1A, 1B, 1C, 3A
U.G.: 1C, 3B
S.G: 1C, 3B
K.S.: 1C, 3B
A.M.: 1C, 3B
P.A.: 1C, 3B
M.P.F.: 1C, 3B
H.H.: 1A, 1B, 3B

Disclosures

Ethical Compliance Statement: Written informed consent for genetic testing and photo/video materials were obtained from the parents. The study was conducted in accordance with the Declaration of Helsinki and approved by the relevant institutional review boards.We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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