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Clinical and Molecular Characterization of the *GLA* c.1124G>C (p. Gly375Ala) Variant in Colombian Patients with Fabry Disease: A Retrospective Cohort Study

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Abstract

Background: Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the GLA gene, resulting in deficient α-galactosidase A activity and progressive multi-organ involvement. The GLA c.1124G>C (p.Gly375Ala) variant is currently classified as a variant of uncertain significance (VUS), with scarce evidence regarding its clinical expression, particularly in Latin American populations. In this context, we aimed to characterize the demographic, clinical, biochemical, and therapeutic features of Colombian patients with FD carrying this variant.

Methods: We conducted a retrospective observational cohort study including all patients with FD harboring the GLA c.1124G>C (p. Gly375Ala) variant evaluated at Hospital Universitario San José de Popayán between 2015 and 2023. Data were extracted from medical records, including demographics, organ involvement (cardiac, neurologic, renal, dermatologic, and others), enzymatic activity, plasma lyso-Gb3 levels, treatment history, and follow-up outcomes. Descriptive and sex-stratified analyses were performed.

Results: Sixteen patients were identified (50% male; mean age 40±13.5 years), predominantly from rural and low socioeconomic backgrounds. Mean age at diagnosis was similar between sexes. Enzymatic activity was reduced in both males and females, with residual activity observed across the cohort. Plasma lyso-Gb3 levels were normal or mildly elevated. Renal involvement was more frequent in males, with higher creatinine levels (p=0.035). Multisystem involvement was common (93.8%), with a median of four affected systems. Dermatologic manifestations were most frequent, followed by central and peripheral nervous system and cardiac involvement. Treatment discontinuation occurred in 10 patients, mainly due to access barriers; therapy switching was documented in five cases.

Conclusions: Although classified as a VUS, the GLA c.1124G>C variant was associated with a late-onset, predominantly oligo systemic phenotype with variable expressivity, consistent with non-classic FD. Healthcare access limitations emerged as key determinants of treatment continuity, underscoring the need for variant-specific characterization and improved care pathways in underserved populations.

Keywords: Fabry disease, GLA gene, c.1124G>C variant, lysosomal storage disorders, missense mutation, enzyme replacement therapy.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene that reduce α-galactosidase A activity [1-3]. Progressive accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) contributes to multisystem involvement, including angiokeratomas, corneal findings, chronic kidney disease, hypertrophic cardiomyopathy, arrhythmias, and cerebrovascular events [4-6]. Without disease-specific therapy, life expectancy is shortened in both males and females [7].

FD spans a phenotypic continuum. The classic phenotype typically begins in childhood or adolescence and is associated with very low or absent enzyme activity, early neuropathic pain, hyperhidrosis, heat intolerance, gastrointestinal symptoms, skin lesions, and progressive renal and cardiac disease [1,8,9]. Later-onset (non-classic) presentations usually retain residual α-galactosidase A activity and may initially appear organ-predominant, most often cardiac, renal, or neurologic [8,9]. This spectrum is clinically relevant in heterozygous females, in whom disease expression is variable and may be delayed because of X-chromosome inactivation patterns and other biologic factors [8]. In this setting, interpretation of variants of uncertain significance (VUS) requires integration of genotype with clinical findings, family segregation, and biomarkers. Plasma lyso-Gb3 has been used to support diagnostic classification and phenotypic stratification in selected contexts, although its performance is lower in some late-onset presentations and in females, so it is best interpreted alongside clinical evaluation and complementary testing [8,10-13].

More than 1,000 *GLA* variants have been described, and many remain classified as VUS, limiting genotype–phenotype correlation and therapeutic decision-making [6,14,15]. The *GLA* c.1124G>C (p.Gly375Ala) variant has been reported in different populations and is currently catalogued as a VUS, with limited detailed clinical and biochemical characterization in Latin America [14,16]. In Colombia, FD is recognized as a rare disease under Law 1392 of 2010 and Law 1438 of 2011 [17], yet regional access barriers may delay diagnosis and continuity of care. We aimed to describe the sociodemographic, clinical, biochemical, and treatment characteristics of Colombian

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patients carrying GLA c.1124G>C (p. Gly375Ala) evaluated at Hospital Universitario San José de Popayán between 2015 and 2023.

Materials and Methods

Study design and setting

We conducted an observational, descriptive, retrospective cohort study based on medical record review. The analysis included all patients diagnosed with FD carrying the *GLA* c.1124G>C (p. Gly375Ala) variant who were evaluated at the Hospital Universitario San José in Popayán, Cauca (Colombia) between January 2015 and December 2023. The overall objective was to characterize the sociodemographic, clinical, biochemical, and molecular profile of this cohort, as well as to describe organ-specific manifestations, therapeutic management, follow-up conditions, and potential genotype–phenotype correlations.

Study population

The target population consisted of individuals with a confirmed diagnosis of FD established through α-galactosidase A enzymatic activity testing and *GLA* gene molecular analysis. The accessible population comprised all patients first assessed at the hospital's clinical genetics service during the study period. The inclusion criteria were a confirmed diagnosis of FD carrying the *GLA* c.1124G>C (p. Gly375Ala) variant, the availability of complete institutional medical records, and documented follow-up after diagnosis. Patients without follow-up records were excluded. As this was a descriptive study based on the available population, no sample size calculation was performed; the cohort included all detected cases (n=16).

Variables and data sources

Information was collected on sociodemographic characteristics (age, sex, place of residence, socioeconomic status, and education level), clinical manifestations (age at diagnosis and involvement in dermatologic, central nervous system, peripheral nervous system, cardiac, rheumatologic, gastrointestinal, ophthalmologic, auditory, renal, and mental health domains), biochemical parameters (plasma α-galactosidase A activity and serum globotriaosylsphingosine [lyso-Gb3] levels), renal function (serum creatinine and estimated glomerular filtration rate [eGFR]), and treatment-related aspects (type of specific therapy, adherence, treatment modifications, and reasons for discontinuation). Data were obtained exclusively from institutional medical records and laboratory reports. To minimize transcription errors, two independent investigators reviewed all records retrospectively.

Laboratory procedures

α-galactosidase A activity was measured in dried blood spots using a standard fluorometric assay in an external reference laboratory, with results expressed in nmol/h/mL (equivalent to μmol/L/h). This method has very high analytical sensitivity (around 100%) but a lower specificity (about 96%) than assays performed on leukocyte preparations, so all diagnoses were confirmed by *GLA* sequencing in the clinical context. Serum lyso-Gb_3 concentrations were quantified by liquid chromatography–tandem mass spectrometry (LC–MS/MS) and reported in nmol/L according to the laboratory standard. Renal function was assessed using serum creatinine, and eGFR was estimated with the CKD-EPI equation standardized to 1.73 m^2 of body surface area, according to KDIGO 2013 guidelines [18].

Statistical analysis

Descriptive statistics were used to summarize the cohort characteristics. Continuous variables were expressed as means and standard deviations or as medians and interquartile ranges according to their distribution. Comparisons by sex were performed using the Mann–Whitney U test for nonparametric continuous variables and Fisher's exact test for categorical variables. All analyses were carried out using R software, version 4.4.1 [19]. The proportion of missing data was below 10%, and no imputation methods were applied.

Ethical considerations

The study was approved by the Ethics Committee of the Faculty of Health Sciences at Universidad del Cauca (Acta 6.1-3.24/31, October 29, 2024) and by the Biomedical Research Ethics Committee of the Hospital Universitario San José de Popayán (Approval No. 56-2024). According to Colombian regulations (Resolution 8430 of 1993), retrospective studies based on anonymized clinical records are classified as research without risk and do not require individual informed consent. Both committees waived the requirement for informed consent. The study was conducted in accordance with Colombian regulations and the principles of the Declaration of Helsinki [20].

Results

Individuals of both sexes carrying the *GLA* c.1124G>C (p. Gly375Ala) variant were identified in the department of Cauca in southwestern Colombia. The geographic distribution showed confirmed cases in the municipalities of Popayán, Patía, La Vega, and Angelia (Figure 1).

Genealogical analysis revealed that carriers belong to two extended families, related to each other, in which multiple members had clinical histories compatible with FD. The pedigree identified an inheritance pattern consistent with X-linked transmission and showed several affected individuals across different generations (Figure 2).

Baseline cohort characteristics

Sixteen patients with a confirmed diagnosis of FD carrying the *GLA* c.1124G>C (p. Gly375Ala) variant were evaluated at the Hospital Universitario San José in Popayán between 2015 and 2023. Sex distribution was balanced, with 8 males (50%) and 8 females (50%). The mean age at analysis was 40.0 years (SD 16.0) in males and 40.0 years (SD 11.0) in females, with no statistically significant differences between groups. Mean age at diagnosis was similar in both sexes: 32.8

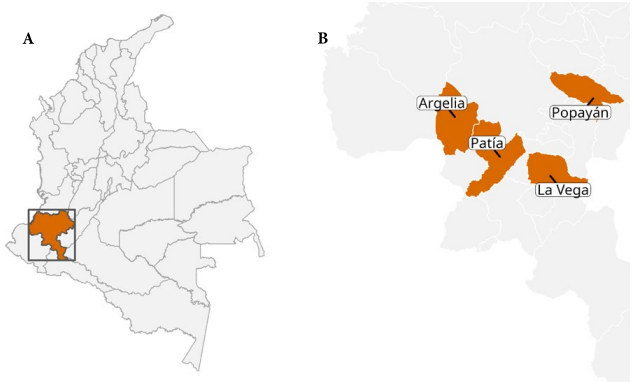

Figure 1. Geographic distribution of carriers of the *GLA* c.1124G>C (p. Gly375Ala) variant. (A) Map of Colombia with the department of Cauca highlighted. (B) Enlarged view of Cauca showing municipalities with identified carriers: Popayán, Patía, La Vega, and Argelia

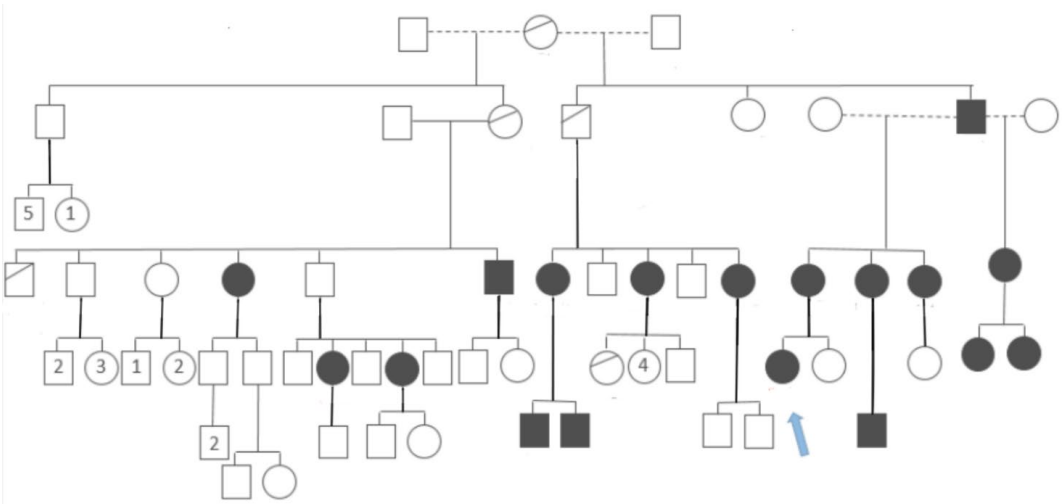

Figure 2. Genealogy showing the index case (indicated by a blue arrow) and individuals affected by the mutation. Squares represent males and circles represent females; filled symbols correspond to affected individuals.

Table 1. Sociodemographic and baseline characteristics of patients with Fabry disease by sex.

Characteristic	Males (n=8)	Females (n=8)	P value
Current age (years), mean (SD)	40.0 (16.0)	40.0 (11.0)	>0.99
Age at diagnosis (years), mean (SD)	32.8 (16.8)	32.6 (10.6)	0.84
Socioeconomic status, n (%)*			>0.99
1	7 (88%)	6 (75%)	
2	1 (12%)	2 (25%)	
Ethnic group, n (%)			—
Mestizo	8 (100%)	8 (100%)	
Education, n (%)			0.76
Primary school	5 (63%)	3 (38%)	
Secondary school	2 (25%)	2 (25%)	
Unknown	1 (13%)	3 (38%)	

*Socioeconomic status according to the Colombian national stratification system: stratum 1 = lowest socioeconomic level; stratum 2 = low–middle level.

SD: standard deviation. P values were obtained using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

years (SD 16.8) in males and 32.6 years (SD 10.6) in females (P = 0.8). Time from diagnostic confirmation to evaluation ranged from 2 to 15 years, with a median follow-up of 8 years (Table 1).

Sociodemographic characteristics

All participants self-identified as Mestizo and resided in the department of Cauca. Most lived in rural areas (87.5%, n=14), whereas 12.5% (n=2) lived in municipal capitals. Socioeconomic stratum 1 predominated (81.2%, n=13), followed by stratum 2 (18.8%, n=3), with no significant sex differences (P > 0.9). Regarding education, 62.5% (n=10) had completed primary education, 25% (n=4) secondary education, and 12.5% (n=2) had no formal schooling. All patients were enrolled in the subsidized health insurance regime.

Baseline enzymatic biomarkers

Baseline α-galactosidase A activity was reduced in all patients compared with the reference range of the reporting laboratory (normal ≥15.3 nmol/h/mL). Mean activity in males was 11.0 nmol/h/mL (SD 2.5; range 8.2–14.5), whereas females had a mean of 4.5 nmol/h/mL

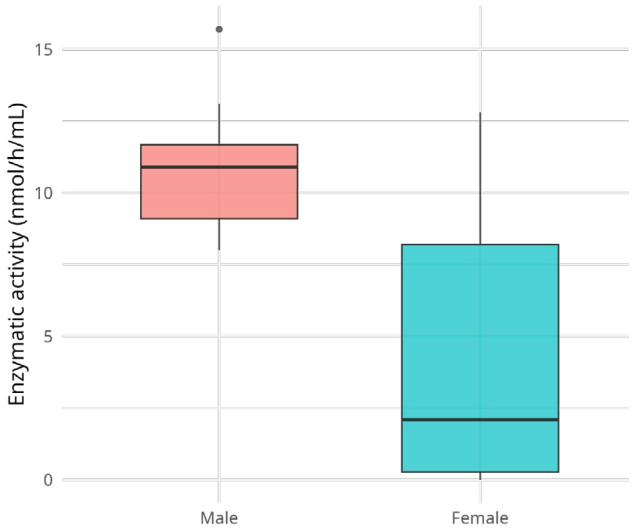

Figure 3. Baseline distribution of α-galactosidase A enzymatic activity by sex. Boxplot showing activity values (nmol/h/mL) in males and females. Data were calculated from 12 patients with available information. Lines represent medians, boxes interquartile ranges, and dots individual values. P = 0.052 (Mann–Whitney U). Baseline information was captured at first patient visit, which may have been done after start of enzyme replacement therapy (ERT).

(SD 5.5; range 0.8–12.3). The difference between sexes did not reach statistical significance (P = 0.052, Mann–Whitney U). The lower mean activity observed in females, opposite to the pattern usually described in classic X-linked FD, should be interpreted considering the small sample size and the use of a fluorometric dried blood spot assay rather than leukocyte-based testing (Figure 3).

Regarding lyso-Gb3, baseline data were available for 8 patients (5 males and 3 females). The laboratory reference value was ≤1.8 nmol/L. In males, concentrations ranged from 1.2 to 1.6 nmol/L, with most values close to the upper normal limit. In females, two patients had values within the reference range (1.4 and 1.5 nmol/L), and one showed a mildly elevated level of 2.5 nmol/L. In several cases, the first

lyso-Gb3 measurement was obtained after Fabry-specific therapy had already started, so these values likely underestimate pretreatment substrate burden (Figure 4).

Renal function

The mean eGFR was 66.6 mL/min/1.73 m² (SD 47.4) in males and 96.8 mL/min/1.73 m² (SD 38.6) in females (P = 0.11). Although this difference did not reach statistical significance, the lower values observed in men suggest greater impairment of renal function in this group (Table 2).

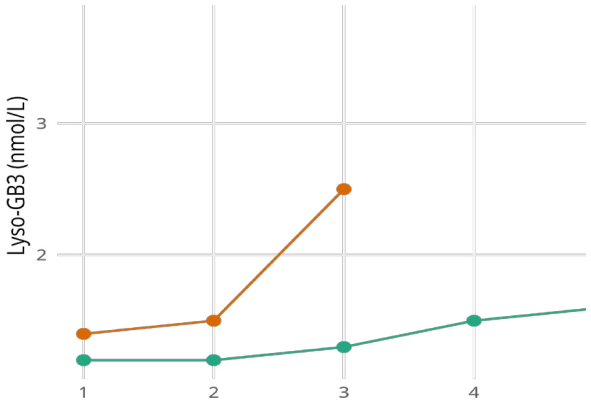

Figure 4. Distribution of serum lyso-Gb3 levels by sex.
Individual patient values are shown (n = 8; 5 males and 3 females). The dashed line indicates the normal threshold (< 4 nmol/L). The orange line corresponds to males and the green line to females.

Table 2. Renal function parameters and biomarkers by sex.

Variable	Males (n=8)	Females (n=8)	P-value
α-Gal A enzymatic activity (nmol/h/mL), mean (SD)	11.0 (2.5)	4.5 (5.5)	0.052
Lyso-Gb3 (nmol/L), median (IQR)	1.3 (1.2-1.5)	1.5 (1.4-1.5)	0.44*
Serum creatinine (mg/dL), mean (SD)	5.8 (8.1)	1.6 (2.2)	**0.035**
Estimated GFR (mL/min/1.73 m²), mean (SD)	66.6 (47.4)	96.8 (38.6)	0.11

SD: standard deviation; IQR: interquartile range; α-Gal A: α-galactosidase A; lyso-Gb3: globotriaosylsphingosine; eGFR: estimated glomerular filtration rate. *Mann–Whitney U test.

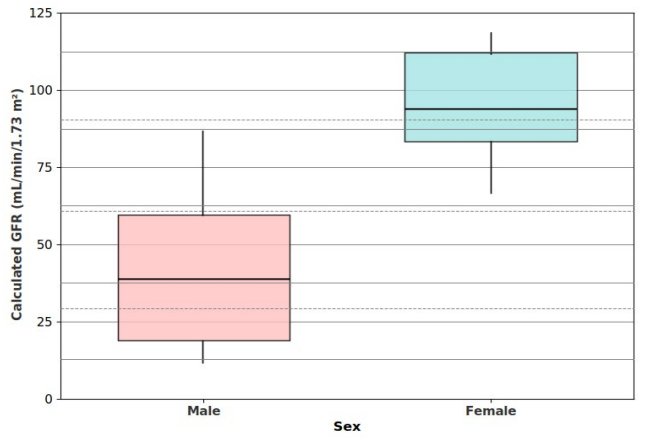

Figure 5. Comparison of eGFR by sex. Boxplot showing the distribution of values (mL/min/1.73 m²) in males and females.

Serum creatinine concentrations were significantly higher in males (5.8 mg/dL, SD 8.1) than in females (1.6 mg/dL, SD 2.2; P = 0.035), including two male patients with levels above 10 mg/d (Figure 5).

Clinical manifestations by organ system

Multisystem involvement predominated in this cohort (Figure 6). Fifteen of 16 patients (93.8%) had involvement of two or more organ systems (median, 4 systems; mean, 4.5; range, 1–7). Systems were assessed across nine domains (dermatologic, central nervous system, peripheral nervous system, cardiac, rheumatologic, gastrointestinal, ophthalmologic, auditory, and mental health). A domain was classified as affected when at least one Fabry-related manifestation was documented at baseline or during follow-up.

Dermatologic involvement was present in 15/16 patients (93.8%) and included telangiectasias and angiokeratomas among affected individuals. Central nervous system involvement was recorded in 12/16 (75.0%), most commonly categorized as other neurologic events/symptoms (10/16, 62.5%). Peripheral nervous system involvement occurred in 11/16 (68.8%) and included heat intolerance (12/16, 75.0%), acroparesthesias (10/16, 62.5%), hyperhidrosis (7/16, 43.8%), and exercise intolerance (1/16, 6.2%). Cardiac involvement was documented in 8/16 (50.0%), including conduction abnormalities (5/16, 31.2%), left ventricular hypertrophy (3/16, 18.8%), and other cardiac findings (6/16, 37.5%). Rheumatologic involvement was present in 8/16 (50.0%), most often pain or burning in the hands/feet (6/16, 37.5%), severe osteomuscular pain episodes (2/16, 12.5%), and other symptoms (1/16, 6.2%). Gastrointestinal involvement occurred in 7/16 (43.8%), including diarrhea (2/16, 12.5%), abdominal pain (2/16, 12.5%), nausea (1/16, 6.2%), and constipation (1/16, 6.2%).

Ophthalmologic involvement was present in 6/16 (37.5%) and included cornea verticillata (2/16, 12.5%), decreased visual acuity (2/16, 12.5%), and conjunctival vessel tortuosity (1/16, 6.2%). Auditory involvement occurred in 4/16 (25.0%), including tinnitus (4/16, 25.0%), hearing loss (3/16, 18.8%), and vertigo (2/16, 12.5%). Renal involvement was documented in 3/16 (18.8%). Mental health involvement was recorded in 1/16 (6.2%) and corresponded to depression documented in the medical record (Figure 6).

Follow-up and treatment data

Longitudinal follow-up was available for 12 patients (75%) with a mean duration of 6.2 years (range, 2–12). Four male patients (33.3%) showed progression of renal involvement, as evidenced by increased serum creatinine and decreased eGFR. Female patients didn't exhibit significant renal deterioration during follow-up. Treatment information was available for 14 patients (87.5%), of whom 71.4% received enzyme replacement therapy (ERT) with agalsidase Alfa and 28.6% received migalastat. Documented adherence had a median of 85% (range, 60–95%) (Table 3).

Treatment continuity

Only five patients (31.3%) maintained their initial therapy throughout the follow-up period. Eleven of 16 patients (68.8%) had at least one episode of temporary or permanent treatment discontinuation, mainly related to administrative difficulties within the health system and suspension of infusions during the COVID-19 pandemic. One female patient permanently discontinued migalastat because of drug intolerance (6.3% of the cohort; 1 of 11 patients with any discontinuation). Overall adherence ranged from 50% to 100%, with lower values in patients who experienced prolonged interruptions.

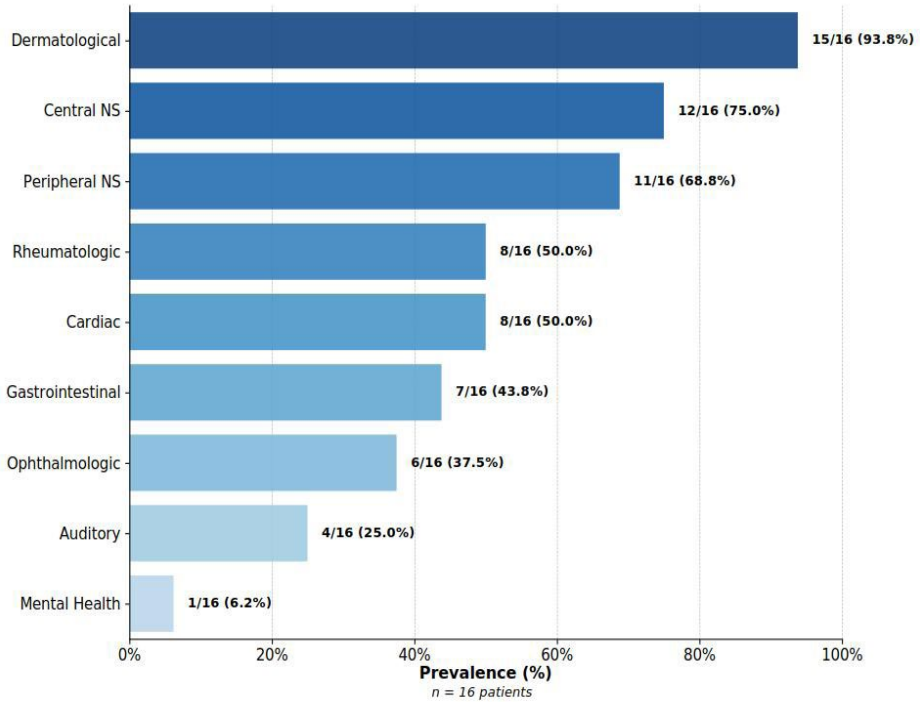

Figure 6. Prevalence of clinical manifestations by organ system.
Horizontal bar chart with percentages and absolute numbers of affected patients (n=16). NS: nervous system.

Table 3. Characteristics of specific treatment and clinical course by sex.

Variable	Males (n=8)	Females (n=8)	P value
Initial therapy, n (%)			>0.99
Agalsidase alfa	6 (75%)	6 (75%)	
Migalastat	2 (25%)	2 (25%)	
Age at treatment initiation (years), mean (SD)	33.6 (15.1)	33.5 (10.8)	0.95
Time from diagnosis to treatment (months), median (IQR)	14.5 (12-17)	13.0 (2-17)	0.63
Treatment duration (months), median (IQR)	31.0 (12-55)	22.0 (9-39)	0.42
Treatment adherence* (%), median (IQR)	75 (60-90)	80 (70-95)	0.31
Patients with documented discontinuation, n (%)	6 (75%)	5 (62.5%)	>0.99

SD: standard deviation; IQR: interquartile range. P values calculated using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Calculations were performed only for patients with available data. *Adherence was defined as the proportion of scheduled doses of specific therapy that were actually received.

Table 4. Distribution of patients by initial therapy, reasons for discontinuation, and second-line treatment in the Fabry disease cohort (n=16).

Initial therapy	No. of patients	Discontinuations (n)	Main reason	Switched (n)	Second therapy used
Migalastat	5	3	Intolerance (1), administrative difficulties or COVID-19 (2)	2	Agalsidase alfa
Agalsidase alfa	10	7	Administrative procedures, pandemic-related suspension, low adherence, access problems (≥5)	3	Migalastat
No data (ND)	1	—	—	—	—
Total	16	10	Predominance of administrative and access-related causes	5	Alternation between both therapies

Therapy switching between migalastat and agalsidase Alfa occurred in five patients (31.3%), usually after administrative interruptions or reassessment of mutation amenability (Table 4).

Discussion

This study describes for the first time in Colombia the clinical, biochemical, and sociodemographic characteristics of individuals carrying the *GLA* c.1124G>C (p. Gly375Ala) variant associated with FD [16]. The substitution of guanine by cytosine at position 1124 of the *GLA* gene results in a glycine-to-alanine change at position 375 of the α-galactosidase A enzyme. This variant has been reported in individuals evaluated for FD and has been functionally assessed in mutation series [14]. In addition, other changes at the same position have been associated with the disease by Iwafuchi et al. [21], Sawada et al. [22], and Yoshida et al. [23], where patients were reported to have Fabry-related clinical manifestations and low enzyme activity levels

(with some residual activity) in both males and females. In ClinVar, this variant is classified as "uncertain significance" (ID:217412), while CENTOGENE and ACMG consider it likely pathogenic (class 2) [14,16,21]).

Emerging evidence suggests that some missense *GLA* variants can promote protein misfolding and proteostatic dysfunction, with downstream activation of endoplasmic reticulum stress and the unfolded protein response. These mechanisms have been proposed as contributors to phenotypic variability, particularly in variants that retain residual enzyme activity [13,24]. This framework aligns with the concept of an "AGALopathy," in which altered protein processing and stability may influence the clinical course beyond the degree of substrate accumulation alone [24].

The clinical findings in our cohort show a heterogeneous phenotype, with dermatological and neurological manifestations predominating, and more severe renal involvement in males. These results are consistent with previous reports on other FD variants [8,9].

In our cohort, mean α-Galactosidase A activity was lower in females than in males, although individual values overlapped and the difference did not reach statistical significance. This pattern differs from the typical presentation of classic FD in which men generally show more profound enzyme deficiency, while females demonstrate wider variability due to residual enzyme activity and X-chromosome inactivation [8]. In our study, most females had residual enzymatic activity and preserved glomerular filtration rates relative to males, consistent with delayed renal involvement in many heterozygous female patients, although variability in clinical and biochemical expression remained evident across both sexes.

With respect to biomarkers, lyso-Gb3 values were low and heterogeneous. This pattern may reflect the uncertain clinical significance of the variant under study and the fact that some baseline lyso-Gb3 measurements were obtained after Fabry-specific therapy had already started, which can underestimate pretreatment substrate burden. Prior functional studies also indicate that variants classified as of uncertain significance may have heterogeneous effects on enzyme processing substrate accumulation, reinforcing the need for complementary functional and longitudinal studies to clarify the clinical relevance of p. Gly375Ala [8,13].

Overall, the clinical and biochemical profile in our cohort is compatible with the spectrum described for nonclassical or later-onset Fabry presentations, where residual enzymatic activity and relatively low lyso-Gb3 levels can coexist with clinically relevant organ involvement and diagnostic uncertainty in individual carriers [8,11,13]). In our dataset, most patients (15/16; 93.8%) had involvement of two or more organ systems; however, a single organ system typically exhibited a more severe compromise—the central and peripheral nervous systems in females and the renal system in males. These findings emphasize that later-onset presentations often show a wide variable expressivity and that phenotype assignment should integrate clinical findings with biomarkers and longitudinal assessment [8,11]. In addition to the primary GLA variant, biological modifiers such as variability in enzyme activity among females and proteostatic stress mechanisms have been proposed as contributors to heterogeneity across Fabry phenotypes [8,13,25].

Therapy adherence and continuity were limited. Only five patients maintained the initial treatment throughout follow-up, while ten experienced discontinuations, mostly due to administrative barriers and difficulties in accessing the health system. This pattern is consistent with reports from Latin America and other developing regions, where the availability of targeted therapies is restricted by non-clinical factors [25]. The switch between agalsidase Alfa and migalastat was motivated in some cases by the identification of "amenable" mutations or by restarting treatment after administrative interruptions, reflecting the fragility of therapeutic continuity in the local context.

Comparison with international series is limited, as most published studies focus on classical or late-onset variants with confirmed pathogenicity [6]. Published data on p. Gly375Ala remain scarce. Lukas et al reported this substitution as part of a broader series of GLA mutations and showed that changes at residue 375 can alter enzyme processing and activity [14]. Additional screening and registry reports from Asian and European cohorts have identified carriers of p. Gly375Ala or other substitutions at this position, but phenotypic descriptions are often brief and longitudinal data on renal, cardiac, or dermatologic outcomes are lacking [16,21–23]. Our cohort adds detailed characterization of organ involvement, biomarker profiles, and treatment exposure in a Latin American population, including evidence of renal decline in a subset of men despite relatively low lyso-Gb_3 levels.

Our study is subject to several limitations. The small sample size and retrospective design limit the ability to establish definitive genotype–phenotype correlations and to robustly evaluate disease progression and treatment response. The absence of complete biomarker data in some patients and frequent therapy interruptions introduce measurement and follow-up biases.

Nevertheless, as most patients were diagnosed through family screening, leading to disease diagnosis across age groups, sexes and disease stages allowing a thorough description of the disease. This study also provides relevant information to characterize an under-studied variant and underscores the need for more effective health policies to ensure timely diagnosis and treatment continuity in rare diseases in Colombia.

Conclusions

Colombian patients carrying the GLA c.1124G>C (p. Gly375Ala) variant exhibited wide variable expressivity and a heterogeneous clinical profile; however, disease manifestations were typically characterized by a more severe involvement of a single predominant organ system (central and peripheral nervous system in females and the renal system in males). The enzymatic activity showed variable reduction, with lyso-Gb3 levels normal or low. Therapy response and adherence were mainly compromised by administrative and access barriers rather than pharmacological intolerance.

The clinical and genetic characterization of this familial variant highlights the importance of integrating genotype–phenotype correlation with longitudinal follow-up and, when uncertainty persists, additional diagnostic approaches such as extended genetic evaluation and selected tissue-based assessments in carefully defined clinical contexts. This approach may facilitate more precise diagnosis, support therapeutic decision-making, and help anticipate clinical progression in affected individuals.

This study expands local knowledge of a poorly characterized variant and emphasizes the need to improve access to molecular diagnosis and guarantee continuity of Fabry-specific therapies in Colombia. Prospective, functional, and multicenter studies are

required to clarify the clinical significance of this familial variant and optimize patient management.

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Conflicts of Interest

Marcela Daza and Edison Montenegro are employees of Takeda Colombia SAS and do not hold stock/options in Takeda Pharmaceutical Company Ltd. The remaining authors declare no financial or personal conflicts of interest that could have inappropriately influenced the conduct of this research.

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Data Availability

Anonymized data supporting the findings of this study are available upon reasonable request to the BIMAC Group (Environmental Molecular Biology and Cancer), subject to ethical approval and compliance with confidentiality requirements.

Authorship

All authors actively participated in the conceptualization of the study, data collection and validation, interpretation of results, and manuscript preparation. All authors have reviewed and approved the final version of the article and take responsibility for its content.

References

1. Germain, D. P. (2010). Fabry disease. Orphanet Journal of Rare Diseases, 5, 30.
2. Mehta, A., Clarke, J. T. R., Giugliani, R., Elliott, P., Linhart A et al. FOS Investigators. (2009). Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey. Journal of Medical Genetics, 46(8), 548–552.
3. Zarate, Y. A., & Hopkin, R. J. (2008). Fabry's disease. The Lancet, 372(9647), 1427-1435.
4. Fernández, A., Rodríguez-González, M. J., & Gómez, J. E. (2022). Enfermedad de Fabry. Revista Colombiana de Cardiología, 28(92), 6376.
5. Shah, J. S., Hughes, D. A., Sachdev, B., Tome, M., Ward, D., Asgari, F., Elliott, P. M., & Mehta, A. B. (2005). Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. American Journal of Cardiology, 96(6), 842–846.
6. Lenders, M., Menke, E. R., & Brand, E. (2025). Progress and Challenges in the Treatment of Fabry Disease. BioDrugs, 39(4), 517–535.
7. Waldek, S., Patel, M. R., Banikazemi, M., Lemay, R., & Wilcox, W. R. (2009). Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry. Genetics in Medicine, 11(11), 790–796.
8. Ortiz, A., Germain, D. P., Desnick, R. J., Politei, J., Mauer, M., Burlina, A., West, M., Hughes, D. A., Wilcox, W. R., & Hopkin, R. J. (2018). Fabry disease revisited: Management and treatment recommendations for adult patients. Molecular Genetics and Metabolism, 123(4), 416–427.
9. Arends, M., Wanner, C., Hughes, D., Mehta, A., Oder, D., Watkinson, O. T., Elliott, P. M., Tricster, G. E., Biegstraaten, M., & Hollak, C. E. M. (2017). Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study. Journal of the American Society of Nephrology, 28(5), 1631–1641.
10. Aerts, J. M., Groener, J. E., Kuiper, S., Donker-Koopman, W. E., Strijland, A., Ottenhoff, R., van Roomen, C., de Mirza, M., Wijburg, F. A., Linthorst, G. E., Vedder, A. C., Rombach, S. M., Cox-Brinkman, J., Somerharju, P., Boot, R. G., Hollak, C. E. M., & van Breemen, M. J. (2008). Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proceedings of the National Academy of Sciences of the United States of America, 105(8), 2812–2817.
11. Niemann, M., Rolfs, A., Störk, S., Bijnens, B., Breunig, F., Beer, M., Ertl, G., Wanner, C., & Weidemann, F. (2014). Gene mutations versus clinically relevant phenotypes: lyso-Gb3 defines Fabry disease. Circulation: Cardiovascular Genetics, 7(1), 8–16.
12. Smid, B. E., van der Tol, L., Cecchi, F., Elliott, P. M., Hughes, D. A., Linthorst, G. E., Timmermans, J., Weidemann, F., West, M. L., Biegstraaten, M., & Hollak, C. E. M. (2014). Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. International Journal of Cardiology, 177(2), 400–408.
13. Cairns, T., Müntze, J., Gernert, J., Spada, M., Hiromasa, O., & Hughes, D. A. (2018). Hot topics in Fabry disease. Postgraduate Medical Journal, 94(1118), 709–713.
14. Lukas, J., Scalia, S., Eichler, S., & Rolfs, A. (2016). Functional and Clinical Consequences of Novel α-Galactosidase A Mutations in Fabry Disease. Human Mutation, 37(1), 43–51.
15. Lau, K., Üçeyler, N., Cairns, T., & Hughes, D. A. (2022). Gene variants of unknown significance in Fabry disease: Clinical characteristics of c.376A>G (p.Ser126Gly). Molecular Genetics & Genomic Medicine, 10(5), e1912.
16. Germain, D. P., Oliveira, J. P., Bichet, D. G., & et al. (2020). Use of a rare disease registry for establishing phenotypic classification of previously unassigned GLA variants: a consensus classification system by a multispecialty Fabry disease genotype–phenotype workgroup. Journal of Medical Genetics, 57(8), 542–551.
17. Instituto Nacional de Salud. (2023). Informe de eventos de enfermedades huérfanas-raras. Colombia - 2023.
18. Levin, A., Stevens, P. E., Bilous, R. W., & et al. (2013). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements, 3(1), 1–150.
19. R Core Team. (2025). R: A Language and Environment for Statistical Computing (Version 4.5.2). R Foundation for Statistical Computing.
20. World Medical Association. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA, 310(20), 2191–2194.
21. Iwafuchi, Y., Maruyama, H., Morioka, T., & et al. (2017). Enzyme replacement therapy in a patient of heterozygous Fabry disease: clinical and pathological evaluations by repeat kidney biopsy and a successful pregnancy. CEN Case Reports, 6(2), 210–214.
22. Sawada, T., Kido, J., Sugawara, K., & et al. (2020). Detection of novel Fabry disease-associated pathogenic variants in Japanese patients by newborn and high-risk screening. Molecular Genetics & Genomic Medicine, 8(11), e1502.
23. Yoshida, S., Kido, J., Sawada, T., & et al. (2020). Fabry disease screening in high-risk populations in Japan: a nationwide study. Orphanet Journal of Rare Diseases, 15(1), 220.
24. Živná, M., Dostálová, G., Barešová, V., & et al. (2022). AGAL misprocessing-induced ER stress and the unfolded protein response: lysosomal storage-independent mechanism of Fabry disease pathogenesis?. bioRxiv, 2022.09.27.509714.
25. Iriart, J. A. B., Nucci, M. F., Muniz, T. P., & et al. (2019). Da busca pelo diagnóstico às incertezas do tratamento: desafios do cuidado para as doenças genéticas raras no Brasil. Ciência & Saúde Coletiva, 24, 3637-3650.