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An Overlooked Family with a Rare Mutation for Fabry Disease

Fabry Hastalığı için Nadir Bir Mutasyon Taşıyan Gözden Kaçan Bir Aile

ABSTRACT

Fabry disease is a rare disorder characterized by multi-organ involvement, caused by mutations in the *GLA* gene. Although more than 1,000 mutations have been identified in the *GLA* gene, the discovery and detection of new mutations continue to enhance this dataset. We report a patient examined at our clinic for heart valve disease, who had a history of kidney transplantation and hemodialysis. With a high clinical suspicion, we diagnosed Fabry disease and will discuss its significant impact on the family. Effective family screening allowed us to identify unaffected family members, thus preventing or mitigating potential future organ involvement. Additionally, the mutation found in this family, although rarely reported before, is still described as a variant of uncertain significance (VUS) in some sources. We believe this finding will make a valuable contribution to genetic literature.

Keywords: Fabry disease, *GLA* gene, family screening, genetics

ÖZET

Fabry hastalığı, *GLA* gen mutasyonlarının neden olduğu, çoklu organ tutulumuna neden olan nadir bir hastalıktır. *GLA* geninde bugüne kadar 1000'den fazla mutasyon tanımlanmış olsa da yeni mutasyonların tespiti ve raporlanması bu verileri zenginleştirmektedir. Kalp kapak hastalığı nedeniyle kliniğimizde muayene edilen, böbrek nakli ve hemodiyaliz öyküsü olan bir hastayı sunuyoruz. Fabry hastalığını yüksek klinik şüphesi olması nedeniyle teşhis ettik ve bu şüphelenmenin aile üzerindeki önemli etkisini anlatacağız. Etkin aile taraması sayesinde henüz etkilenmemiş aile bireylerini tespit ederek ileride gelişebilecek organ tutulumlarını önledik veya azalttık. Klinik faydalarının yanı sıra, bu ailede tanımlanan mutasyon daha önce çok az sayıda rapor edilmiş olup bazı kaynaklarda hala önemi belirsiz bir varyant (VUS) olarak tanımlanmaktadır. Bu bakışla genetik literatürüne de katkı sağlayacağına inanıyoruz.

Anahtar Kelimeler: Fabry hastalığı, *GLA* geni, aile taraması, genetik

CASE REPORT
OLGU SUNUMU

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Fabry disease is a rare X-linked lysosomal storage disorder (LSD) characterized by the accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids within various tissues and organs.[1] It was first described by Johannes Fabry and William Anderson in the early 20th century and has since been recognized as a complex genetic disorder with diverse clinical manifestations.[2] Fabry disease typically manifests in a range of symptoms that often appear during childhood or adolescence and progressively worsen over time. Common symptoms include acroparesthesia, angiokeratomas, hypohidrosis, hearing loss, gastrointestinal disturbances, and ocular abnormalities.[3] Moreover, Fabry disease can lead to severe complications such as renal failure, cardiomyopathy, stroke, and premature death.[1,3]

The underlying pathophysiology of Fabry disease stems from mutations in the *GLA* gene, located on the X chromosome at Xq22.1.[4] The *GLA* gene encodes the enzyme alpha-galactosidase A (α-Gal A), which is responsible for the hydrolysis of Gb3. In individuals with Fabry disease, mutations in the *GLA* gene lead to deficient or dysfunctional α-Gal A activity, resulting in the accumulation of Gb3 in various tissues.[5] To date, over 1,000 *GLA* gene mutations have been identified and are cataloged in databases such as https://www.hgmd.cf.ac.uk/ and www.dbfgp.org/dbFgp/fabry.[6] Genetic testing can range from targeted searches for specific *GLA* gene variants to comprehensive

screening. In addition to genetic testing, family screenings of diagnosed patients are equally crucial for identifying the index patient. Typically, index patients receive a diagnosis after organ involvement has occurred, limiting the benefits of treatment. However, detecting family members who do not yet exhibit organ involvement can offer substantial advantages, preventing potential tissue damage in the future through early intervention and treatment.

Herein, we report a rare case of familial Fabry disease (FD) associated with an uncommon missense mutation [c.160C>T (p.L54F)] in the *GLA* gene. Our aim is to highlight the importance of appropriate family screening in identifying unaffected family members.

Case Report

A 50-year-old male patient was admitted to our clinic with complaints of shortness of breath and fever. His medical history revealed that he underwent mitral valve repair surgery in 2005. He also received a kidney transplant from his mother in 2006 due to end-stage renal disease. Unfortunately, after 11 years, the transplanted kidney failed, and he has been on hemodialysis for the past three years. Electrocardiography (ECG) showed sinus rhythm with nonspecific ST-T wave changes.

Transthoracic echocardiography (TTE) demonstrated mild left ventricular hypertrophy and a failed mitral ring annuloplasty with severe mitral regurgitation (MR). To ascertain the specific etiology of the severe MR, transesophageal echocardiography (TEE) was performed. The TEE revealed severe transvalvular regurgitation and a 3 mm hypoechoic mobile mass on the posterıor part of the mitral valve ring. C-reactive protein and procalcitonin levels were mildly elevated. Although the blood cultures were negative for infective endocarditis, the severity of the mitral regurgitation led the heart team to decide on surgical intervention.

The presence of mild hypertrophy observed on echocardiography, coupled with the recurrence of renal failure following transplantation, raised suspicions of Fabry disease in the patient (Figure 1 A, B). Upon further questioning, the patient reported experiencing burning sensations in his feet, lack of sweating, and difficulty gaining weight. He also had sensorineural hearing loss. The patient came from a family of 11 siblings, two of whom were undergoing hemodialysis at different centers. Additionally, some of his siblings also had similar complaints. Surprisingly, none of the family members had undergone diagnostic tests for Fabry disease, and no investigations had been conducted within the family to identify the underlying cause. Given these significant clinical indicators, the index patient's α-Gal A enzyme level was 0.50 nmol/ml/hour (> 2.5 nmol/ml/hour), and the Lyso-GB3 level obtained from a blood sample was 2.76 ng/ml (< 1.3 ng/ml). Sanger sequencing of the *GLA* gene was performed on peripheral blood samples, detecting a hemizygous *GLA* (NM_000169.3) c.160C>T, p. Leu54Phe missense variant. This variant was absent in the GnomAD exomes database (PM2) and localized in a hotspot region of the gene (PM1). Missense mutations are a common mechanism of disease in *GLA*-related Fabry disease (PP2). Following the proband's diagnosis, other family members were also called in for clinical screening.

ABBREVIATIONS

ECG	Electrocardiography
ERT	Enzyme replacement therapy
FD	Fabry disease
Gb3	Globotriaosylceramide
LSD	Lysosomal storage disorder
MR	Mitral regurgitation
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VUS	Variant of uncertain significance

The proband (II-4) had an additional 10 siblings, of whom two were already on hemodialysis. Among these siblings, six out of ten individuals exhibited positive *GLA* gene mutations upon screening. Furthermore, in the assessment of the children of these siblings, a total of four individuals were found to carry positive *GLA* gene mutations. The pedigree of the family is illustrated in Figure 1C. While this mutation was previously linked to Fabry disease, it remained classified as a variant of uncertain significance (VUS) in some databases, necessitating segregation analysis. Subsequent analysis confirmed that this mutation is pathogenic.

Family members identified with positive gene mutations underwent comprehensive evaluations to assess organ involvement, including cardiac, renal, ocular, neurological, and dermatological assessments. Detailed echocardiographic assessment and cardiac magnetic resonance imaging were performed (Figure 1D-F). The clinical characteristics of family members are summarized in Table 1. We determined that the variant is primarily of maternal origin; however, due to the proband's mother's (I-4) reluctance to participate in a detailed clinical assessment, we could not obtain information regarding her organ involvement. The eldest brother (II-7) of the index case exhibited significant cardiac, renal, and ocular involvement, prompting the initiation of enzyme replacement therapy (ERT). ERT was also initiated for the other female sibling (II-9) due to renal involvement. The proband's two siblings (II-11 and II-14) were undergoing hemodialysis, and both exhibited cardiac involvement, leading to the initiation of ERT for both. Additionally, one of the two siblings who started treatment (II-18) had neurological, dermatological, and ocular involvement, while the other (II-20) exhibited cardiac, renal, ocular, and gastrointestinal organ involvement. ERT was initiated for both, as well as for the 21-year-old son (III-4) of II-9 with cardiac and gastrointestinal involvement and the 16-year-old son (III-6) of II-11 with renal and gastrointestinal involvement. The 6-year-old daughter (III-10) of II-14 had genetic positivity, but no signs of the disease were evident yet, so treatment was not initiated. Similarly, the 4-year-old daughter (III-13) of II-18 showed no organ involvement necessitating the initiation of treatment.

As a result, enzyme replacement therapy was initiated in nine patients, including the proband, who underwent successful redo mitral valve surgery. A multidisciplinary team formulated a follow-up plan for two asymptomatic children under 8 years old. The proband's mother also refused the treatment.

Informed consent has been obtained from all patients mentioned in the text.

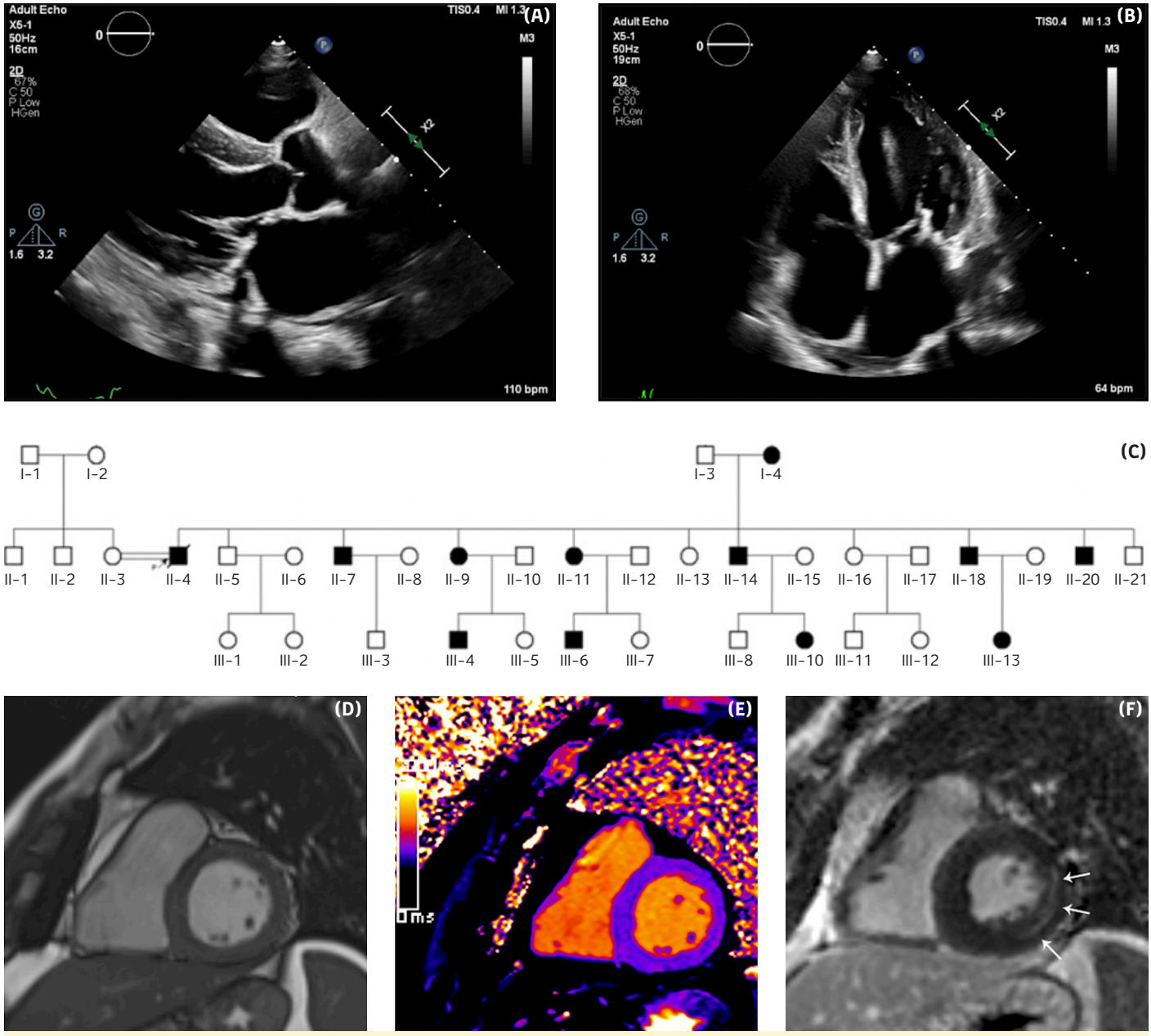


Figure 1. (A) Echocardiography showing mild left ventricular hypertrophy in the proband, viewed from the parasternal long axis. (B) Apical 4-chamber view of the proband's echocardiography, illustrating mild hypertrophy and a failed mitral ring annuloplasty. (C) Pedigree chart of the family. (D) Cardiac magnetic resonance imaging of patient II-7. A short-axis cine image captured in the end-diastolic phase displays left ventricular hypertrophy. (E) Decreased T1 mapping values observed in cardiac magnetic resonance imaging (CMR). (F) Short-axis view of late gadolinium enhancement (LGE) at the basal inferolateral segment on CMR (indicated by white arrows).

Discussion

This case report underscores the importance of recognizing clinical red flags in Fabry disease and highlights the crucial role of family screening following diagnosis. Through family screening, individuals without obvious signs of the disease were identified, leading to early intervention. Additionally, this case report demonstrates the relationship between a specific missense *GLA* gene mutation and FD, which, although previously reported, remains controversial in some sources.

Fabry disease is a relatively rare condition, with an estimated annual incidence ranging from approximately 1:40,000 to 1:117,000 individuals.[7] However, due to its diverse and varied clinical presentation, there is a considerable likelihood of underdiagnosis. The wide array of clinical manifestations seen in FD results in a broad spectrum of symptoms experienced by both hemizygous and heterozygous patients. In heterozygous patients, the phenotypic presentations show even greater variability, influenced by factors such as the specific *GLA* mutation and X chromosome inactivation profiles

Table 1. Demographic and Clinical Features of Family Members

	II-4	II-7	II-9	II-11	II-14	II-18	II-20	III-4	III-6	III-10	III-13	I-4
Age	50	47	46	45	39	35	32	21	16	6	4	78
Gender	M	M	F	F	M	M	M	M	M	F	F	F
Genotype	Hm	Hm	Ht	Ht	Hm	Hm	Hm	Hm	Hm	Ht	Ht	Ht
Enzyme Level	0.5	0.2	18.8	27.5	0.5	5.6	0.2	0.5	0.4	17.8	15.5	N/A
Lyso-b Level	2.76	5.39	< 0.8	< 0.8	4.16	5.58	5.45	5.38	5.23	< 0.8	< 0.8	N/A
Cardiac Features	+	+	–	+	+	–	+	+	–	–	–	N/A
Rhythm	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR	N/A
PR Interval	164	154	134	112	150	136	120	110	104	112	122	N/A
LVEF	60	45	60	45	65	60	60	65	65	70	70	N/A
IVS	12.4	13.4	10.4	12.3	11.7	9	8	7	8	6	6	N/A
PW	11	10.1	10	11.4	9.5	8	8	7	7	6	6	N/A
GLS	-10.7	-12.5	-14.6	-17.9	-15.8	-17.6	N/A	N/A	N/A	N/A	N/A	N/A
LGE on CMR	N/A	+	–	–	N/A	–	+	+	–	N/A	N/A	N/A
Low T1 on CMR	N/A	+	–	+	N/A	–	–	–	–	N/A	N/A	N/A
Troponin-T	65	9	4	31	21	4	6	4	7	N/A	N/A	N/A
NT-proBNP	1953	281	12	1786	1147	11	10	10	10	N/A	N/A	N/A
Renal features	+	+	+	+	+	–	+	–	+	–	–	N/A
Creatinine	5.5	0.9	0.6	6.1	6.7	0.7	1	0.8	0.7	0.5	0.4	N/A
eGFR	10	98	106	7	9	112	99	128	122	126	122	N/A
Proteinuria	N/A	+	+	N/A	+	–	+	–	+	–	–	N/A
Neurologic	+	–	–	+	–	+	+	–	–	–	–	N/A
Dermatologic	–	–	–	–	+	+	–	–	–	–	–	N/A
Ocular	+	+	+	+	–	+	+	–	–	–	–	N/A
GIS	+	–	–	+	–	–	+	+	+	–	–	N/A

Lyso-Gb3, Globotriaosylsphingosine; LVEF, Left Ventricular Ejection Fraction; IVS, Interventricular Septum; PW, Posterior Wall; GLS, Global Longitudinal Strain; LGE, Late Gadolinium Enhancement; CMR, Cardiac Magnetic Resonance Imaging; eGFR, Estimated Glomerular Filtration Rate; GIS, Gastrointestinal System; Hm, Hemizygous Mutation; Ht, Heterozygous Mutation.

in different tissues. Given the significant heterogeneity in disease progression, experts in the scientific community have increasingly focused on establishing potential correlations between genotypes and phenotypic expressions of *GLA*.[8] Various databases, such as the international database of genotypes and phenotypes for FD, have been instrumental in optimizing clinical management. Nonetheless, it is important to note that many *GLA* variants are either absent or remain unclassified in these specialized gene databases.[9,10]

Fabry disease is inherited in an X-linked manner, making males more susceptible to severe phenotypes.[1] Genetic testing is crucial for confirming the diagnosis. Depending on the patient's phenotypic characteristics, analysis may be limited to the *GLA* gene. However, if the phenotype is not typical for FD, more comprehensive genetic testing can be performed to include other diseases in the differential diagnosis. Our proband patient exhibited clear renal manifestations of the FD phenotype, including renal transplant and recurrent renal failure despite the transplant. Additionally, the evaluation of heart valve disease in the patient prompted consideration of FD, and subsequent diagnostic tests confirmed the diagnosis. In our index case, a missense mutation was detected at nucleotide c.160 in codon 53 of exon 1. While some previous publications have mentioned the association of this mutation with Fabry disease, they have not emphasized the mutation's patient-specific clinical effects and pathogenicity.[11,12] Also, these reports lack segregation analysis, a crucial criterion for determining the variant's pathogenicity, and data regarding the variant's association with clinical findings are limited. Consequently, there is conflicting information about the pathogenicity of this mutation in current extensive databases, and in some sources, it is classified as a VUS. Family segregation analysis provides crucial information about the pathogenicity of the discovered variant when multiple family members are affected.[13] Family members were screened for the discovered variant in the index case. Thanks to the clinical features identified in this family, the variant was clearly determined to be pathogenic. As a result, family screening enabled many affected individuals to receive a diagnosis.

Although the cardiac involvement pattern in our case appears to be mild hypertrophy, the importance of screening for cardiac and renal involvement in family members, where clinical manifestations have not yet become apparent, is demonstrated. In fact, besides the index case, the disease

has been detected in a total of 11 family members, and nine of them, excluding the two hemodialysis patients, do not show evident clinical signs of the disease yet. However, the identification of findings associated with the disease in detailed renal, cardiac, neurologic, ocular, auditory, and other metabolic tests in these individuals has provided an indication for initiating treatment. Indeed, advanced imaging modalities revealed subclinical cardiac involvement in two individuals who carried the mutation but exhibited no clinical symptoms. Additionally, proteinuria was detected in three individuals, indicating renal involvement. It is important to note that classical findings such as angiokeratomas, acroparesthesia, hypohidrosis/anhidrosis, and corneal opacities may not be present in the cardiac variant of Fabry disease, which is commonly encountered by adult cardiologists. The importance of initiating treatment during the subclinical phase is unquestionably high in terms of enhancing patient survival and reducing morbidity. Therefore, early diagnosis of unaffected family members, particularly those in childhood, is crucial in managing the disease effectively.

The majority of Fabry disease families possess a unique pathogenic variant, and even individuals with the same pathogenic variant can exhibit significant phenotypic variation.[3] As a result, efforts to establish genotype–phenotype associations have been challenging. We believe it is critical to characterize the clinical features of this mutation and to evaluate its severity and prognosis. The detection of subclinical renal and cardiac involvement, as well as overt renal involvement after family screening, indicates that this rare mutation impacts both renal and cardiac functions.

The involvement of female heterozygotes for Fabry disease remains controversial, with significant variability in clinical manifestations attributed to X chromosome inactivation profiles.[10] Clinical signs in heterozygous females range from being asymptomatic during a normal lifespan to as severe as those seen in afflicted males. Among our cohort of heterozygous females identified through family screening, one-fifth required hemodialysis for five years due to end-stage renal disease, with the etiology remaining unclear. These findings support the notion that dominant expression of the mutant *GLA* allele and X chromosome inactivation may influence kidney disease progression in female Fabry patients. Further exploration of these mechanisms is essential for improving our understanding and optimizing clinical management strategies.

One of the most notable points in our patient's case is that in 2008, approximately 15 years before our diagnosis, no evaluation for Fabry disease was conducted prior to the renal transplantation, despite the patient's kidney donor being the mother, who is the source of the disease. Furthermore, during the subsequent period when the patient's siblings underwent hemodialysis, no investigation for Fabry disease was conducted, indicating a low level of awareness about the condition. We emphasize that raising awareness is the crucial initial step in managing Fabry disease. It facilitates the identification of patients through accessible diagnostic tests, enables the detection of asymptomatic individuals through family screening, and promotes the early initiation of treatment.

Conclusion

Due to the wide spectrum of clinical findings associated with Fabry disease, the diagnosis may be delayed, as in the case of our patient. Genetic studies are useful for diagnosing the disease. Family genetic screening is important to more accurately determine the pathogenicity of the detected variant, to detect asymptomatic family members early, and to provide genetic counseling to the family.

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Informed Consent: Patient consent was obtained and is available upon request.

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