

Case Report

Identification of a Novel *GLA* Variation (p.Val269Leu) in a Pediatric Patient with Classic Fabry disease: A Case Report

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Received: January 31, 2020; Accepted: February 10, 2020; Published: February 20, 2020

Abstract

Fabry Disease (FD) is an X-linked disease caused by variants at *GLA* gene, producing deficient activity of α -galactosidase. An enzyme, leading to progressive lysosomal accumulation of globotriaosylceramide (GL3) and globotriaosylsphingosine (Lyso-Gb3) in cells. More than 900 *GLA* variants have been associated with FD, some of them with uncertain pathogenicity. Plasma LysoGb3 is a useful diagnostic tool and considered a potential indication for early Enzyme Replacement Therapy (ERT). However, in pediatric population, the genotype and biomarkers measurement are often not enough to define phenotype and to decide the timely initiation of ERT. We report a novel missense hemizygous mutation, c.805G>C (p.Val269Leu) which caused Fabry nephropathy in a 2 year old male with normal biomarkers.

Introduction

Fabry Disease (FD) is an inherited, genetic condition caused by defects in the *GLA* gene that are carried by the X-chromosome and thus can be transmitted by the mother and father. Defects in the *GLA* gene cause deficient or absent lysosomal α -Gal An activity and consequently accumulation of glycosphingolipids mainly GL-3. The progressive GL-3 accumulation in tissues results in cellular and organ damage across the body [1].

More than 900 *GLA* variants have been reported to date, certain *GLA* mutations are associated with classic Fabry disease and others with later-onset phenotype [2]. However there is often not enough evidence across individuals for full phenotypic characterization, especially in pediatric population [3].

Measurement of biomarkers like Lyso-Gb3 in plasma has become appreciated as a useful diagnostic tool and considered useful as potential indication for early Enzyme Replacement Therapy (ERT) [4]. However in pediatric population the genotype and biomarkers measurement are often not enough to define phenotype and to decide the timely initiation of ERT. [5].

Clinical Case

We report a new *GLA* variation in 2-year-old male who was born in Mexico City. His 28-year-old uncle with chronic renal insufficiency was diagnosed with Fabry disease, his 30-year-old mother was an asymptomatic carrier. (Figure 1)

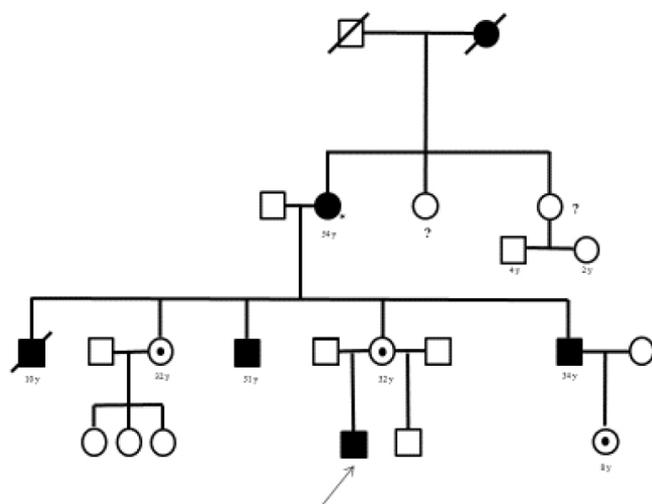


Figure 1. Genographics

On clinical assessment the patient complained of acroparesthesia in the hands and the feet and experienced substantial irritability during the episodes of pain. The physical examination was unremarkable, normal weight and height for age and normal developmental milestones. The enzymatic activity assay in dry blood spot revealed reduced α -galactosidase. An enzymatic activity (0.39nmol/ml/hr; normal range 1.04–5.9 nmol/ml/hr).

We genetically analyzed all coding parts of the *GLA* gene via PCR and direct sequencing. Molecular analysis revealed that the patient

was hemizygous for a missense mutation of exon 6 of the *GLA* gene c.805G>C (p.Val269Leu). The mutation was previously not described and the p.Val269Leu mutation to our knowledge was detected only in our patient and his family (mother and uncle).

A thorough multisystemic assessment was performed to search for other clinical features of Fabry disease, but no gastrointestinal, cutaneous, ocular, audiological, cardiologic, neurologic, respiratory or renal involvement was found, only with no significant proteinuria. (Table 1)

Table 1. Clinical Features.

Clinical features of patient with V269L mutation	
Age	2 years
Gender	Male
α -galactosidase A (normal 1.04–5.9 nmol/ml/hr)	0.39
Lyso Gb3 (<5 ng/ml)	BQL
Plasma GL-3 (<7 μ g/mL)	3.8
Urine GL-3 (<7 μ g/mL)	BQL
Symptoms	
Hypohidrosis	No
Angiokeratoma	No
Neuropathic pain	Yes
Gastrointestinal	No
Dyspnea	No
Cardiac	
EKG	Normal
IVSD(mm)	4
LV mass (g/m ²)	64
Renal	
eGFR(Schwartz ml/min)	115
Proteinuria (g/24h)	No-significant
Serum creatinine (mg/dl)	0.36
Neurological	
MRI brain	Normal
Neuropathy	Temperature analgesia

BQL * Bellow quantification levels

The patient's Lyso-Gb3 plasma level was normal (below quantification levels) measured by tandem mass spectrometer. Moreover, solid-phase chromatography demonstrated that the patient's Plasma GL-3 level was normal and liquid chromatography of urinary GL-3 level was within normal range. We continued with outpatient follow-up visits for a year and because of the aggressive phenotype of the other members of the family and the presence of acroparesthesia, we decided to perform a kidney biopsy that showed significant GL3 accumulation in several types of kidney cells; GL3 inclusions were

present in glomerular endothelial cells, tubular epithelial cells and mesangial cell inclusions were also found. (Figure 2–3)

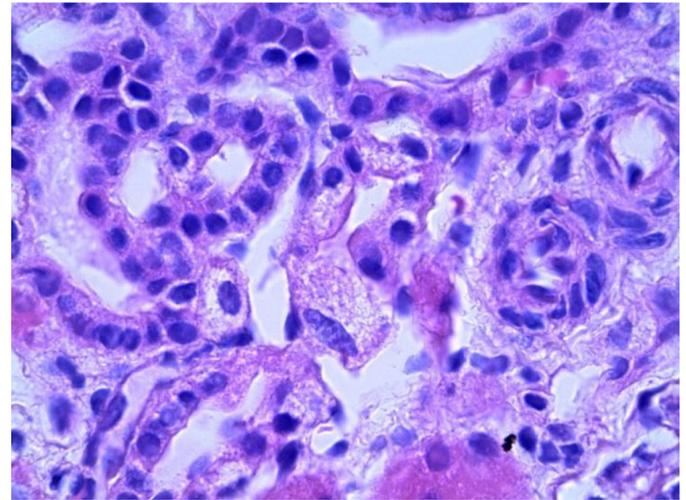


Figure 2. Distal tubules showing abundant inclusions with cytoplasmic expansion (PAS 40X).

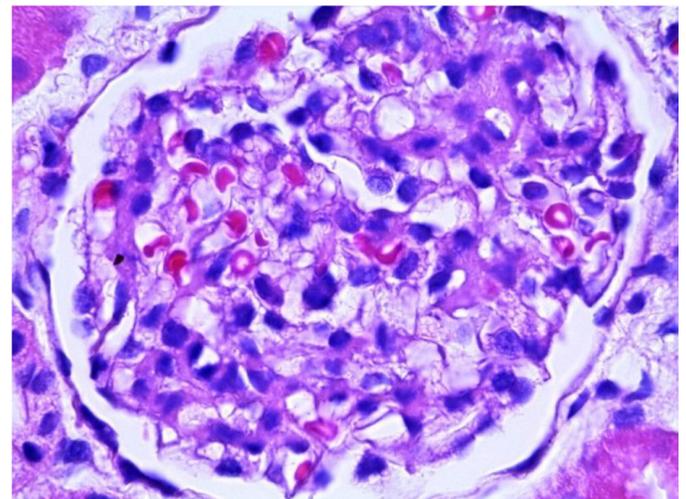


Figure 3. Glomerulus with epithelial cells showing cytoplasmic expansion that becomes vacuolated (PAS 40X).

Electron microscopy showed numerous electron-dense multi-lamellar inclusions in the epithelial cytoplasm with podocyte effacement, typical of Fabry disease. (Figure 4)

Enzyme replacement therapy with agalsidase beta was initiated at 1 mg/kg every other week; during the course of treatment the patient presented a diminished frequency of acroparesthesia.

Discussion

To our knowledge this is the first report of pathogenicity of the p.Val269Leu variant. Three other pathogenic missense mutations have been reported, affecting the same amino acid: p.Val269Met [6], p.Val269Ala [7] and p.Val269Gly, (8) one variant classified as with unknown significance, though without any clinical condition provided (p.Val269Glu)[9], all pointing out a potentially putative role of this amino acid in the protein.

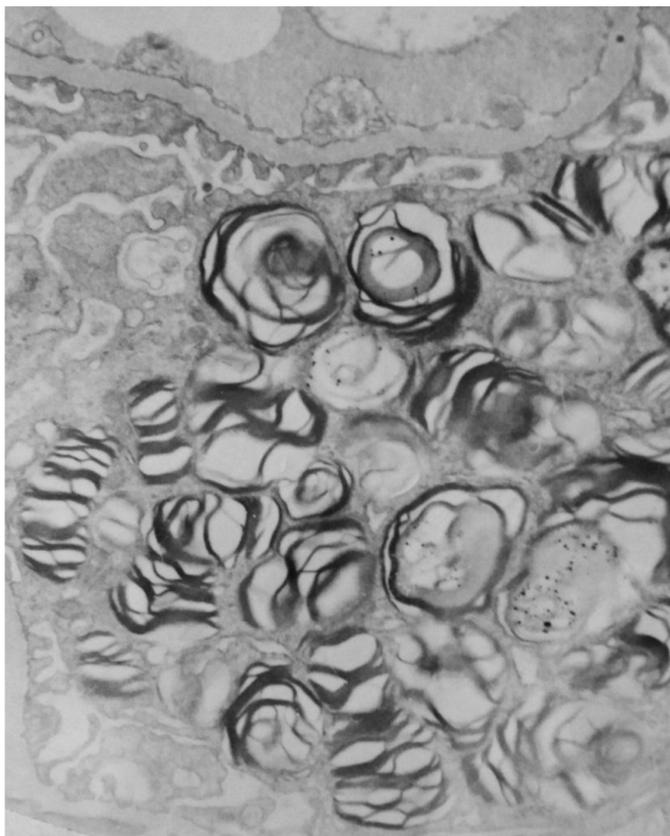


Figure 4. Electronic microscopy showing podocytes with myelin figures and zebra bodies in cytoplasm (4,500x).

The p.Val269Met mutation was first found in a male patient with classic FD phenotype, together with the p. Asp264Tyr mutation [6]. In vitro analyses demonstrated that while the p.Val269Met mutation led to an approximately 10 per cent of expressed wild-type enzymatic activity, together with the p.D264Y variant, it led to a non-detectable activity in plasma and leukocytes[6]. The p.Val269Ala and p.Val269Gly variants were also detected in patients with classical FD [7–8], and the deleterious effect of the mutations have been confirmed by in vivo measurements of biomarker levels.

Since their first reports, an international reference laboratory confirmed the p.Val269Met variant 65 patients in total (heterozygous/homozygous/hemizygous: 44/0/21, resp.), while p.Val269Ala was confirmed in 4 patients (3/0/1) and p.Val269Gly in 5 patients (2/0/3).

In this case the *GLA* variant p.Val269Leu demonstrated to be pathogenic in a very young patient with organ tissue damage (kidney and skin biopsy) despite normal biomarkers (lysoGb3, urine GL3 and plasma GL3) highlighting the importance of histologic assessment in children to timely decide initiation of ERT.

Conclusion

In conclusion, we identified a novel missense mutation in *GLA*, p.Val269Leu, in a 2-year-old male with classic Fabry disease diagnosed with kidney and skin biopsy despite normal biomarkers. The histologic findings provided organ damage information that helped us decide the initiation of ERT. The identification of this novel mutation will

enable clinicians and genetic counselors to have better understanding of Fabry disease.

The issue of timely initiation of ERT in childhood is an increasingly important debate, although lysoGb3 is a useful marker, histologic assessment including kidney and skin biopsy may provide more definitive information about organ injury related to FD and better inform treatment decisions, especially when the especially when the *GLA* variants are novel or variants of uncertain significance.

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Citation:

Cerón-Rodríguez M, Castillo-García D, Miltenberger Miltenyi G and Ramón-García G (2020) Identification of a novel *GLA* mutation (p.Val269Leu) in a pediatric patient with classic Fabry disease: a case report. *J Mol Genet*, Volume 3(1): 1–3.