Archives of Current Medical Research
Arch Curr Med Res 2026; 7(3): 511-518

Received: 07 January 2025
Revised: 26 April 2026
Accepted: 04 May 2026
DOI: 10.47482/acmr.1858374

ORIGINAL ARTICLE

Fabry Disease Screening in Kidney Transplant Recipients: A Single-Center Retrospective Study

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Abstract

Background: Fabry disease (FD) is an X linked lysosomal storage disorder caused by deficient α galactosidase A (α GAL A) activity, leading to progressive multisystem involvement, including kidney disease. Evidence on FD screening in kidney transplant recipients is limited. We aimed to evaluate the results of FD screening tests requested due to clinical suspicion in kidney transplant recipients followed at a tertiary referral center.

Methods: This single center retrospective observational study included 59 kidney transplant recipients for whom FD screening was requested between January and February 2022. Dried blood spots (DBS) were used in both sexes. Female recipients underwent direct GLA next generation sequencing (NGS) from DBS without enzyme testing. Male recipients underwent fluorometric measurement of α GAL A activity from DBS; cases with low/borderline activity underwent confirmatory GLA NGS. Genetic analyses were performed at Düzen Laboratory in Ankara. Clinical and demographic data were extracted from electronic records.

Results: Mean age was 54.80±12.30 years and 27 recipients were female. Among 32 male recipients, α GAL A activity was ≤2.5 nmol/mL/h in three cases; confirmatory GLA NGS was negative in all. Two female recipients had heterozygous GLA variants [c.937G>T (p.Asp313Tyr, D313Y) and c.894T>C (p.Asn298=)] without overt FD phenotype in available records.

Conclusions: Enzymatic abnormalities and/or GLA variants may be identified in kidney transplant recipients even in small cohorts. Borderline enzyme activity results and variants of uncertain significance should be interpreted together with genetic confirmation and careful clinical correlation.

Keywords: Fabry disease; Kidney transplantation; Alpha galactosidase A; GLA gene; Screening.

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INTRODUCTION

Fabry disease (FD) is an X linked lysosomal storage disorder caused by pathogenic variants in the GLA gene leading to deficiency or absence of lysosomal α galactosidase A (α GAL A). The enzymatic defect results in progressive accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in vascular endothelium and multiple organs, most notably the kidneys, heart, and nervous system (1,2). Kidney involvement typically manifests with albuminuria/proteinuria and progressive loss of glomerular filtration rate and may ultimately lead to end stage kidney disease requiring dialysis or kidney transplantation (1,2).

Because disease specific treatment options such as enzyme replacement therapy and pharmacological chaperones are available, early recognition of FD remains clinically important, particularly in patients with kidney disease who may present with non specific findings or atypical phenotypes (2–4). While FD is rare in the general population, with estimates of incidence varying across studies, targeted case finding strategies have been advocated in selected high risk populations (1,3).

Screening approaches differ by sex. In males, measurement of α GAL A activity is typically used as the first tier test, whereas in females enzymatic activity may be within the reference range due to random X chromosome inactivation; therefore, molecular genetic testing is often required for diagnosis (3,4). Dried blood spot (DBS) sampling offers logistical advantages for both enzymatic assays and genetic testing and is commonly used in screening programs (5).

Over the last decade, multiple screening studies have evaluated FD prevalence in chronic kidney disease cohorts, including dialysis and transplant populations. A large systematic review and meta analysis of screening studies reported low pooled prevalence of pathogenic GLA variants overall, but highlighted that diagnostic yield may be higher in selected high risk subgroups such as kidney replacement therapy and transplant recipients (6,7). Variant classification substantially affects the estimated prevalence and the interpretation of screening results, particularly when variants of uncertain significance or benign/pseudodeficiency alleles are detected (8).

Data from Türkiye suggest that FD is uncommon but not negligible among patients receiving kidney replacement therapy. In a multicenter screening study including 5657 patients on renal replacement therapy, FD prevalence was reported as 0.31% (9). Several single center studies in kidney transplant recipients from Türkiye have reported occasional pathogenic variants and a number of variants of uncertain significance, supporting the feasibility of transplant population screening when clinically indicated (10–13). In this context, we aimed to evaluate the results of FD screening tests requested due to clinical suspicion in kidney transplant recipients followed at Ankara Bilkent City Hospital.

MATERIALS AND METHODS

This was a single center, retrospective observational study conducted at the Nephrology Clinic of the Ankara Bilkent City Hospital. The study evaluated FD screening tests that had been requested as part of routine clinical care due to clinical suspicion regarding the primary kidney disease etiology.

Adult (≥18 years) kidney transplant recipients were included. Screening was not applied universally to the entire transplant cohort; rather, it was requested in recipients in whom FD was considered in the differential diagnosis. These indications are detailed in the following paragraph.

In line with international consensus recommendations (3,4), the following testing indications were applied at our center: (i) unexplained or atypical primary kidney disease, particularly when a definitive histopathological or clinical diagnosis was lacking at the time of kidney replacement therapy initiation; (ii) end-stage kidney disease before the age of 50 years without an established etiology; (iii) a family history compatible with X-linked inheritance or a known FD diagnosis in a relative; (iv) suggestive extrarenal features documented in the medical record, such as acroparesthesia or neuropathic pain, angiokeratoma, hypohidrosis, cornea verticillata, sensorineural hearing loss, unexplained left ventricular hypertrophy, or cryptogenic stroke at a young age; and (v) the presence of low-grade or unexplained proteinuria together with one or more of the above features. Female recipients with a positive family history were screened irrespective of phenotypic severity, given the variable expressivity of FD in heterozygotes.

Dried blood spots (DBS) were obtained from all participants. In male recipients, α GAL A enzymatic activity was measured from DBS as the first tier test; cases with low or borderline activity (≤2.5 nmol/mL/h) underwent confirmatory molecular analysis of the GLA gene. In female recipients, direct molecular analysis of the GLA gene from DBS was performed without enzymatic testing, given the known limitations of α GAL A activity assays in heterozygous females (3,4).

The DBS α GAL A assay was performed using a fluorometric method. The substrate 4 methylumbelliferyl α D galactopyranoside and the inhibitor N acetyl D galactosamine were used. After incubation at 37°C for 17 hours, the reaction was stopped and fluorescence was recorded (excitation 366 nm, emission 442 nm). Calibration was performed with 4 methylumbelliferone. The reference cut off was defined as >2.5 nmol/mL/h.

Genetic analyses were performed at Düzen Laboratory (Ankara, Türkiye). DNA was extracted from DBS, and the GLA gene was sequenced using next generation sequencing (NGS). Clinically relevant variants were confirmed using Sanger sequencing. Variant interpretation followed the American College of Medical Genetics and Genomics and the Association for Molecular Pathology consensus criteria (14).

Demographic characteristics (age, sex), donor type (living vs deceased), time since transplantation, and available clinical/laboratory parameters were extracted from electronic medical records. Kidney function was assessed using serum creatinine and estimated glomerular filtration rate (eGFR), and proteinuria values recorded closest to the screening date were collected when available. Evidence for cardiac or neurologic involvement compatible with FD was assessed from available echocardiography, electrocardiography, neurology consultations, imaging reports, and problem lists.

Descriptive statistics were used. Continuous variables are presented as mean±standard deviation or median (interquartile range) depending on distribution. Categorical variables are presented as counts (n) and percentages (%). Statistical analyses were performed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 59 kidney transplant recipients were included. Baseline demographic and clinical characteristics are summarized in Table 1. Mean age was 54.80±12.30 years, and 27 recipients (45.8%) were female. Among the 56 recipients with recorded donor type, deceased donor transplantation was more frequent than living donor transplantation. (Table 1).

The screening algorithm and outcomes are summarized in Table 2. α GAL A activity was measured in 32 male recipients using DBS; three cases had α GAL A activity ≤2.5 nmol/mL/h (Figure 1). Confirmatory GLA NGS performed in these three male recipients did not identify pathogenic variants (Table 3).

Table 1. Demographic and clinical characteristics of participants (n=59)

Variable	Value
Age (years), mean±SD	54.80±12.30
Sex (Female/Male), n (%)	27 (45.8) / 32 (54.2)
Donor type (n=56), n (%)	Living 24 (42.8) / Deceased 32 (57.2)
Time since transplantation (months) (n=56), median (IQR)	111.30 (55.20–135.10)
Time since transplantation (months) (n=56), mean±SD	119.00±42.10

Abbreviations: SD, standard deviation; IQR, interquartile range.

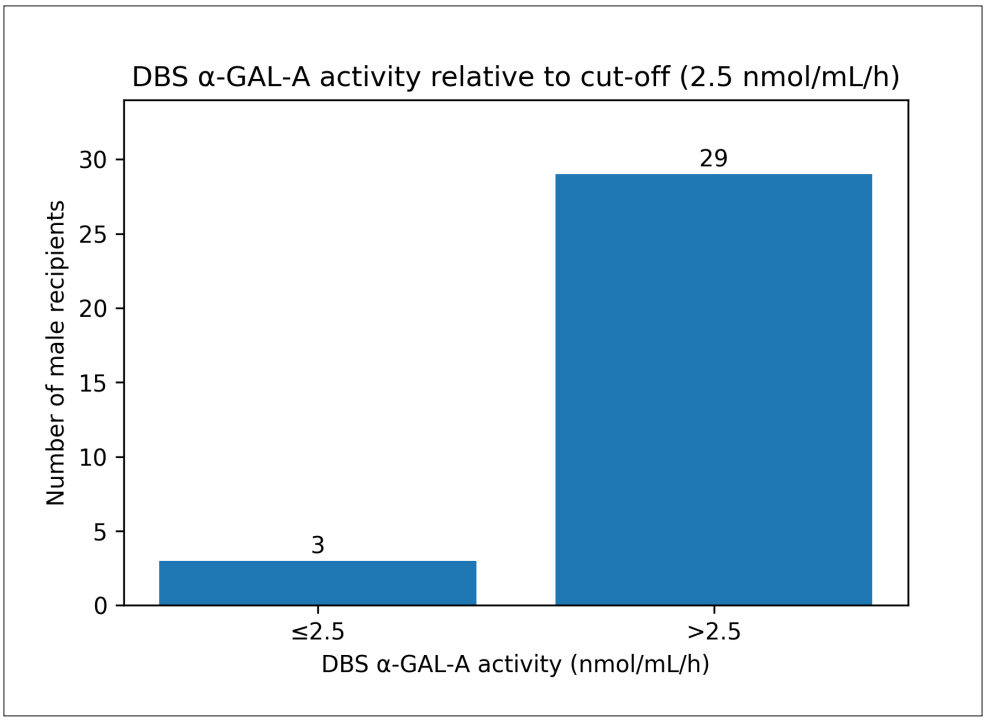


Figure 1. Distribution of DBS α GAL A activity relative to the cut off among male kidney transplant recipients (cut off: 2.5 nmol/mL/h). Abbreviations: DBS, dried blood spot; α GAL A, alpha galactosidase A; nmol/mL/h, nanomol per milliliter per hour.

Table 2. Fabry screening algorithm and outcomes (n=59)

Step	n	Outcome
DBS α GAL A activity measurement (male recipients)	32	α GAL A ≤2.5 nmol/mL/h in 3 cases
GLA NGS from DBS (all female recipients)	27	Heterozygous GLA variant in 2 cases
GLA NGS in males with low α GAL A	3	No pathogenic variant detected

Abbreviations: DBS, dried blood spot; α GAL A, alpha galactosidase A; NGS, next generation sequencing.

Table 3. Male cases with low α GAL A activity (n=3)

Case	Age	Donor	Time since transplantation (months)	α GAL A (nmol/mL/h)	GLA NGS
1	67	Deceased	163	1.98	Negative
2	39	Deceased	55	2.34	Negative
3	44	Living	130	2.06	Negative

Abbreviations: DBS, dried blood spot; α GAL A, alpha galactosidase A; NGS, next generation sequencing.

All 27 female recipients underwent GLA NGS directly from DBS. Two female recipients had heterozygous GLA variants reported: c.937G>T (p.Asp313Tyr, D313Y) and c.894T>C (p.Asn298=) (Table 4). In available records, these individuals had stable graft function, low grade proteinuria, and no documented cardiac hypertrophy, arrhythmia, stroke, or other neurologic findings suggestive of overt FD. Both variants were detected as germline heterozygous changes through DBS-based GLA next-generation sequencing, and neither was identified in the male recipients of our cohort. The c.937G>T (p.Asp313Tyr) variant is a missense substitution that is well represented in population databases, with a global allele frequency of approximately 0.3% and a non-Finnish European frequency of approximately 0.45% in gnomAD; in ClinVar it is most commonly classified as benign or likely benign and has been recurrently described as a pseudodeficiency allele associated with reduced plasma α-GAL-A activity but preserved enzyme stability at lysosomal pH (15–17). The c.894T>C (p.Asn298=) variant (dbSNP rs869312444) is a synonymous change that does not alter the encoded amino acid; it is rare in population databases and is currently classified as likely benign in ClinVar by multiple clinical laboratories (last evaluated April 2024), with no consistent evidence of pathogenicity reported to date (17).

DISCUSSION

In this single center retrospective study, we evaluated FD screening tests requested due to clinical suspicion in kidney transplant recipients. No recipient had a clearly pathogenic GLA variant consistent with a definitive diagnosis of FD. However, we observed two heterozygous GLA variants in female recipients and low/borderline α GAL A activity in three male recipients without confirmatory pathogenic variants. These findings underscore that abnormal screening results, including variants of uncertain significance or enzymatic borderline values, can be encountered in transplant populations and require careful interpretation.

Our findings should be interpreted in the context of the expected low prevalence of FD among kidney transplant recipients. In a systematic review and meta analysis of screening studies in chronic kidney disease, Linares et al. reported a low pooled prevalence of pathogenic GLA variants overall, with an estimated prevalence around 0.28% among kidney transplant recipients; importantly, a substantial proportion of detected variants were benign or of uncertain significance (6). Similarly, Monda et al. emphasized that the classification of GLA variants has a major impact on prevalence estimates in screening studies, and that inclusion of benign and pseudodeficiency alleles can lead to overestimation (8).

Türkiye based studies provide additional context. Yalın et al. screened 5657 patients receiving renal replacement therapy and reported a prevalence of 0.31% (9). In single center transplant cohorts, Erdoganmus et al. reported at least one pathogenic mutation alongside several variants of uncertain significance (10), while Aktaş et al. highlighted the detection of the D313Y variant in a kidney transplant recipient (11). Can et al. further reported identification of a Fabry family following screening of transplant recipients, illustrating the potential cascade testing benefit even when index case detection is rare (12). In our cohort, the absence of a clearly pathogenic

Table 4. Female cases with reported GLA variants (n=2)

Case	Age	Donor	Time since transplantation (months)	GLA variant	Proteinuria (g/day)	eGFR (mL/min/1.73 m²)	Cardiac involvement	Neurologic involvement
1	40	Living	56	c.937G>T (p.Asp313Tyr, D313Y)	0.2	62	None	None
2	63	Deceased	137	c.894T>C (p.Asn298=)	0.3	58	None	None

Abbreviations: eGFR, estimated glomerular filtration rate; NGS, next generation sequencing.

variant may reflect the relatively small sample size, the targeted (rather than universal) screening strategy, and differences in the transplant population case mix (18).

Interpretation of the D313Y variant remains challenging. D313Y has been described as a pseudodeficiency allele associated with reduced α GAL A activity in plasma without classic FD manifestations in many carriers, and its clinical relevance has been debated (15,16). More recent reports suggest that some carriers may present with organ manifestations; therefore, careful phenotyping and biomarker correlation are recommended when D313Y is detected (19). For synonymous or intronic variants such as p.Asn298=, functional impact is often unclear; in the absence of supportive clinical features, such variants are frequently considered likely benign or of uncertain significance and should be interpreted with caution, ideally within an expert genetics framework (8,14).

In male recipients, borderline α GAL A activity without a pathogenic GLA variant highlights a key issue in screening programs: enzymatic assays may yield false positive or indeterminate results due to pre analytical factors, assay variability, or non Fabry causes. Current recommendations support confirmatory molecular testing for males with low enzyme activity and emphasize that females require molecular diagnosis regardless of enzyme activity (3,4). DBS based assays are widely used and are practical for transplant settings; however, cut offs and laboratory methods vary, which may affect test performance (5).

From a clinical perspective, identifying FD in transplant recipients remains important primarily for extrarenal disease management and family screening. Kidney transplantation generally provides good graft and patient survival in FD, but cardiac and neurologic involvement may continue to progress, and disease specific therapy (e.g., enzyme replacement therapy or newer agents) may remain indicated to mitigate systemic complications (20,21). Therefore, transplant centers should maintain awareness of FD, especially in recipients with unexplained primary kidney disease, suggestive extrarenal findings, or family history.

This study has limitations. The sample size was modest and derived from a single center. Screening was targeted based on clinical suspicion and thus does not provide a prevalence estimate applicable to the entire transplant population. Retrospective data extraction limited the uniformity of phenotyping, and biomarkers such as lyso Gb3 were not available. Nonetheless, our data provide real world experience on FD screening practices in a high volume transplant center and emphasize the need for confirmatory genetic testing and careful clinical correlation when abnormal screening results are encountered.

In kidney transplant recipients screened due to clinical suspicion, borderline enzymatic results or heterozygous GLA variants may be detected even when definitive pathogenic mutations are absent. Such findings should prompt careful interpretation with confirmatory genetics and clinical correlation, particularly with respect to extrarenal manifestations and family screening.

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Abbreviations List

FD: Fabry disease
α-GAL-A: alpha-galactosidase A
GLA: alpha-galactosidase A gene
Gb3: globotriaosylceramide
lyso-Gb3: globotriaosylsphingosine
DBS: dried blood spot
NGS: next-generation sequencing
eGFR: estimated glomerular filtration rate
ERT: enzyme replacement therapy
ACMG: American College of Medical Genetics and Genomics
AMP: Association for Molecular Pathology

Ethics Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (Approval Date: 21.12.2025; Approval Number: TABED 1-25-1998). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The study did not involve any animal subjects.

Consent for Publication

Not applicable. The manuscript does not contain any individual person's identifiable data, images, or videos.

Availability of Data and Materials

The data supporting the findings of this study are stored digitally in the institutional electronic medical record system and in a de-identified study database held by the corresponding author. The data are available from the corresponding author upon reasonable request, subject to institutional data protection regulations.

Competing Interests

The authors declare that they have no financial or non-financial competing interests related to this study.

Funding

The authors received no financial support for the research, authorship, or publication of this article. There is no funding source.

Authors' Contributions

Idea/Concept: OB, MŞK. Design: OB, MŞK. Control/Supervision: MŞK. Data Collection and/or Processing: OB. Analysis and/or Interpretation: OB, MŞK. Literature Review: OB. Writing the Article: OB. Critical Review: MŞK. References and Fundings: OB.

Acknowledgements

None. No person other than the listed authors contributed to this study in a manner that would require acknowledgement.