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Genotype–Phenotype Spectrum of 52 Mexican Patients With Fabry Disease: A Novel *GLA* Variant With Atypical Phenotype

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ABSTRACT

Introduction: Fabry disease (FD) is a rare lysosomal type 3 disorder with an X-linked inheritance pattern caused by pathogenic variants in the *GLA* gene. This study aimed to describe the genotype and phenotype of 52 Mexican patients with FD.

Methods: We included 12 patients with clinical and molecular diagnosis of FD treated at our institution and 40 FD Mexican patients already reported in the literature.

Results: The most frequent manifestations were acroparesthesias (71.2%), hypohidrosis or anhidrosis (48.1%), heat intolerance (46.2%), and proteinuria (42.3%). Renal and neurological manifestations were more prevalent in males than females. Cardiac involvement included hypertrophic cardiomyopathy and Wolf–Parkinson–White arrhythmia. Cornea verticillata was seen in 14 patients (26.9%) and angiokeratomas in 15 (28.8%). We identified 14 variants in the *GLA* gene in Mexican patients with FD. We found a novel variant *GLA* c.122C>G that causes an atypical FD phenotype with predominantly neurological involvement in two unrelated patients, one of them with a forthright clinical and radiological overlap of Multiple Sclerosis and normal biological biomarkers, thus requiring a renal biopsy that helped confirm the diagnosis of FD.

Conclusions: The genotype and phenotype of Mexican patients with FD are similar to other populations. Atypical phenotype of FD, such as the one associated with the novel variant c.122C>G, can be a diagnostic challenge, as it can be mixed up with MS. Our findings confirm the limitations of noninvasive diagnostic methods and the necessity of the renal biopsy when the clinical suspicion of FD is high.

1 | Introduction

Fabry disease (FD) was first described in 1898 independently by two dermatologists, "Fabry" and "Anderson" (OMIM #301500) (Anderson 1898; Fabry 1898). It is a rare lysosomal type 3 disorder with an X-linked inheritance pattern. The prevalence of this disease ranges from 1:8454 to 1:117,000; however, it is believed to be underestimated due to some poorly recognized

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symptoms (Meikle et al. 1999; Houge and Skarbøvik 2005; Branton et al. 2002).

FD is caused by mutations in the *GLA* gene, which lead to a deficiency in the enzyme alpha-galactosidase A (α-Gal), resulting in the accumulation in multiple cell types (e.g., podocytes, cardiomyocytes, and vascular endothelial and arterial smooth muscle) of glycosphingolipids, particularly globotriaosylceramide (Gb3) and its deacylated form, globotriaosylsphingosine (lyso-Gb3). This accumulation is responsible for the gradual multisystemic damage associated with the disease (Tuttolomondo et al. 2021).

According to the Ensembl database, there are 56,929 reported variants in the *GLA* gene (including single nucleotide polymorphisms and somatic variants), and at least 929 have been associated with FD (classified as pathogenic and likely pathogenic variants) (Fiona Cunningham 2022). Most of these variants are private, occurring in single or a few families. Determining a possible genotype–phenotype association is challenging due to intrafamilial phenotypic variability (Ortiz et al. 2018).

To date, there are two phenotypes associated with FD: "classic" and "non-classic", the latter also known as "late onset" or "atypical". The classic form is characterized by little or null α-Gal enzyme activity (< 1%–3%; strictly 1%, though some authors report up to 3%). This phenotype is associated with an earlier onset (in childhood or early adolescence) and a more severe clinical presentation. Cardinal features include angiokeratomas (present in up to 40%), acroparesthesias triggered by stress, temperature changes, or physical activity, and cornea verticillata (considered the most sensitive diagnostic finding) (Michaud et al. 2020; MacDermot, Holmes, and Miners 2001; Zarate et al. 2010).

Other manifestations include proteinuria, which can lead to kidney function impairment and subsequently to chronic kidney disease (CKD); cardiovascular involvement, namely concentric left ventricular hypertrophy, arrhythmias, and hypertrophic cardiomyopathy; and cerebrovascular manifestations including transient ischemic attacks (TIA), strokes, and chronic cerebral white matter hyperintensities (present in two-thirds of patients). The latter is particularly important because it can mimic multiple sclerosis (MS). Cardiovascular and cerebrovascular manifestations are considered the leading causes of mortality in patients with FD (Michaud et al. 2020; Zarate et al. 2010).

Nonspecific manifestations associated with this disorder include hearing loss, hypohidrosis, tremors, abdominal pain, diarrhea, vomiting, and, less frequently, hyperhidrosis. Conversely, the "non-classic" phenotype is associated with α-Gal enzyme activity in higher levels (3%–35%). This phenotype typically presents later in life and may involve single-organ dysfunction or a milder overall presentation. However, enzyme activity in females is inconsistent, as they can have normal values; therefore, it is not a reliable parameter for distinguishing between the "classic" and "non-classic" forms (van der Veen et al. 2020).

FD can affect both males and females; however, males with FD typically exhibit a more severe phenotype due to hemizygous variants. Heterozygous females may range from asymptomatic carriers to clinically affected individuals, often influenced by skewed X chromosome inactivation. Nevertheless, they generally present with a milder phenotype (Echevarria et al. 2016).

Gb3 and lyso-Gb3 are considered FD biomarkers and can be measured in the plasma and urine of patients with a suspected FD. They have been proposed as potential diagnostic markers, especially in patients found to have a *GLA* variant of uncertain significance (VUS). Additionally, they serve as parameters to monitor disease activity and treatment response (Simonetta et al. 2020).

In males, the diagnosis is determined by α-Gal reduced enzyme activity with a molecular test confirming the presence of a variant in the *GLA* gene, which fulfills the pathogenicity criteria according to the American College of Genetics and Genomics (ACGM). As previously mentioned, in females, α-Gal activity may fall within the normal range, thus requiring molecular testing to confirm the diagnosis. Furthermore, when the pathogenicity of a detected mutation is uncertain and/or α-Gal activity is in the "gray zone" range (3%–35%), a biopsy of affected tissue is recommended to search for intracellular Gb3 inclusions (Desnick et al. 2003; Laney et al. 2013; Gal, Hughes, and Winchester 2011).

There are two types of treatment for FD, non-specific therapies, such as adjuvant medications and interventions according to the symptoms presented, and targeted therapies. The latter includes enzyme replacement therapy (ERT) (agalsidase alfa and beta) and chaperone therapy which enhances chaperone-mediated correct folding activity. It is the only FDA-approved oral treatment available for FD, and its use is confined to specific missense mutations (van der Veen et al. 2020).

This study aims to report 12 new FD cases with molecular confirmation diagnosed in a tertiary hospital in Mexico City, including two with a novel variant causing a nonclassic FD phenotype with predominant neurological involvement. In addition, we reviewed the literature on previously reported Mexican FD cases.

2 | Materials and Methods

This protocol was approved by the Investigation Committee and the Ethics Investigation Committee of the National Institute of Medical Sciences and Nutrition "Salvador Zubiran" (REF: 4997). We included data of 12 patients from 7 nonrelated families with clinical suspicion and molecular confirmation of FD treated at our institution between January 1st of 2014 and December 31 of 2022. Family pedigrees and renal biopsy reports were obtained from clinical records. When available, enzymatic activity at the moment of diagnosis, plasma Lyso-Gb3, and plasma and urine Gb3 were documented. These measurements were conducted by external laboratories using a uniform methodology. The activity of α-Gal was determined from dried blood spot cards using an enzyme-specific substrate and analyzed via ultrahigh performance liquid chromatography–tandem mass spectrometry (LC–MS/MS). Concentrations of Lyso-Gb3 were extracted from plasma, and Gb3 from both plasma and urine, and quantified using the same LC–MS/MS technique. Molecular testing involved polymerase chain reaction (PCR) amplification and sequencing of all seven exons, as well as specific regions within

intron four, of the *GLA* gene, including the coding sequences and immediate flanking intron sequences.

We used PubMed to search for articles reporting FD cases from Mexico. The keywords used were: Fabry, *GLA* variants, and Mexico. We included the clinical phenotype of four Mexican patients with FD reported by Ramos-Kuri (Ramos-Kuri et al. 2014) and 36 by Gutiérrez-Amavizca (Gutiérrez-Amavizca et al. 2014). Also, we retrieved *GLA* variants found in Mexican FD patients from three studies (Ramos-Kuri et al. 2014; Gutiérrez-Amavizca et al. 2017; Navarrete-Martínez et al. 2017). Variants were classified according to the American College of Medical Genetics and Genomics (ACMG).

To compare the clinical characteristics of male and female patients with FD, chi-square tests were used when the sample size was sufficient; otherwise, Fisher exact tests were applied. Statistical analyses were conducted using IBM SPSS Statistics for Macintosh, version 25.0 (IBM Corp., Armonk, NY, USA). A p-value of < 0.05 was considered statistically significant.

3 | Results

We identified 52 Mexican patients with FD, 12 new cases, and 40 previously reported in the literature. Clinical manifestations of the 52 patients are detailed in Table 1. Additionally, Supplementary Table S1 provides a comprehensive overview of all the clinical features and diagnostic evaluations performed on the 12 new patients. The most frequent manifestation in both sexes was acroparesthesias (37/52, 71.2%), followed by hypohidrosis or anhidrosis (25/52, 48.1%), heat intolerance (24/52, 46.2%), and proteinuria (22/52, 42.3%). Renal manifestations, including proteinuria, and chronic kidney disease (CKD) were more prevalent in males than females. The ocurrence of proteinuria in males was statistically significant with an odds ratio (OR) of 4 (95% CI: 1.21-13.13, $p = 0.02$). CKD also showed a significant difference, with males exhibiting a higher prevalence with an OR of 6.11 (95% CI: 1.184-31.536, p=0.02). This was also the case for neurological manifestations, except for ischemic stroke, which showed no significant difference between sexes. Cardiac manifestations included hypertrophic cardiomyopathy,

TABLE 1 | Clinical characteristics of 52 Mexican patients with Fabry disease.

Clinical manifestations	Total ($n = 52$) n (%)	Male ($n = 28$) n (%)	Female ($n = 24$) n (%)	p	OR	95% CI
Renal						
Proteinuria	22 (42.3)	16 (57.1)	6 (25.0)	**0.02**	4	[1.22–13.14]
CKD	12 (23.1)	10 (35.7)	2 (8.3)	**0.02**	6.11	[1.18–31.54]
Kidney transplant	4 (7.7)	4 (14.3)	0 (0)	0.11[a]	—	—
Neurological						
Ischemic stroke	6 (11.5)	5 (17.9)	1 (4.2)	0.19[a]	5	[0.54-46.20]
Acroparesthesia	37 (71.2)	25 (89.3)	12 (50.0)	0.002	8.33	[1.97–35.18]
Heat intolerance	24 (46.2)	17 (60.7)	7 (29.2)	**0.02**	3.75	[1.17–11.99]
Hypo/Anhidrosis	25 (48.1)	20 (71.4)	5 (20.8)	**< 0.001**	9.50	[2.64–34.23]
Epilepsy	1 (1.9)	0 (0)	1 (4.2)	—	—	—
Cardiac						
Hypertrophic cardiomyopathy	10 (19.2)	6 (21.4)	4 (16.7)	0.73[a]	1.36	[0.34-5.54]
Arrhythmia	3 (5.8)	1 (3.6)	2 (8.3)	0.59[a]	0.41	[0.04-4.80]
Pulmonary hypertension	1 (1.9)	1 (3.6)	0 (0)	—		—
Ocular						
Cornea verticillata	14 (26.9)	11 (39.3)	3 (12.5)	**0.03**	4.53	[1.08–18.89]
Retinal vessel tortuosity	1 (1.9)	1 (3.6)	0 (0)	—		—
Skin						
Angiokeratomas	15 (28.8)	14 (50.0)	1 (4.2)	**< 0.001**	23.0	[2.72–194.47]
Gastrointestinal						
Diarrhea	18 (34.6)	11 (39.3)	7 (29.2)	0.44	1.57	[0.49–5.02]
Abdominal pain	16 (30.8)	12 (42.9)	4 (16.7)	0.41	3.75	[1.01–13.88]

[a]Fisher's exact test.
Note: Statistically significant differences are marked in bold.

primarily affecting the left ventricle. The most common arrhythmia was Wolf–Parkinson–White. Cornea verticillata was seen in 14 patients (26.9%) and angiokeratomas in 15 (28.8%); the latter was found mainly in males (14 vs. 1, OR: 23, 95% CI: 2.72-194.46; $p < 0.001$). Gastrointestinal manifestations included diarrhea in 18 out of 52 patients (34.6%) and abdominal pain (16/52, 30.8%).

We report two patients with a novel variant (c.122C>G) and atypical phenotype, summarized in Table 2. Patient 1 is a 37-year-old previously healthy woman who presented two strokes at 34 and 36 years of age, which left facial paralysis and right hemiparesis as sequelae. Brain MRI is shown in (Figure 1). An echocardiogram showed concentric left ventricular hypertrophy and preserved left ventricular ejection fraction (56%). Patient 2 is a 28-year-old male. At 26 years, he presented dizziness, vertical diplopia, ataxia, and muscle weakness predominantly on the left side of the body. A brain MRI demonstrated a periventricular hyperintensity and subacute infarction in the cerebellar peduncle. Laboratory tests revealed elevated serum creatinine, hyperazotemia, and hyperuricemia. He began rehabilitation, which improved muscle weakness. A new MRI showed white matter abnormalities (WMA), such as juxtacortical, periventricular, and subcortical supratentorial demyelinating lesions in brain MRI and demyelinating lesions at C3-4, C4-5, and C5-C6, in spine MRI (Figure 1), resembling MS. However, in follow-up laboratories, persistently elevated creatinine was noted. FD was suspected; thus α-Gal was measured, documenting a normal-low activity (11%). *GLA* gene sequencing was conducted, where the c.122C>G variant was identified. The echocardiogram revealed concentric remodeling of the left ventricle without any evidence of clots. Additionally, a carotid artery Doppler ultrasound, an electrocardiogram, and a Holter monitor were performed to comprehensively exclude a cardioembolic origin as the cause of the TIA. A renal biopsy revealed the vascular changes described in atypical FD, such as intimal fibroplasia and hyperplasia of the muscular layer (light microscopy), as well as a few classic zebra bodies in tubular epithelial cells, observed on transmission electron microscopy (Figure 2), confirming FD. Due to the clinical suspicion of MS, a lumbar puncture showed two oligoclonal bands in cerebrospinal fluid (CFS). Cascade genetic testing was conducted on the patient's mother, documenting she was heterozygous for the same variant. Laboratory evaluation indicated renal insufficiency, evidenced by a creatinine level of 1.97 mg/dL. She has recently been referred to our institution for an expanded diagnostic and therapeutic approach, with further investigations currently underway.

A summary of 14 different variants in the *GLA* gene associated with Mexican patients with FD is presented in Figure 3, Table 3. Four were recurrent variants: c.1088G>A, c.639+4A>T, c.50_54del, and c.122C>G. The majority were missense variants

TABLE 2 | General, clinical, and biochemical of the patients with c.122C>G variant.

	Patient 1	Patient 2
General characteristics		
Current age	37	28
Sex	Female	Male
Origin	Mexico City	Mexico City
Clinical manifestations		
Age of onset	34	26
Renal	No	Proteinuria
Neurological	Ischemic stroke	Ischemic strokes and demyelinating lesions on brain and cervical column
Cardiac	Concentric left ventricular hypertrophy Supraventricular tachycardia	Left ventricular concentric remodeling
Ocular	No	No
Skin	No	No
Gastrointestinal	No	No
Biochemical characteristics		
Alpha-galactosidase (nmol/mL)	3.37	3.36
Alpha-galactosidase activity (%)	11	11
Plasma Gb3 (μg/mL)	4.5	1.95
Plasma Lyso-Gb3 (ng/mL)	< 0.3	< 0.30
Urine Gb3 (μg/mmol)	2999	< 44

Note: Alpha-galactosidase normal range 0.89–29.8 nmol/mL. Plasma Gb3 normal range 1.37–4.04 μg/mL. Plasma Lyso-Gb3 normal range < 0.3 ng/mL. Urine Gb3 normal range 0–16 μg/mmol.

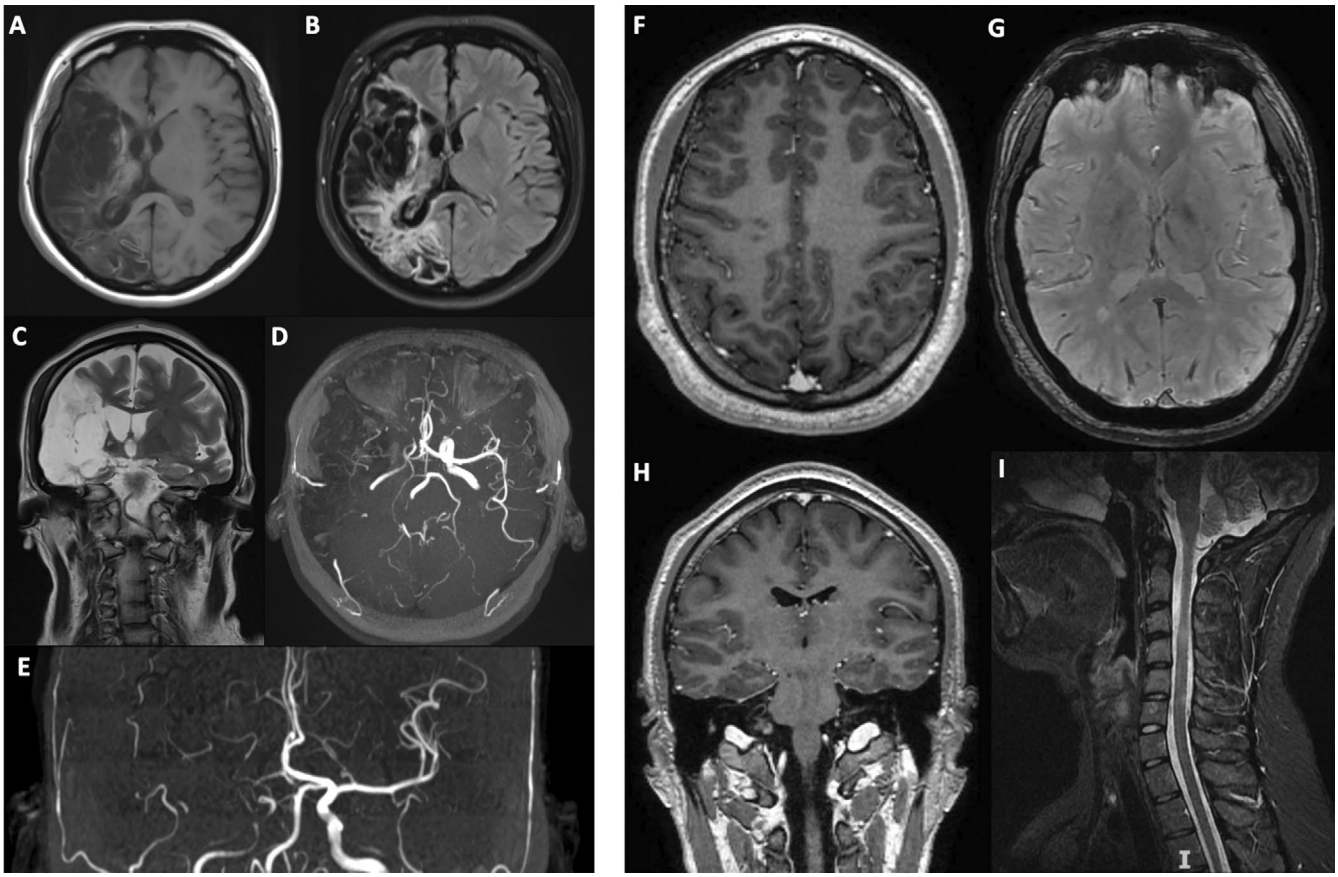

FIGURE 1 | Brain MRI of Patient 1 (A–E) and brain and spine MRI of Patient 2 (F–I) with variant c.122C>G. Patient 1 MRI in (A) T1, (B) Flair, (C) T2, and (D and E) TOF shows the absence of vascular flow in the right middle cerebral artery in its entirety with decreased flow from the extracranial left carotid artery, resulting in frontoparietoccipital infarction. Patient 2 brain MRI in (F) T1 and (G) SWAN shows juxtacortical, periventricular, and subcortical supratentorial demyelinating lesions, ovoid in shape, and those parallel to the lateral ventricles present the central vein sign. (H) The infratentorial demyelinating lesion is located in the periventricular region of the middle cerebellar peduncle and is hypointense on T1 (black hole). Patient 2 spine MRI in (I) STIR showed demyelinating lesions involving lateral portions, mainly at the level of C3-4, C4-5, and C5-C6, with no data of acute inflammatory activity with contrast media.

(9/14, 64.3%) and were located predominantly in exon 1 (4/14, 28.6%) and 6 (3/14, 21.4%).

4 | Discussion

The clinical phenotype identified in our study of Mexican FD patients is similar to what has been reported in other populations. Specifically, heterozygous women in our cohort presented kidney manifestations less frequently than males, unlike cardiac and ophthalmological involvement, which showed no statistical difference between the sexes (Eng et al. 2007). Although neurological findings were more prevalent in males than females, this could be attributed to the later age of presentation typically observed in women (Sims et al. 2009).

Three studies on Mexican patients with FD and molecular confirmatory tests have been published (Ramos-Kuri et al. 2014; Gutiérrez-Amavizca et al. 2017; Navarrete-Martínez et al. 2017). Table 3, Figure 3 show the pathogenic variants identified in this population. Notably, of the 14 different variants reported to date in the Mexican population with FD, variants in exon 1 and 6 accounted for 50% (7/14) of the total. This finding could suggest that exons 1 and 6 are hotspot regions for FD in our population. Further studies are necessary to elucidate this possible association.

We identified two novel *GLA* variants c.50_54del and c.122C>G. Although initially characterized as a VUS, the c.122C>G was reclassified as a likely pathogenic variant according to the ACMG, meeting the following criteria: PM1 (moderate pathogenic): nonsynonymous variant located in one site mutational hot/spot and/or critical and functional domain. PM2 (moderate): extremely low frequency in gnomAD population databases. PP2 (supporting): missense variant in a gene with a low rate of benign variants. PP4 (supporting): patient's phenotype.

This variant was found in one female (Patient 1) and one male (Patient 2) from our sample (Table 2). Interestingly, both presented with the "non-classic" phenotype with predominantly neurological involvement (strokes and WMA). However, the age of onset was earlier in Patient 2 (26 vs. 33 years). Both patients exhibited similar enzymatic levels at diagnosis (Patient 1 = 3.77 nmol/mL and Patient 2 = 3.36 nmol/mL). Nevertheless, Patient 1 showed elevated levels of both biomarkers

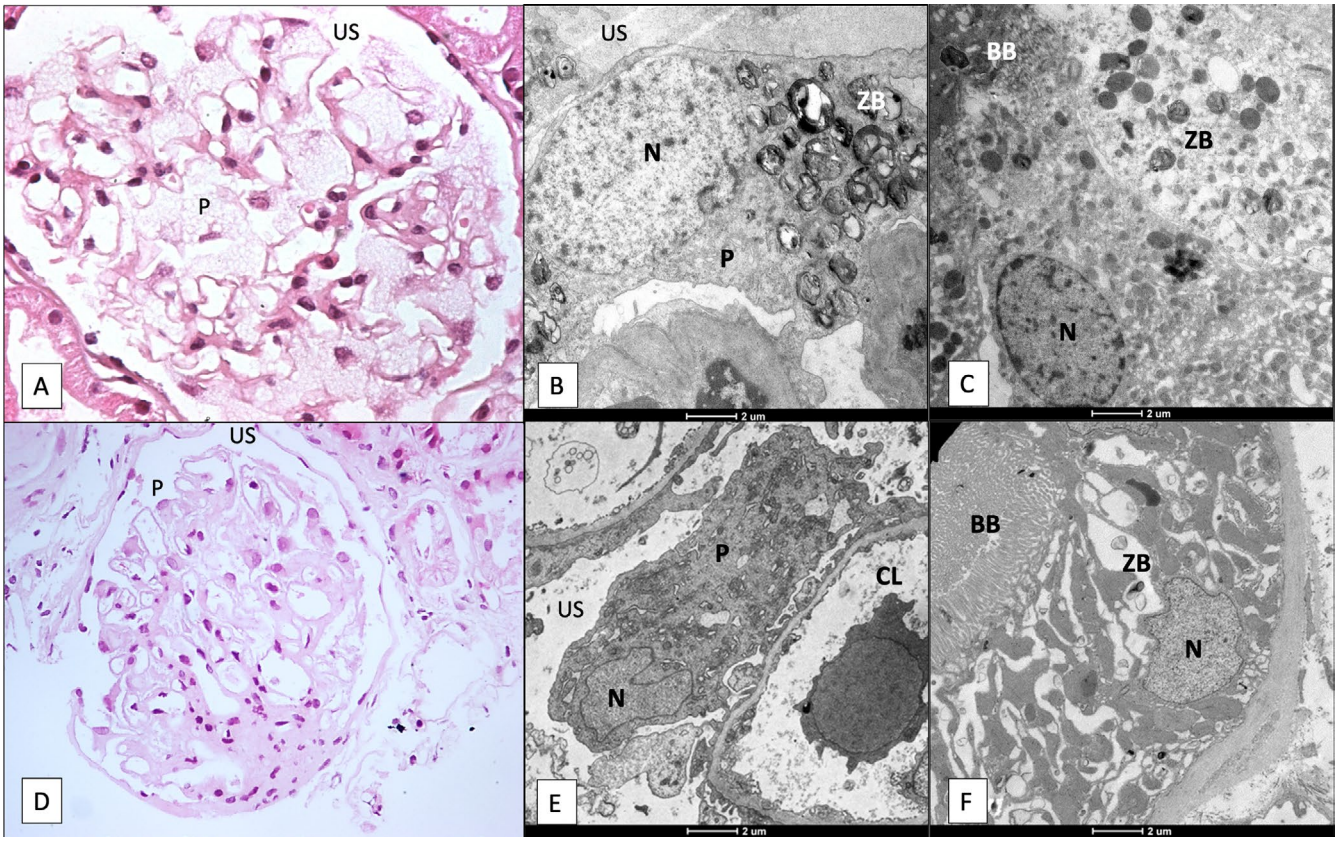

FIGURE 2 | Morphologic comparison between classic and atypical Fabry disease. Images A through C correspond to a renal biopsy of a classic case of FD, and images D through F correspond to a renal biopsy of the atypical FD case (Patient 2). Images A and D are cross-sections of the renal cortex showing glomeruli stained with hematoxylin and eosin (H&E). Images B–F correspond to light microscopy. Classic FD is characterized by enlarged podocytes with foamy cytoplasm (A); while atypical FD lacks such characteristic changes (D and E). Ultrastructurally, classic FD is recognized for the presence of abundant zebra bodies in the cytoplasm of podocytes (B), tubular epithelial cells (C), in atypical FD there are a few zebra bodies (F). P, podocyte; US, urinary space; N, nucleus; ZB, Zebra bodies; CL, capillary lumen; BB, brush border.

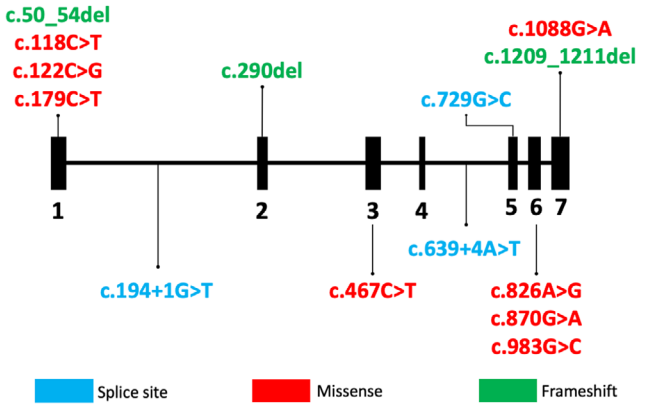

FIGURE 3 | Pathogenic variants in the *GLA* gene reported in Mexican patients with Fabry disease. Exons are numbered from 1 to 7. Splice site, missense, and frameshift variants are marked in blue, red, and green, respectively.

(Plasma-Gb3 = 4.5 μg/mL and Urine-Gb3 = 2999 μg/mL), while Patient 2, had normal levels. Consequently, a biopsy was performed on Patient 2, confirming the FD diagnosis. The later age of symptom onset in Patient 1 could be partially explained by skewed inactivation of the X chromosome; however, this does not explain the very similar α-Gal activity in both individuals or the discrepancy in the biomarker levels, despite both sharing the same clinical features and the *GLA* c.122C>G variant.

Although biomarkers for FD have proven their usefulness in multiple studies for screening patients with clinical suspicion or in those with newly identified variants, certain limitations must be considered when using them as part of the assessment. Normal biomarker levels do not rule out FD. When the clinical suspicion is high and other etiologies have been excluded, the diagnostic evaluation should include a biopsy of any affected organ to search for Gb3 deposits. Also, Auray Blais et al. demonstrated that the glomerular filtration rate does not correlate with Gb3 excretion levels (Auray-Blais et al. 2017). This could explain why Patient 2, who presented with Stage III CKD, had normal biomarker levels, while in Patient 1, with Stage I CKD, exhibited significantly elevated urine Gb3-levels (2999 μg/mmol).

Knowledge about new biomarkers associated with FD continues to expand, such as miRNAs (Mir21, Mir200, miR21-5p, and miR19a-3p) and Gb3 analogs, with potential clinical applications (diagnosis, disease activity, response to treatment, and prognosis). Further studies are required to determine the utility of incorporating these markers into the evaluation of patients with suspected FD (Xiao et al. 2019).

TABLE 3 | *GLA* variants reported in Mexican patients with Fabry disease.

Study	Nucleotide change	Protein change	Exon	Type	Families
Present study	c.50_54del	p.Arg17Profs*12	1	Frameshift	2
Gutiérrez-Amavizca (20)	c.118C>T	p.Pro40Ser	1	Missense	1
Present study	c.122C>G	p.Thr41Ser	1	Missense	2
Navarrete-Martínez (21)	c.179C>T	p.Pro60Leu	1	Missense	1
Present study	c.194+1G>T	p.?	1i	Splicing	1
Ramos-Kuri (18)	c.260delA	p.Glu87Glyfs*34	2	Frameshift	1
Ramos-Kuri (18)	c.467C>T	p.Ala156Val	3	Missense	1
Gutiérrez-Amavizca (20)	c.639+4A>T	p.?	4i	Splicing	2
Ramos-Kuri (18)	c.729G>C	p.Leu243Phe	5	Missense	1
Present study	c.826A>G	p.Ser276Gly	6	Missense	1
Navarrete-Martínez (21)	c.870G>A	p.Met290Ile	6	Missense	1
Gutiérrez-Amavizca (20)	c.983G>C	p.Gly328Ala	6	Missense	1
Gutiérrez-Amavizca (20) and Navarre te-Martínez (21)	c.1088G>A	p.Arg363His	7	Missense	3
Gutiérrez-Amavizca (20)	c.1209_1211delAAG	c.Arg404del	7	Deletion	1

FD diagnosis can be challenging, especially in the context of novel variants and atypical phenotypes. In such cases, a biopsy can aid in guiding the diagnosis. Although histological changes such as podocyte enlargement, vacuolization of podocytes, endothelial and tubular epithelial cells, and the presence of zebra bodies in transmission electron microscopy are helpful and reliable findings in classic FD diagnosis, atypical FD cases often lack myeloid and zebra bodies (Figure 2). In addition, similar structures to zebra bodies are present in silicon nephropathy and pseudolipidosis induced by amiodarone, chloroquine, and hydroxychloroquine, highlighting the importance of clinical context (Finn 2015).

Patients with exclusively neurological symptoms, such as small vessel ischemic disease and nonspecific WMA, may be misdiagnosed with MS. It has been observed that approximately 5%–10% of FD patients have received a misdiagnosis of MS, particularly in cases where the α-Gal enzyme activity is > 3% (associated with the "non-classic" form) and female patients since random X chromosome inactivation can be a factor that leads to milder symptoms and a later age of onset (Jurašić, Bašić Kes, and Zavoreo 2019).

The diagnosis of MS is based on clinical criteria, MRI findings, and oligoclonal bands in CSF. WMA in MS are attributed to inflammation, whereas in FD, they are associated with vasculopathy. Spinal MRI imaging has been proposed as a complementary test to distinguish between FD and MS. However, one limitation noted by previous authors is that clinical findings in spinal MRI could be underdiagnosed in FD, as it is not routinely performed in these patients (Böttcher et al. 2013; Fellgiebel et al. 2009). CSF could also help distinguish FD from MS as the presence of oligoclonal bands is strongly suggestive of MS. Nevertheless, some patients with FD have been reported to have mild pleocytosis, possibly due to an aseptic inflammatory process triggered by the stored lipids acting as foreign bodies (Böttcher et al. 2013).

Recently Olivera et al. identified exclusively elevated levels of Lyso-Gb3 in patients with FD. This finding demonstrates that Lyso-Gb3 is specific for this disorder, and could serve as a helpful parameter to rule WMA associated with MS in patients where clinical findings are inconclusive for distinguishing between the two conditions (Olivera et al. 2020).

Despite the clinical overlap of MS and FD, Patient 2 presented various confounding factors, transforming this case into a diagnostic odyssey for the medical team. Following a detailed work-up for both entities, we concluded that the patient exhibited an atypical FD presentation. The following points led to this conclusion:

1. Oligoclonal bands have a high sensitivity for MS (up to 98%) but lower specificity (87%) since they have been reported in other inflammatory and non-inflammatory conditions (Böttcher et al. 2013; Dobson et al. 2013; Bernitsas et al. 2017; Pannewitz-Makaj et al. 2020). Notably, in some patients with FD, oligoclonal bands are reported in lower proportions (fewer than four bands), making their presence insufficient to conclude a MS diagnosis (Bernitsas et al. 2017).
2. The patient presented an episode of cerebellar and brainstem symptoms (ataxia and diplopia). During this episode, an MRI revealed a subacute infarction in the cerebellar peduncle. A follow-up MRI performed months later demonstrated WMA without evidence of the prior infarction. Therefore, these symptoms were probably due to a TIA, as described in previous studies on patients with FD (Böttcher et al. 2013).

3. The patient has unquestionable findings of FD, including renal biopsy and a molecular confirmatory test.
4. Although the patient presented WMA in the brain and brainstem, there was no involvement of the corpus callosum, a finding that is highly suggestive of MS (Jurašić, Bašić Kes, and Zavoreo 2019; Ugga et al. 2018).
5. Spinal MRI findings have also been associated with FD (Böttcher et al. 2013; Fellgiebel et al. 2009).

The ability to differentiate between these two entities is critical. The therapeutic approach is distinctive. A misdiagnosis could result in erroneous or delayed treatment, leading to irreversible organ damage. In the case of FD, different studies have reported a decrease in the progression rate of the disease, surveillance, and quality of life if ERT is prescribed promptly (Ortiz et al. 2016).

5 | Conclusion

This study highlights the genotype and phenotype spectrum of the Mexican patient with FD. In addition, we describe the atypical clinical phenotype of patients with the novel variant c.122C>G with predominantly neurological involvement. Our findings underscore the diagnostic challenges posed by atypical clinical phenotypes of FD. As we have learned from this case, FD can represent a diagnostic challenge. It is important to consider the limitations of noninvasive methods, such as enzyme activity and biological biomarkers, and to pursue a comprehensive diagnostic approach, including renal biopsy when the clinical suspicion of FD is high. Although CSF and MRI imaging can aid in the diagnosis of FD or MS, further studies are necessary to identify additional findings that can help differentiate between the two, when clinical phenotype overlaps.

Author Contributions

Tamara N. Kimball and **Pamela Rivero-García:** conceptualization, investigation, methodology, formal analysis, writing – original draft. **Eduardo R. Argaiz:** methodology, formal analysis, writing – original draft. **Jorge Eduardo Gaytan-Arocha:** supervision, review and editing. **Norma Ofelia Uribe Uribe:** resources, supervision, review and editing. **Juan José Morales Suárez:** conceptualization, methodology, supervision, resources, writing – review and editing. All authors have review, editing, approval of the final version of the manuscript.

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Ethics Statement

This is an observational, retrospective study, which was approved by the Investigation Committee and Ethics Investigation Committee of our Institution (REF 4997).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data will be made available on request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.