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Novel GLA mutation in a high-consanguinity region: insights from Fabry disease screening in Turkiye

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ABSTRACT

Aims: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficient α-galactosidase A (α-Gal A) activity, leading to the accumulation of globotriaosylceramide in multiple organ systems. Its early diagnosis remains a challenge, particularly in high-risk populations. This study aimed to determine the prevalence of FD among hemodialysis patients in Eastern and Southeastern Turkiye, regions with a high rate of consanguineous marriages.

Methods: Between 2015 and 2019, 613 adult patients undergoing maintenance hemodialysis across five provinces were screened for α-Gal A activity using dried blood spot testing. Patients with reduced enzyme levels underwent confirmatory testing through leukocyte enzyme assays and GLA gene sequencing.

Results: Reduced α-Gal A activity was identified in 15.7% of patients. Genetic analysis in 58 individuals revealed no mutations in males. However, two unrelated female patients were found to carry the same GLA gene variant, c.116C>A (p.T39K), which has not been previously reported in gnomAD or ClinVar databases. The overall prevalence of genetically confirmed FD in this cohort was 0.32%.

Conclusion: This is the first regional screening study of FD in Eastern and Southeastern Turkiye. The identification of a novel GLA mutation in a high-consanguinity population underscores the importance of genetic screening in dialysis patients and highlights the need for region-specific diagnostic and counseling strategies.

Keywords: Fabry disease, hemodialysis screening, GLA gene, consanguinity

INTRODUCTION

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by mutations in the GLA gene, which encodes the enzyme α-galactosidase A (α-Gal A).[1] Deficiency or absence of α-Gal A activity leads to the systemic accumulation of globotriaosylceramide (Gb3) and its derivatives in lysosomes, ultimately resulting in multi-organ damage.[2-4] Organs most commonly affected include the kidneys, heart, and nervous system.[5-7] Renal involvement is a hallmark of FD and can begin early, even in asymptomatic individuals.[8,9] Gb3 accumulation contributes to podocyte injury, proteinuria, and progressive decline in renal function, often culminating in end-stage renal disease (ESRD).[10]

The GLA gene, located on chromosome Xq22, is highly polymorphic with over 1000 variants described to date.[11] Most GLA variants are private, and novel mutations continue to be reported, especially in populations with high rates of consanguinity.[12,13] In these regions, genetic phenomena such as the founder effect and increased homozygosity may amplify the prevalence and clinical expression of otherwise rare pathogenic alleles.[14,15]

Eastern and Southeastern Turkiye are known for their elevated rates of consanguineous marriages.[16,17] Such demographic characteristics increase the prevalence of autosomal recessive and X-linked disorders, leading to regional clustering of genetic diseases. Therefore, these regions represent a high-risk population for Fabry disease screening.[33]

Previous studies conducted in Western and Mediterranean regions of Turkiye have reported Fabry disease prevalence among dialysis patients between 0.1% and 0.2%.[18,19] Comparable studies from Europe and Asia have shown prevalence rates ranging from 0.2% to 0.3% in dialysis cohorts.[20-22] By contrast, our study revealed a prevalence of 0.32%, which appears slightly higher than both national and international reports, possibly reflecting the genetic characteristics of this region.

Although several international studies have assessed the prevalence of FD in dialysis populations from Turkiye, data

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particularly from high-risk regions where consanguinity rate is high, remain scarce.[18-21] Therefore, this study aims to determine the prevalence of Fabry disease in dialysis populations from Eastern and Southeastern Turkiye, regions characterized by high consanguinity and a unique genetic background, in order to provide insights for future screening and counseling strategies.

METHODS

Ethics

This study was approved by the Kahramanmaraş Sütcü İmam University Faculty of Medicine Scientific Researches Ethics Committee (Date: 27.07.2015, Decision No: 13). All data were anonymized, and the study was conducted in accordance with the Declaration of Helsinki.

Study Design and Participants

We performed a prospective, multicenter, cross-sectional, screening study between October 2015 and February 2019. We recruited adult patients with ESRD undergoing maintenance hemodialysis (HD), from five dialysis centers located in the East and Southeast regions of Turkiye.

Patients under the age of 18 or without confirmed ESRD were excluded. A total of 613 patients were enrolled the study. Among the patients screened, no one had been diagnosed with FD.

Screening Procedure and Clinical Evaluation

Peripheral blood and dried blood spot (DBS) samples were collected from each participant. The first 98 patients were analyzed at Universitätsklinikum Hamburg-Eppendorf, where α-Gal A enzyme activity was measured using a mass spectrometry-based assay and reported in pmol/spot/21 hours. The remaining 515 patients were tested at ARCHIMED Life Science GmbH (Vienna), using a plasma-based fluorometric assay with results reported in µmol/L/h.

Because of the methodological and unit differences between the two laboratories, enzyme activity values were evaluated separately. For the Vienna cohort, values below 1.2 µmol/L/h were considered reduced. For the Hamburg group, enzyme activity below 140 pmol/spot/21 h was considered low, based on manufacturer guidance. Patients with low enzyme activity according to their respective laboratory criteria were referred for confirmatory genetic testing. GLA gene sequencing was performed using the MiSeq next-generation sequencing platform (Illumina, San Diego, CA, USA) and interpreted according to ACMG guidelines.[23]

Statistical Analysis

Data analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean±standard deviation (SD), while categorical variables were reported as frequencies and percentages. Prevalence of Fabry disease was calculated as a proportion of confirmed cases among the total screened population. Comparisons with other regional prevalence data were made using the Chi-square test, with a p-value <0.05 considered statistically significant.

RESULTS

A total of 613 patients undergoing HD were screened for FD. Of those patients, more than half of them were male (59.9%, n=368) and the mean age was 54.2±15.4 years. The underlying etiologies of ESRD among the screened patients were as follows: diabetic nephropathy (27.6%), hypertensive nephrosclerosis (21.9%), chronic glomerulonephritis (14.8%), autosomal dominant polycystic kidney disease (7.5%), obstructive nephropathy (4.4%), other causes (6.9%), and unknown etiology (16.9%).

Enzyme activity analysis was performed in two reference laboratories using different methods. The first 98 patients were tested at Universitätsklinikum Hamburg-Eppendorf using a DBS assay, where the mean α-Gal A enzyme activity in male patients was 283.4±124.6 pmol/spot/21 h (range: 93.27-700.29). In female patients, the mean α-Gal A enzyme activity was 3.42±1.96 µmol/L/h (range: 0.92-7.85) in the Vienna cohort, and 356.2±128.5 pmol/spot/21 h (range: 110.34-720.44) in the Hamburg cohort. These values were significantly higher compared to male patients, consistent with the X-linked inheritance of Fabry disease. The remaining 515 patients were tested at ARCHIMED Life Science Laboratory (Vienna) using a plasma-based fluorometric assay, with male patients exhibiting a mean α-Gal A enzyme activity of 2.14±1.58 µmol/L/h. Demographic and clinical characteristics are shown in Table.

Table. Demographic and clinical data of the patients

	Patients (n=613)
Age, years (mean±SD)	54.2±15.4
Gender, male, n (%)	368 (59.9%)
Enzyme values of male patients	
pmol/spot/21h (n=67)	283±124.6
µmol/L/h (n=298)	2.14±1.58
Patients with low α-Gal A, n (%)*	
Male	31 (5.1%)
Female	27 (4.4%)
Patients with mutation, %	2/613 (0.32%)

*Patients with low α-Gal A underwent genetic testing (n=58), SD: Standard deviation, FD: Fabry disease

Among the 613 screened patients, 96 individuals (15.7%) were identified as having low α-Gal A enzyme activity based on laboratory-specific thresholds. Of these, 58 patients (31 male, 27 female) underwent molecular genetic testing for GLA gene mutations. The remaining patients either declined further evaluation or were lost to follow-up. Enzyme activity in the remaining 517 patients (84.3%) was within the normal reference range.

Two unrelated female patients were found to carry the same novel missense variant, c.116C>A (p.T39K), located in exon two of the GLA gene. The diagnostic flowchart is presented in Figure. This variant was not previously reported in genomAD or ClinVar and no other known pathogenic variants were detected.[24,25] In silico predictive tools indicated that the p.T39K variant is likely to be functionally damaging. The PolyPhen-2

score was 0.98, classifying the mutation as "probably damaging," while the SIFT score was 0.01, suggesting the amino acid substitution is "deleterious" to protein function.[26] Based on enzymatic deficiency, clinical phenotype, and bioinformatic evidence, the c.116C>A (p.T39K) variant was interpreted as likely pathogenic, supporting the diagnosis of FD in these two patients.

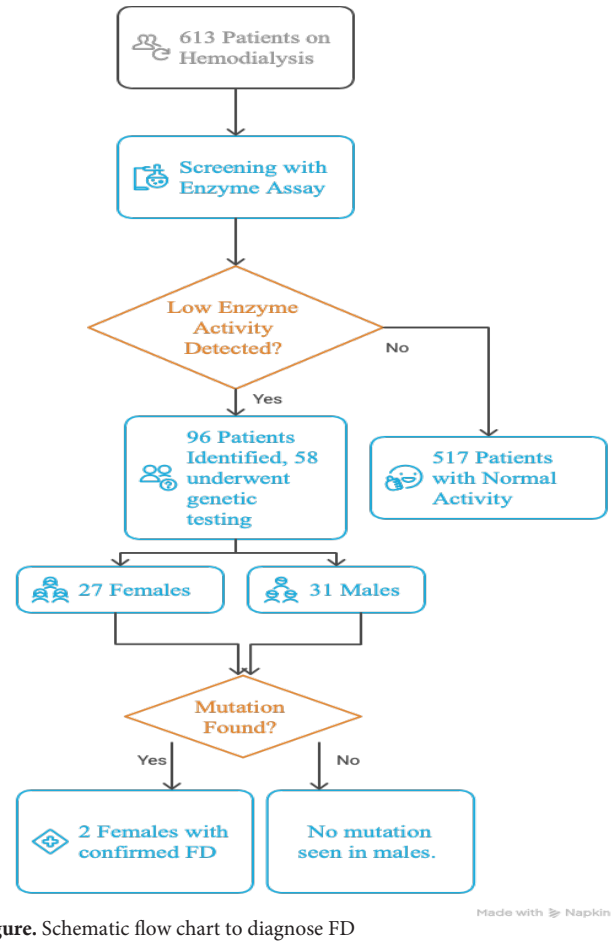

Figure. Schematic flow chart to diagnose FD

Schematic diagnostic flow chart used to identify FD in the study population. Patients were stratified based on laboratory-specific thresholds, and those with low α-Gal A activity were referred for genetic confirmation by GLA sequencing.

FD: Fabry disease

Clinical Features of Mutation-Positive Patients

Case 1: A 45-year-old female patient with ESRD of unknown etiology had been undergoing hemodialysis for five years. She reported intermittent numbness in her hands and feet, as well as mild exercise intolerance. Physical examination was unremarkable with no dermatological abnormalities. Transthoracic echocardiography revealed mild left ventricular hypertrophy (LVH). Genetic analysis identified the c.116C>A (p.T39K) mutation in the GLA gene. In the context of genetic findings, neuropathic symptoms, and cardiac involvement, the patient was classified as having a non-classical Fabry disease phenotype. Family members declined genetic screening.

Case 2: A 38-year-old female patient, previously diagnosed with hypertension and proteinuria, had been undergoing hemodialysis for two years due to ESRD. She reported intermittent numbness in her extremities and occasional dizziness. She also had acroparasthesia. Angiokeratomas or corneal abnormalities were not observed on physical examination. Transthoracic echocardiography revealed mild LVH. Genetic analysis confirmed the presence of the c.116C>A (p.T39K) variant in the GLA gene. While the patient did not exhibit classical features of FD, the combination of neuropathic symptoms and cardiac involvement was consistent with a possible non classical phenotype. Her family declined genetic testing. Discussion

This study represents the first systematic screening of FD among adult HD patients in Eastern and Southeastern Turkiye, regions with high rates of consanguineous marriage. Among 613 screened patients, two unrelated females were found to carry a previously unreported GLA gene variant, c.116C>A (p.T39K), resulting in an FD prevalence of 0.32%. While this figure aligns with the upper range of prevalence estimates from other high-risk populations, the identification of a novel variant in two patients from a geographically and demographically specific region warrants careful interpretation.

Although Fabry disease is an X-linked disorder and male patients are generally more severely affected, female heterozygotes may also present with significant clinical manifestations.[35] In our cohort, mean enzyme activity values in females were higher than those in males, as expected due to random X-chromosome inactivation. However, the wide range observed in female enzyme activities highlights the heterogeneity of biochemical presentation in this group, supporting the need for genetic confirmation in female patients.

The methodological differences between mass spectrometry (DBS samples, Hamburg cohort) and fluorometric assays (plasma samples, Vienna cohort) may have influenced the distribution of enzyme activity values. Previous studies have reported variability in inter-assay correlation, with mass spectrometry providing higher sensitivity for low enzyme activity detection.[28,29] In our study, enzyme activity thresholds were defined according to laboratory-specific cutoffs, which may limit direct comparison between cohorts. Nonetheless, both methods consistently identified individuals with reduced enzyme activity, and subsequent genetic testing confirmed the absence of false-positive results. This highlights that while methodological differences exist, both testing strategies are reliable for screening dialysis populations, provided that laboratory-specific reference ranges are applied.

Previous studies conducted in patients receiving renal replacement therapy (RRT) have reported the prevalence of Fabry disease to be generally between 0.2% and 0.3%.[18,27-31] A large screening study from Turkiye reported a prevalence of 0.12% in HD patient group.[18] Consistent with these findings, the prevalence in our study was 0.32%, further supporting the reliability of our screening results. Our findings suggest that regional genetic characteristics-particularly high rates of consanguinity-may play a critical role in the expression and aggregation of rare or novel GLA variants. This is consistent with previous studies that describe the enrichment of private mutations and rare alleles in consanguineous populations due to founder effects and increased homozygosity.[32,33]

The c.116C>A (p.T39K) variant identified in both patients had not been previously reported in genomic databases such as gnomAD or ClinVar.[24,25] In silico analyses strongly supported its pathogenicity; PolyPhen-2 classified the substitution as "probably damaging" (score: 0.98), while SIFT predicted it to be "deleterious" (score: 0.01).[26] These bioinformatic predictions, in combination with reduced α-Gal A activity and consistent clinical findings support the interpretation of this variant as likely pathogenic. However, the functional impact of the p.T39K variant has not yet been validated through in vitro studies. This step is particularly important, as demonstrated by other variants such as p.D313Y, which was initially classified as pathogenic but later reinterpreted as benign following functional and clinical reassessment.[34]

Both patients exhibited features suggestive of non-classical or late-onset FD, lacking hallmark signs such as angiokeratomas or corneal opacities, yet presenting with acroparesthesia and cardiac involvement. Such presentations are well documented in female heterozygotes, who may have residual enzyme activity and more attenuated or organ-specific phenotypes.[35] These cases highlight the need for genetic confirmation in females, even when enzymatic activity is only mildly reduced, as X-linked inheritance complicates the interpretation of biochemical results.

The study has several important clinical implications. First, these findings support the incorporation of FD screening into routine nephrology protocols in endemic or genetically vulnerable regions. Second, the discovery of a region-specific GLA variant emphasizes the need for geographically tailored screening programs and the development of national mutation registries. Third, early identification of FD provides an opportunity for timely initiation of disease-specific therapies, including enzyme replacement therapy (ERT) or pharmacologic chaperones in amenable genotypes.[36,37]

Limitations

This study has some limitations. First, no functional validation studies were conducted to assess the impact of the p.T39K variant on enzyme function, folding, or stability. Such analyses are critical for confirming pathogenicity, particularly for novel variants. Second, segregation analysis could not be performed, as family members declined genetic testing. This limited our ability to establish inheritance patterns and strengthen genotype-phenotype correlations. Third, although female patients were included in the enzyme-based screening, α-Gal A activity may remain within normal limits in heterozygous females due to X-chromosome inactivation. As a result, some cases may have been missed. Incorporating direct genetic testing for all female patients could have improved diagnostic accuracy in this group.

CONCLUSION

As a result, this study identified a novel likely pathogenic GLA variant (p.T39K) in two unrelated female HD patients from a high-consanguinity region in Turkiye. These findings highlight the importance of targeted screening in genetically vulnerable populations and suggest that region-specific GLA mutations may contribute to underrecognized cases of FD in nephrology practice. Further functional and family-based studies are warranted to validate the pathogenicity of the p.T39K variant and to assess its frequency in broader regional cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kahramanmaraş Sütcü İmam University Faculty of Medicine Scientific Researches Ethics Committee (Date: 27.07.2015, Decision No: 13).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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