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CASE REPORT

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A rare homozygous p.Arg87Trp variant of the *GBA* gene in Gaucher disease: A case report

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Abstract

Gaucher disease (GD) is a rare metabolic disorder due to pathogenic variants in the *GBA* gene. We report the first case of the rare p.Arg87Trp pathogenic variant (formerly known as R48W) of the *GBA* gene in the Tunisian population. A female Arab patient was assessed at the age of 26 due to abdominal distension, bone pain, and headache since she was 25. Physical examination revealed splenomegaly, rib deformation, lumbar scoliosis, and upper limb tremor. Bone marrow was infiltrated by Gaucher cells. The patient was homozygous for the rare p.Arg87Trp variant which is known to be associated with a mild phenotype. This report highlights the necessity of screening the Tunisian population for this rare variant.

KEYWORDS

Gaucher disease, *GBA* gene, p.Arg87Trp, R48W, rare pathogenic variant

1 | INTRODUCTION

Gaucher disease (GD) is a rare inherited metabolism disorder with a prevalence of about 1:50,000 in the general population[1] but as high as 1:855 in the Ashkenazi Jewish population.[2] It was described for the first time in 1882 by Philippe Gaucher in a 34-year-old patient with splenomegaly but without neoplasm.[3] It is the most common lysosomal storage disorder[1] due to a deficiency of β-glucocerebrosidase, a lysosomal enzyme,[4] which results in an accumulation of its substrate, glucosylsphingosine (lyso-Gb1), in macrophages, inducing their transformation into Gaucher cells.[5] The infiltration of bone marrow, spleen, and liver by Gaucher cells results in cytopenia, splenomegaly, hepatomegaly, and bone lesions.[5]

The phenotype is variable, but three forms of the disease, sharing the same enzyme defect, have been recognized based on age of onset, clinical signs, and neurological manifestations. Type 1 GD (non-neuropathic, OMIM 230800) is the most common and is characterized by hepatosplenomegaly, cytopenia, and bone involvement (avascular osteonecrosis, osteoporosis, fractures, and lytic lesions). Types 2 (acute neuropathic, OMIM 230900) and 3 (subacute neuropathic, OMIM 231000) are characterized by neurological impairment, within the first year of life and in childhood, respectively.[6]

These distinctions are not absolute, and it is increasingly recognized that neuropathic GD represents a phenotypic continuum, ranging from extrapyramidal syndrome in type 1, at the mild end, to hydrops fetalis at the severe end of type 2.[7] Enzyme replacement therapy became the

standard of care in 1991, and this has transformed the natural history of types 1 and 3 GD.[8]

β-glucocerebrosidase is encoded by the glucosidase beta acid *(GBA)* gene (OMIM 606463) located on chromosome 1 (1q21).[9] *GBA* has a highly homologous pseudogene (*GBAP* with 96% identity), located 16 kb downstream with the same organization of exons and introns as the functional gene, but carrying large deletions in introns 2, 4, 6, and 7, corresponding to *Alu* elements.[10] These highly homologous sequences and physical proximity may lead to gene conversion and crossing over events between *GBA* and *GBAP*, producing mutated complex alleles.[11]

GD is inherited as an autosomal recessive disorder. To date, more than 430 pathogenic variants of *GBA* have been described,[11] some of them are frequent such as c.1226A>G (p.Asn409Ser), c.1448T>C (p.Leu483Pro), and c.84dup,[12] especially in the Ashkenazi population. In Tunisia, the prevalence of GD is 0.92:100,000. Asymptomatic adult forms remain undiagnosed, which underestimates the frequency.[13] Many studies revealed that p.Asn409Ser, p.Leu483Pro, and the complex RecNciI variants are common in Gaucher Tunisian patients.[13-15] The latter is a complex variant derived from *GBA-GBAP* recombinant event (exons 9 and 10), containing three single nucleotide variants [c.1448T>C (p.Leu483Pro), c.1483G>C (p.Ala495Pro), c.1497G>C (p.Val499Val)] and defined by the creation of a NciI restriction site.[16,17] All these Tunisian studies were based on the investigation of the hotspot variants and not the entire sequencing of the *GBA* gene. Therefore, no pathogenic variant was found in some patients.

In this study, we report the clinical and genetic findings of the first Tunisian case of GD related to the rare p.Arg87Trp pathogenic variant.

2 | CASE PRESENTATION

We have examined in the genetic department of the Mongi Slim Hospital a Tunisian female adult patient with type 1 GD. Enzymatic and genetic tests utilized dried blood spot cards (CentoCard®, CENTOGENE AG, Germany). Lyso-Gb1 was quantified by liquid chromatography-mass spectrometry as described previously.[18] The *GBA* gene was analyzed using Sanger sequencing. Informed written consent was obtained from the patient. The study was approved by the Mongi Slim Hospital Ethics Committee.

The propositus was a female patient aged of 26 years old. She presented with abdominal distension, bone pain, and headache since she was 25. Physical examination revealed splenomegaly, rib deformation, lumbar scoliosis, and upper limb tremor. Her parents were consanguineous and healthy. Family history showed a maternal uncle who had a huge splenomegaly at the age of three years old, with spontaneous remission at six. He is currently asymptomatic. The propositus had a brother presented with splenomegaly at the age of one year and a sister with seizures and ecchymosis. Both of them were not investigated and died respectively at the age of three and two years old (Figure 1).

In the index case, pancytopenia was observed in complete blood count. Bone marrow was infiltrated by Gaucher cells. The measurement of plasma concentration of Lyso-Gb1 showed high value (830 ng/μl) above the cutoff of 10 ng/μl. Sequencing of the *GBA* gene revealed the homozygous pathogenic variant c.259C>T; p.Arg87Trp (R48W according to historical nomenclature). Unfortunately, neither the uncle nor the deceased siblings were investigated.

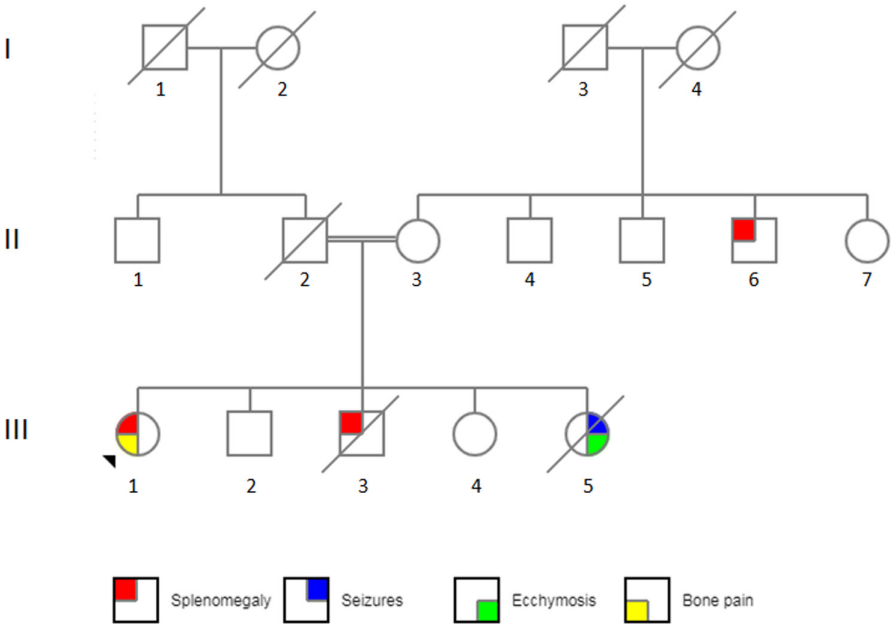

FIGURE 1 Pedigree of the proband's family. The proband (III-1) was assessed for Gaucher disease. Her uncle (II-6), deceased brother (III-3) and sister (III-5) were not investigated

3 | DISCUSSION

The prevalence of GD in Tunisia is estimated to be around 0.92 per 100,000 live births,[13] which is close to that in Egypt.[19] We report the first case of the rare p.Arg87Trp pathogenic variant in the *GBA* gene in the Tunisian population. The index case had a type 1 GD with late onset and mild phenotype. Family history revealed splenomegaly in an uncle and a deceased brother, seizures and ecchymosis in a deceased sister. These family members had limited access to healthcare facilities, so we presume that the uncle had a mild type 1 GD and that the siblings died because of hematologic complications of severe type 1 GD.

3.1 | The mild pathogenic variant

The p.Arg87Trp pathogenic variant was described for the first time by Beutler et al. at the compound heterozygous state in a male Bedouin Arab patient aged of 21 at the diagnosis of GD. Although he had the p.Leu483Pro (the severe pathogenic variant associated with types 2 and 3) on the second allele, he did not show neurological manifestations. In fact, in case of compound heterozygous states, one with mild phenotype and the other with severe phenotype, the overall phenotype is determined by the milder one. The authors also described an Afro-American female patient with the type 1 GD and the p.Arg87Trp variant in the heterozygous form with an unknown variant.[2]

Rockah et al.[20] reported the first case of homozygosity for this variant in a 26-year-old Bedouin Arab. This patient had a very mild phenotype of type 1 GD (moderate thrombopenia and hepatosplenomegaly, no bone pain). Recently, Fateen et al.[21] described the second case of p.Arg87Trp homozygosity in a 10-year-old Egyptian female patient with mild phenotype (hepatosplenomegaly, anemia, and thrombocytopenia).

Therefore, p.Arg87Trp was described as a mild pathogenic variant based on the absence of neurological symptoms when present at compound heterozygous state with a severe pathogenic variant on one hand,[2] and on the mild clinical phenotype when present at the homozygous state on the other hand.[20,21] In fact, Grace et al. proved that cells carrying the p.Arg87Trp variant expressed enzyme with the highest residual activity (≈ 28% with respect to the normal)[22] with levels similar to those from the expressed mild p.Asn409Ser allele (allele protecting against the development of neurological manifestations).[23]

As we reviewed the English literature till 2020, we noticed that this pathogenic variant is rare based on pan-ethnic studies. Its allele frequency varies from 0.5%[24,25] to 1.6%[26] among patients diagnosed with GD. It has been described worldwide (Table 1), mainly in the Chinese population. It was suggested that since there has been limited historical contact between the Bedouin Arab and the Chinese, the pathogenic variant may have occurred more than once in different populations.[27]

In case the phenotype was described, most of the patients with the p.Arg87Trp variant had the type 1 even if compound heterozygous in conjunction with a severe or null allele (Table 1). Our patient presented with splenomegaly, which was seen in all patients who had the p.Arg87Trp variant. Her maternal uncle had spontaneous remission of splenomegaly at the age of six, which is an uncommon disease evolution. Indeed, in a case series of 36 patients who were never treated and non-splenectomized, spleen size spontaneously decreased in only one patient.[28]

Our patient also had bone pain, rib, and back deformation. Bone manifestation is common in GD patients, especially those with the p.Arg87Trp pathogenic variant. It can be particularly severe and lead to leg-length discrepancy or osteomyelitis.[23] Hematologic involvement such as thrombocytopenia and anemia are also common, it can be asymptomatic as in the present case and the ones described in the Arab patients.[20,21]

3.2 | Severe phenotype

In contrast, Grace et al. described a young patient with severe type 1 GD who presented with cachexia, massive hepatosplenomegaly, ascites, and portal hypertension. She had marked anemia and thrombocytopenia. Her *GBA* genotype was p.Arg87Trp/p.Trp218Ter. She had a similarly affected brother, died at age 8, presumably due to complications of severe type 1 GD.[22] If we speculate that the siblings of our index case had a GD, we can consider that this affection can lead to a pleiotropic phenotype, ranging from mild (as the case of her uncle) to severe forms causing death (as the case of her brother and sister). Further investigations among Tunisian patients, especially those with no pathogenic variant identified, are needed to accept or confirm this hypothesis.

Moreover, another mechanism would explain the severe phenotype in the patient's siblings. Indeed, the parents might be compound heterozygous as well (p.Arg87Trp and more severe variants). They could be asymptomatic carriers of the p.Leu483Pro or the complex RecNciI variants since they are responsible for severe phenotypes. Therefore, the brother and sister would be homozygous for the variants leading to type 2 GD.

TABLE 1 Clinical and biological findings of the reported patients with p.Arg87Trp variant in the literature

Patients	Origin	Onset age (years)	Current age (years)	Splenomegaly	Hepatomegaly	Bone involvement	Neurological signs
2	Bedouin Arab	2	21	+		Aseptic necrosis	–
6	African American	7	7	+		–	–
DR	Chinese	3	8	+	+	+	–
1	Indian		20	+	+		
	Bedouin Arab	26	26	+	+	–	–
5	African American			+	+		
3	African American	3	21	+	+	Severe bone pain Leg-length discrepancy Osteomyelitis Hip-replacement	–
1	Lebanese	3	61	+	+	–	
2	Lebanese	2	25	+	+	Bone and joint pain	
I–1	Albanian		44	+	+	Bone pain	
I–2	Albanian		41	+	+	Bone pain	
I–3	Albanian		39	+	+	Bone pain	
II–2	Albanian		15	+	–	–	
II–3	Albanian		8	+	–	–	
89	Indian			+	+		
6	Egyptian	10		+	+		–
	Tunisian	25	30	+	–	Bone pain Rib deformation Lumbar scoliosis	Upper limb tremor

3.3 | Parkinson disease

Although type 1 GD had been designated non-neuropathic, several studies revealed that patients have an increased risk of developing peripheral neuropathy and parkinsonian features. In a cohort of 444 patients with type 1 GD, 2.47% (11/444) developed Parkinson's disease (PD). Mean age at the diagnosis of PD was 55.0±8.8 years (range 40–65 years). In this study, the authors observed the entire spectrum of PD symptoms associated with type 1 GD, from tremor (as in our patient) and rigidity to severe incapacity, and potentially life-threatening disease. There was no association between severity of PD and severity of GD, spleen status, or *GBA* genotype.[29]

These data reveal the lack of strength of the genotype–phenotype correlation[30] and suggest the contribution of other genetic factors.

Complete blood count	Phenotype	GBA genotype	b-Glucosidase activity [% of normal]	Lyso-Gb1 [ng/μl]	Reference
Anemia	Type 1 Mild	p.Arg87Trp / p.Leu483Pro			2
Pancytopenia	Type 1 Mild	p.Arg87Trp /?			2
Anemia Thrombocytopenia	Type 1	p.Arg87Trp / p.Arg159Trp	10		27
Anemia Thrombocytopenia	Type 1 Severe	p.Arg87Trp / p.Trp218Ter	Deficient		22
Thrombocytopenia	Type 1 Mild	p.Arg87Trp / p.Arg87Trp	< 10		20
Pancytopenia	Type 1 Mild	p.Arg87Trp / p.Ser366Asn			37
Anemia Thrombocytopenia	Type 1	p.Arg87Trp / p.Leu483Pro			23
Pancytopenia	Type 1 Mild	p.Arg87Trp / p.Leu483Pro	31		31
Anemia	Type 1 Severe	p.Arg87Trp / p.Leu483Pro	9		31
Thrombocytopenia	Type 1 Severe	p.Arg87Trp / p.Leu422Profs*4		264	38
Thrombocytopenia	Type 1 Severe	p.Arg87Trp / p.Leu422Profs*4		1090	38
Thrombocytopenia	Type 1 Severe	p.Arg87Trp / p.Leu422Profs*4		590	38
Normal platelets	Type 1 Mild	p.Arg87Trp / p.Asn409Ser		49.6	38
Normal platelets	Type 1 Mild	p.Arg87Trp / p.Asn409Ser		76.3	38
Anemia Thrombocytopenia		p.Arg87Trp / RecNcil			25
Anemia Thrombocytopenia	Type 1 Mild	p.Arg87Trp / p.Arg87Trp			21
Pancytopenia	Type 1 Mild	p.Arg87Trp / p.Arg87Trp		830	Current case

3.4 | Genetic modifiers

El-Zahabi et al. described a Lebanese family with two cases that exhibit different manifestations of GD with varying severity, although they represent two generations of the same genotypic disease (p.Arg87Trp/p.Leu483Pro). The child had a more severe clinical presentation than his uncle.[31] Indeed, even monozygotic twins who were homozygous for the p.Asn370Ser pathogenic variant were described with varying degrees of GD severity. This could be explained by the influence of genetic modifiers over GD expression in genetically predisposed individuals.[32]

Genetic modifiers are genes that can affect penetrance, dominance modification, expressivity, and pleiotropy.[33] *CLN8* (Ceroid lipofuscinosis neuronal 8, OMIM 607837) and *GRIN2B* (glutamate ionotropic receptor NMDA type subunit 2B, OMIM 138252) were

reported to be potential modifier genes for GD. CLN8 is a transmembrane protein located in the endoplasmic reticulum, involved in GD-related pathways such as lipid trafficking, membrane trafficking, and autophagy/mitophagy.[34,35] *CLN8* may play a protective role in GD, noting higher expression levels in fibroblasts of patients with milder symptoms.[35] *GRIN2B* encodes a subunit of the NMDA (N-methyl-D-aspartic acid) receptor. An antagonist of NMDA receptor has been shown to significantly increase the lifespan of GD mice.[36] These observations reflect the phenotypic variability in GD patients and the potential role of modifier genes in determining disease phenotypes.

4 | CONCLUSIONS

To our knowledge, this is the third report of the homozygosity of the rare p.Arg87Trp pathogenic variant of *GBA* in the world and the second one in North Africa. Our study illustrates the pleiotropic phenotype caused by this variant as it was described previously. We suggest screening for the p.Arg87Trp variant in the Tunisian patients who were investigated for only the hotspot variants and in whom at least one pathogenic variant was not identified. Additional studies would likely lead to the identification of more cases with this rare variant.

AUTHOR CONTRIBUTIONS

Houweyda JILANI and Faten HSOUMI examined the patient. Arndt ROLFS participated in the biochemical and molecular analysis. Houweyda JILANI wrote the first draft. Imen REJEB and Yasmina ELARIBI participated in the review and the revision of the manuscript. Syrine HIZEM and Molka SEBAI participated in the revision of the manuscript. Lamia BENJEMAA reviewed and revised the results and the manuscript.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data are available by request.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Mongi Slim Hospital.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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