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Fabry disease caused by the *GLA p.Gly183Asp* (*p.G183D*) variant: Clinical profile of a serious phenotype

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ABSTRACT

Background: The detailed clinical phenotype of patients carrying the α-galactosidase gene (*GLA*) *c.548 G > A/p.Gly183Asp* (*p.G183D*) variant in Fabry disease (FD) has not been thoroughly documented in the existing literature.

Methods: This paper offers a meticulous overview of the clinical phenotype and relevant auxiliary examination results of nine confirmed FD patients with the *p.G183D* gene variant from two families. Pedigree analysis was conducted on two male patients with the gene variant, followed by biochemical and genetic screening of all high-risk relatives. Subsequently, evaluation of multiple organ systems and comprehensive instrument assessment were performed on heterozygotes of the *p.G183D* gene variant.

Results: The study revealed that all patients exhibited varying degrees of cardiac involvement, with two demonstrating left ventricular wall thickness exceeding 15 mm on echocardiography, and the remaining six exceeding 11 mm. Impaired renal function was evident in all six patients with available blood test data, two of whom underwent kidney transplantation. Eight cases reported neuropathic pain, and five experienced varying degrees of stroke or transient ischemic attack (TIA).

Conclusion: This study indicates that the *GLA p.G183D* gene variant can induce premature organ damage, particularly affecting the heart, kidneys, and nervous system.

1. Introduction

Fabry disease (FD) is a rare X-linked lysosomal disorder caused by pathogenic variants in the α-galactosidase gene (*GLA*), which encodes the enzyme α-galactosidase A (α-Gal A) [1]. Genetic testing plays a pivotal role in FD diagnosis, with over 1000 different *GLA* variants identified [2]. In 1999, [3]. reported the first discovery of the *GLA c.548 G > A / p.Gly183Asp* (*p.G183D*) gene variant in patients diagnosed with FD. Subsequently, this variant has also been documented by Glass [4], Vedder [5], and Zhang [6]. The FD gene variant database includes four cases of this variant from two families (http://Fabry-database.org/mutants/). However, current literature lacks detailed clinical phenotype descriptions for patients carrying the *p.G183D* variant. This study presents a comprehensive phenotype description of two Chinese families residing in Anhui, China, affected by FD due to the *p.G183D* pathogenic variant.

2. Subjects and methods

2.1. Subjects

Two men, one diagnosed with chronic kidney disease (CKD) at 21 years old and the other with ischemic stroke at 27 years old, underwent screening tests for FD including α-Gal A enzymatic activity and plasmatic Lyso-GL3 levels. The tests revealed the presence of the *p.G183D* variant in the *GLA* gene in both individuals. Subsequently, they were referred to The Cardiomyopathy Cohort of Anhui Province (Anhui-CM,

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Registration No. ChiCTR2300072071) for a comprehensive clinical assessment. Pedigree analysis was conducted for both probands as shown in Fig. 1. This study obtained approval from the hospital ethics committee (Ethical approval No. 2023KY242), and all participants provided written informed consent.

2.2. Genealogy and genetic research

All at-risk relatives of the two probands were invited to participate in screening for FD. Males underwent testing for α-Gal A enzymatic activity, while both males and females underwent testing for plasmatic Lyso-GL3 levels and genetic studies. Individuals identified as heterozygotes for *GLA* pathogenic variants underwent subsequent detailed clinical evaluation. Enzymatic activity of α-Gal A and the biomarker Lyso-GL3 for FD were assessed in dried blood spot samples using tandem mass spectrometry in all patients [7,8,9,10]. Genetic analysis involved DNA isolation from dried blood spots on filter paper, followed by next-generation sequencing (NGS) of the target region. Genomic DNA was extracted from dried blood spots using lysis solution and grinding, amplified by long-range PCR for the entire GLA gene sequence. The resulting amplicons were used to create paired-end libraries, sequenced on an Illumina Novaseq platform, and the data were analyzed to identify relevant variants. Normal values for α-Gal A enzymatic activity and Lyso-GL3 were > 2.2 μmol/l/h and < 1.11 ng/ml, respectively. Diagnosis of FD was based on deficient enzymatic activity in males and the presence of a pathogenic *GLA* gene variant in females [7,1,9].

2.3. Clinical and instrumental evaluation

The clinical protocol entailed a comprehensive multidisciplinary assessment by specialists from Cardiology, Neurology, Ophthalmology, Otorhinolaryngology, and Dermatology. It included blood and urine analyses for quantifying serum creatinine, as well as estimation of glomerular filtration rate (eGFR) using the CKD-EPI formula. Additional assessments comprised an electrocardiogram, echocardiography, cardiac magnetic resonance imaging (MRI), and either a brain MRI or CT scan [11]. The diagnostic criteria for left ventricular high voltage on an electrocardiogram consisted of chest lead readings of R_{V5} or $R_{V6} > 2.5$ mV, $R_{V5} + S_{V1} > 4.0$ mV (male) or > 3.5 mV (female), $R_{aVL} > 1.2$ mV, $R_{aVF} > 2.0$ mV, and $R_I + S_{II} > 2.5$ mV [12,13]. Diagnosis of ST-T abnormalities was based on criteria that included horizontal or downsloping ST-segment depressions >0.05 mV, any type of ST-segment depression >0.1 mV, and flat or inverted T waves in leads other than V_{1-2}, III, or aVF. Left ventricular wall thickness was measured from 2D images taken from the parasternal long axis view in end diastole, and the diagnosis of left ventricular hypertrophy (LVH) was in accordance with American Society of Echocardiography (ASE) guidelines, which define LVH as increased wall thickness ≥ 11 mm for males and ≥ 10 mm for females, not attributable to hypertension, valve disease, or other cardiac overload conditions [14,15].

3. Results

3.1. Family screening of FD

Nine individuals (four males and five females) carrying the *p.G183D* variant were identified by screening at-risk relatives of the probands (see Fig. 1). The primary demographic, clinical, and biochemical characteristics of the patients are outlined in Table 1. Among these individuals, four belonged to Family I, while the remaining five were from Family II. Presently, five patients have commenced enzyme replacement therapy (ERT).

3.2. Biochemical evaluation of FD due to the p.G183D variant

As shown in Table 1, α-Gal-A enzyme activity was reduced in six out of nine patients (66.7%), while Lyso-GL3 levels were elevated in all nine patients (100%).

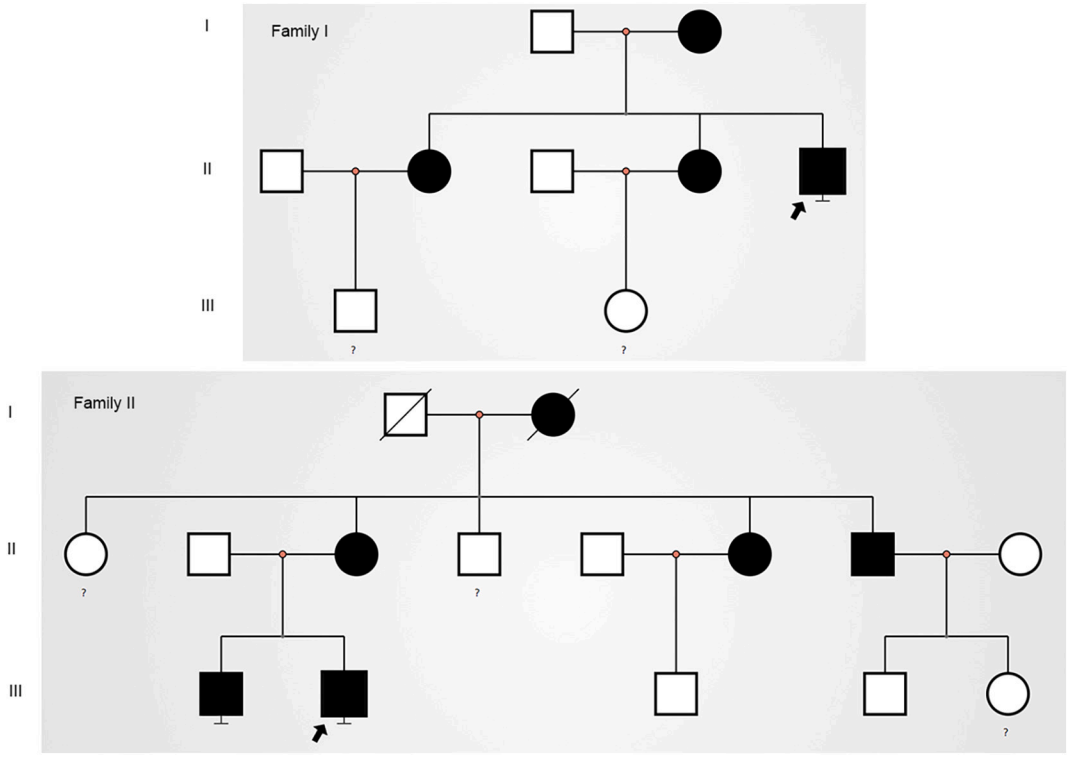

Fig. 1. Pedigrees of the two Fabry disease families with the *p.G183D* variant.
Probands are marked with a black arrow. Question mark denotes subjects unavailable for biochemical and genetic evaluation due to refusal or death.

Table 1
Biochemical evaluation and extracardiac phenotype of subjects with *GLA p.G183D* variant.

Clinical manifestations	Family I				Family II				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Sex (F/M)	M	F	F	F	M	M	M	F	F
Current age (years)	41	70	44	46	30	32	46	56	50
Age at diagnosis (years)	23	70	44	46	28	30	44	54	50
Enzyme replacement therapy	YES	NO	NO	YES	NO	YES	YES	YES	NO
Alpha galactosidase A activity (nmol/h/mL)	0.37	2.30	3.33	1.84	0.38	0.52	0.28	0.79	3.01
Lyso-GL3(ng/mL)	46.25	8.74	6.62	12.00	55.25	49.27	33.09	20.31	6.32
Specific symptoms before 10 years old	Neuropathic pain; Dyshidrosis; Angiokeratoma	None	None	None	Neuropathic pain	Neuropathic pain; Dyshidrosis	Neuropathic pain; Dyshidrosis	Neuropathic pain	Neuropathic pain
Cystatin C (mg/l)	2.54	NA	NA	NA	1.05	1.41	3.09	2.01	1.14
Serum creatinine (umol/L)	247	NA	NA	NA	112.6	115	363	148	66
eGFR (ml/(min·1.73m^2))	28.34	NA	NA	NA	68.56	69.93	15.99	31.9	95.79
Albuminuria	YES	NA	NA	NA	YES	YES	YES	YES	YES
Chronic renal dysfunction	YES	NA	NA	NA	YES	YES	YES	YES	NO
Kidney transplant	YES	NO	NO	NO	NO	YES	NO	NO	NO
Angiokeratoma	YES	NO	NO	NO	NO	NO	NO	NO	NO
Cornea verticillata	YES	NO	NO	NO	NO	NO	NO	NO	NO
Neuropathic pain	YES	NO	YES	YES	YES	YES	YES	YES	YES
Dyshidrosis	YES	NO	NO	NO	NO	NO	NO	YES	NO
Stroke /TIA	YES	YES	YES	NO	YES	NO	NO	YES	NO
Ventosity/abdominal pain	NO	NO	NO	NO	NO	NO	NO	YES	NO
Diarrhea/constipation	YES	NO	NO	YES	NO	NO	NO	NO	NO
Dysacusis	YES	NO	NO	NO	NO	NO	NO	NO	NO

Lyso-GL3, globotriaosylsphingosine; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.

3.3. Clinical phenotype of FD due to the p.G183D variant

As shown in Table 1, six out of the nine patients exhibited specific symptoms before 10 years old. The table shows that five patients, aged between 58 and 70, experienced strokes. Renal complications, including albuminuria and/or chronic renal dysfunction (CKD), were identified in six patients, two of whom underwent kidney transplant procedures. Furthermore, neuropathic pain was documented in eight patients. A subgroup of patients also displayed symptoms related to the skin, eyes, ears, and gastrointestinal system.

3.4. Cardiac involvement by FD due to the p.G183D variant

3.4.1. Cardiac symptoms

Two patients were diagnosed with heart failure, three experienced palpitations or arrhythmias, and two reported symptoms of angina (Table 2).

3.4.2. Laboratory tests

Four patients showed slight elevations in Troponin I (TnI) levels, one patient exhibited a mild increase in creatine phosphokinase-MB (CK-MB) levels, and three patients had elevated NT-proBNP levels (Table 2).

3.4.3. Electrocardiography (ECG)

All patients presented with sinus rhythm. Four patients exhibited a shortened PR interval, three had sinus bradycardia, eight showed left ventricular high voltage, and all displayed ST-T abnormalities (Table 2, Fig. 2, Fig. 3).

3.4.4. Echocardiography (UCG)

The left ventricular ejection fraction (LVEF) was within normal range for all patients. Two patients exhibited slightly enlarged left ventricles, while three patients showed enlargement of the left atrium. Additionally, all nine patients met the diagnostic criteria for left ventricular hypertrophy (LVH), as indicated by a left ventricular wall thickness ranging from 11 to 20 mm in echocardiography. Furthermore, the echocardiography findings indicated a decreased left ventricle global longitudinal strain (LVGLS) in seven patients, and left ventricular diastolic dysfunction in four patients. (Table 2, Fig. 2 and Fig. 3).

3.4.5. Cardiac magnetic resonance (CMR)

Two patients underwent contrast-enhanced cardiac magnetic resonance imaging (CMR), while two patients received CMR scans without contrast due to renal insufficiency. The imaging results from both scans were indicative of Fabry cardiomyopathy, characterized by generalized thickening of the left ventricular wall, reduced left ventricular diastolic function, and delayed gadolinium enhancement (LGE) showing fibrosis in the subbasal lateral region of the left ventricle (Table 2).

4. Discussion

This study offers a systematic description of the clinical phenotypes exhibited by individuals with FD carrying the *p.G183D* gene variant. The research centers on two families assessed by our institution and underscores the impact on the heart, kidneys, and nervous system. The findings reveal that this genetic variation can lead to premature structural and/or functional complications affecting various organs in affected individuals.

4.1. The effect of p.G183D gene variant on GLA enzyme activity

The *GLA* protein structure contains 31 glycines, 14 of which are identified in the point variant list. Glycine, with no side chains, exhibits enhanced flexibility in the main chain compared to other amino acids. The glycines in the variant list can be categorized into two groups: those displaying abnormalities on the Ramachandran plot at the φ/ψ glycine position, and those situated in environments with no side chain space. Point variants of residues with glycine-specific dihedral angles can induce alterations in the peptide backbone. Variants of glycine present in densely packed environments may lead to spatial clashes in proteins [16]. Studies have demonstrated that both types of glycine variants have the potential to disrupt the stability of mutated proteins and impact their

Table 2
Cardiac involvement of subjects with *GLA p.G183D* variant.

Cardiac manifestations	Family I				Family II				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Cardiac symptoms									
Angina	NO	NO	NO	NO	NO	NO	NO	YES	YES
Palpitations or arrhythmias	YES	NO	NO	YES	NO	NO	NO	YES	NO
Heart failure	NO	NO	NO	NO	NO	NO	YES	YES	NO
Laboratory tests									
TnI (ng/ml)	0.09	NA	NA	NA	NA	0.06	0.15	1.06	0.14
CK-MB (IU/L)	10.00	NA	NA	NA	NA	13.00	21.00	18.00	53.00
NT-proBNP (pg/ml)	NA	NA	NA	NA	NA	400.00	3248.00	3965.00	520.00
Electrocardiography									
Sinus rhythm	YES	YES	YES	YES	YES	YES	YES	YES	YES
Sinus bradycardia	YES	YES	YES	NO	NO	NO	NO	NO	NO
Short PR interval	NO	NO	YES	YES	NO	YES	YES	NO	NO
Left ventricular high voltage	YES	YES	YES	YES	YES	YES	YES	YES	NO
ST-T abnormalities	YES	YES	YES	YES	YES	YES	YES	YES	YES
Echocardiography									
IVST (mm)	13.00	14.00	11.00	12.00	11.00	13.40	15.00	16.00	11.50
LVPWT (mm)	13.00	14.00	11.00	12.00	11.00	14.00	18.00	20.00	11.10
LVEF (%)	68.00	63.00	72.00	71.00	72.00	82.00	75.00	70.00	70.00
LAD (mm)	30.00	44.00	31.00	31.00	34.00	41.00	34.00	41.00	37.00
LVEDD (mm)	55.00	55.00	48.00	47.00	47.00	49.00	41.00	45.00	40.00
LVEDV (ml)	149.00	149.00	108.00	101.00	99.00	112.00	72.00	93.00	69.00
LVESD (mm)	34.00	36.00	28.00	28.00	27.00	24.00	23.00	27.00	24.00
LVESV (ml)	47.00	55.00	30.00	29.00	27.00	20.00	18.00	28.00	21.00
Mitral E/A ratio	1.25	0.75	1.55	1.23	1.40	0.97	1.90	0.58	1.08
Mitral E/e′ ratio	9.09	12.00	10.30	8.00	9.41	14.43	11.38	15.14	16.80
LV diastolic dysfunction*	NO	YES	NO	NO	NO	YES	NO	YES	YES
LVGLS (%)	NA	−24.4	−15.3	−16.2	−14.6	−8.8	−8.9	−6.7	−14.0
Cardiac Magnetic Resonance									
LAD (mm)	NA	NA	NA	NA	NA	34.00	23.00	36.00	31.00
RAD (mm)	NA	NA	NA	NA	NA	43.00	40.00	32.00	43.00
LVEDD (mm)	NA	NA	NA	NA	NA	44.00	47.00	43.00	46.00
RVEDD (mm)	NA	NA	NA	NA	NA	24.00	19.00	22.00	30.00
IVST (mm)	NA	NA	NA	NA	NA	16–18	12–14	14–16	14
LVPWT (mm)	NA	NA	NA	NA	NA	11–13	11–13	11–13	6–10
LVEF (%)	NA	NA	NA	NA	NA	59.09	65.74	56.01	60.52
LVEDV (ml)	NA	NA	NA	NA	NA	127.07	159.30	125.21	104.72
LVESV (ml)	NA	NA	NA	NA	NA	52.02	54.57	55.08	41.35
LV mass (g)	NA	NA	NA	NA	NA	170.04	175.54	178.25	91.56
RVEF (%)	NA	NA	NA	NA	NA	46.56	52.50	49.08	58.11
RVEDV (ml)	NA	NA	NA	NA	NA	92.41	92.49	97.78	90.22
RVESV (ml)	NA	NA	NA	NA	NA	49.39	43.93	49.80	37.80
LGE	NA	NA	NA	NA	NA	NA	NA	LV lateral wall, distal anterior wall, and inferior wall	LV proximal anterior septal and lateral wall

TnI, Troponin I; CK-MB, creatine phosphokinase-MB; NT-proBNP, N-terminal pro brain natriuretic peptide; IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricle end-diastolic volume; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; LV, left ventricle; LVGLS, left ventricle global longitudinal strain; RAD, right atrial diameter; RVEDD, right ventricular end-diastolic dimension; RVEF, right ventricular ejection fraction; RVEDV, right ventricle end-diastolic volume; RVESV, right ventricular end-systolic volume; LGE, CMR delayed gadolinium enhancement.

* LV diastolic dysfunction: mitral E/A ratio < 1.0 or mitral E/e′ ratio > 14.

biological functions [17]. The *p.G183D* gene variant is a missense mutation that substitutes the amino acid glycine (Gly) at position 183 with aspartic acid (Asp). In vitro experiments have indicated that this variant could influence enzyme activity [17]. Other variants at this locus, such as *Gly183Ser*, *Gly183Val*, and *Gly183Ala*, have also been observed in patients with Fabry disease [18], hinting at the Gly183 region being a potential hotspot at this locus. The variant site is not currently documented in the normal population databases such as gnomAD, Thousand Genomes, or ExAC, but it is present in the disease-related HGMDpro database. Structural prediction tools like SIFT, Polyphen2, and VariantTaster all predict that this variant might impair the protein's normal function.

The study findings indicated that among the nine patients for whom data was available, six exhibited a reduction in α-Gal A activity. Furthermore, all nine patients demonstrated an elevation in Lyso-GL3 levels, a metabolite of α-Gal A. These results substantiate the significant influence of the *p.G183D* variant on α-Gal A's biological function, suggesting a theoretical foundation for its potential to induce early and

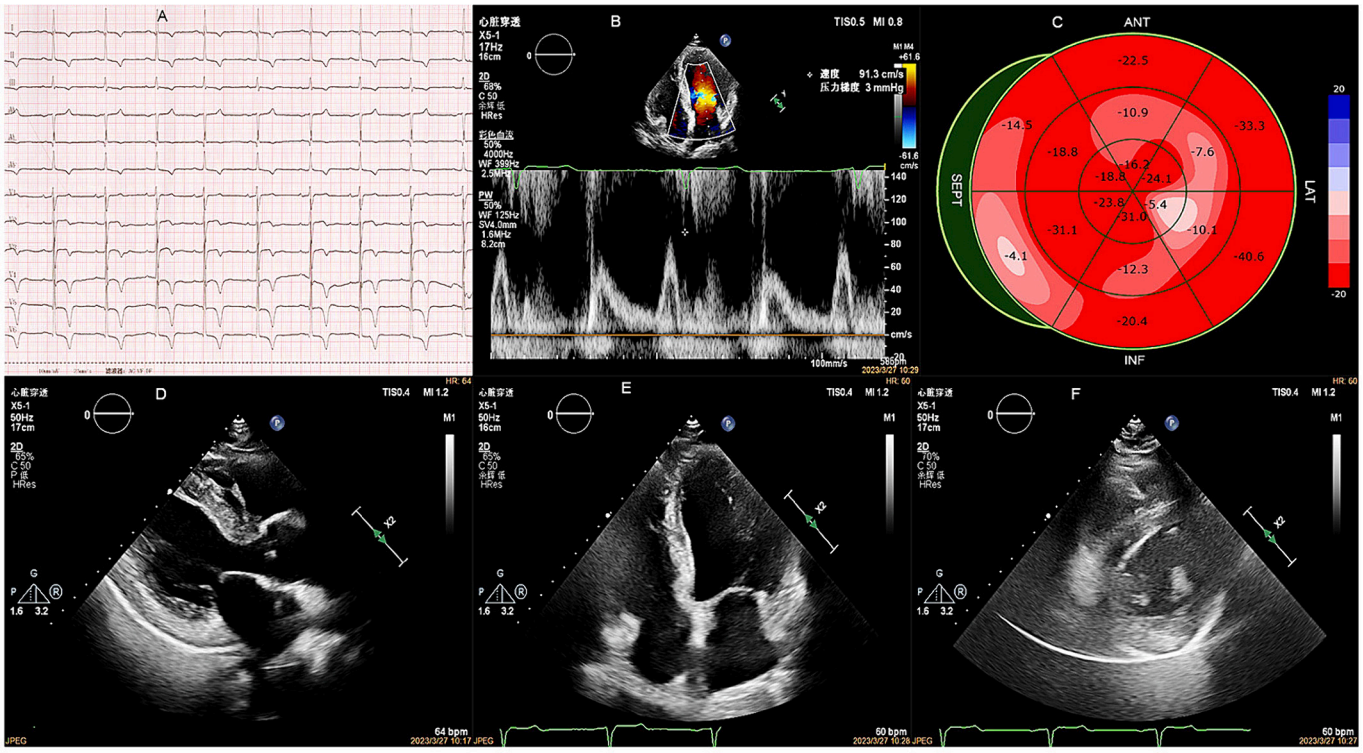

Fig. 2. Representative images of non-invasive cardiac modalities in patient 2.
Electrocardiography showed giant negative T-waves (A). Two-dimensional echocardiography showed reduced diastolic velocities (B) at tissue doppler and longitudinal strain at speckle tracking echocardiography (C). Parasternal long axis and apical long axis shows symmetrical hypertrophy (D, E); echocardiographic binary sign of left ventricular endocardial border (D, E); hypertrophy of papillary muscles in parasternal short axis (F).

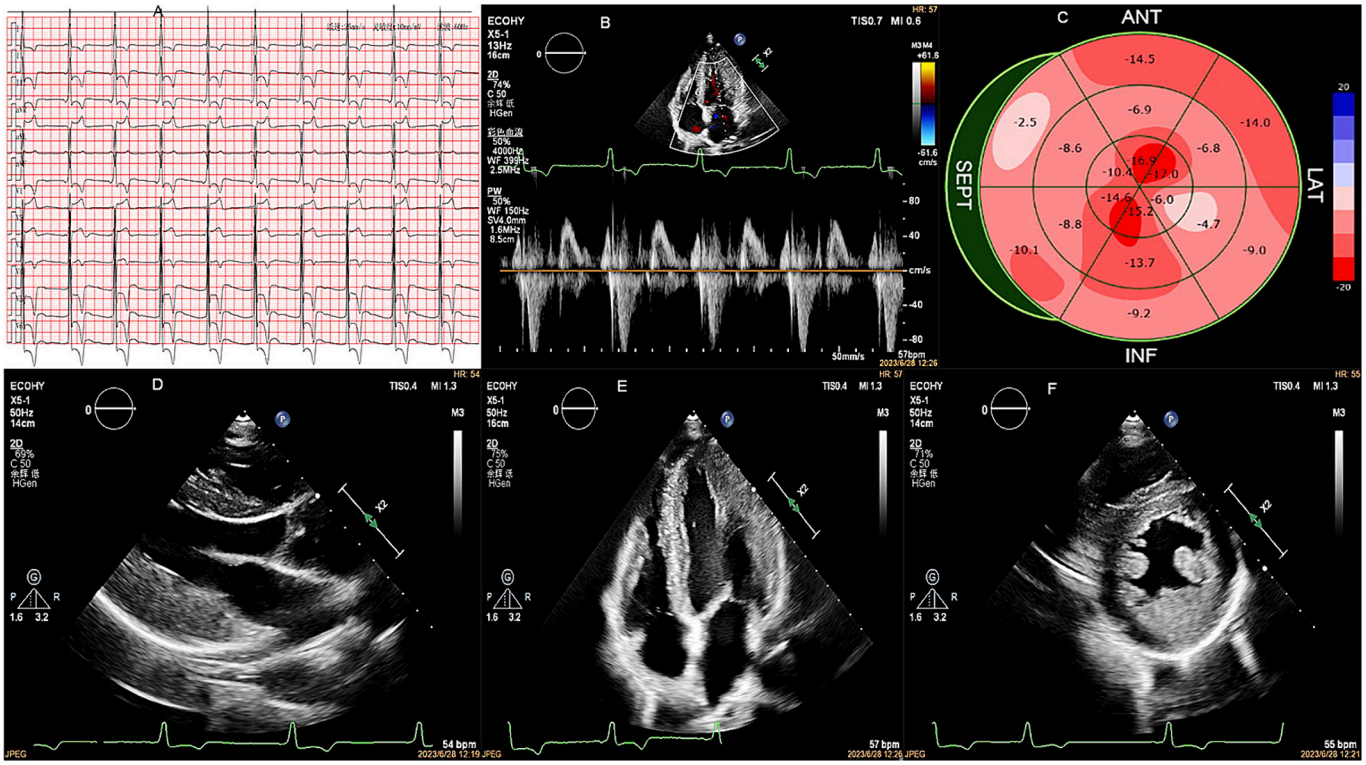

Fig. 3. Representative images of non-invasive cardiac modalities in patient 7.
Electrocardiography showed a short PR interval, giant negative T-waves and horizontal ST-segment depressions (A). Two-dimensional echocardiography showed reduced diastolic velocities (B) at tissue doppler and longitudinal strain at speckle tracking echocardiography (C). Parasternal long axis and apical long axis shows symmetrical hypertrophy (D, E); echocardiographic binary sign of left ventricular endocardial border (D, E); hypertrophy of papillary muscles in parasternal short axis (F).

severe organ dysfunction.

4.2. The effect of p.G183D variant on the function of external organs of the heart

Variations in the *GLA* gene lead to reduced enzyme activity, resulting in the accumulation of glycosphingolipids (GL3) and its derivative Lyso-GL3 in multiple organs like the kidneys, nervous system, skin, and eyes. This buildup causes tissue and organ damage along with associated clinical symptoms [7,1,9]. Literature indicates that early clinical signs in FD patients include limb burning pain, angiokeratoma, and corneal vortex opacity [19]. Among the seven patients examined in the study, five experienced limb burning pain, while only one presented angiokeratoma and corneal vortex opacity. In the initial stages of renal involvement in FD, common symptoms include proteinuria and reduced glomerular filtration rate. By the age of 30, around 30% of patients progress to end-stage renal disease [19]. The study noted kidney impairment in four out of seven patients, with two already undergoing kidney transplant therapy. These findings suggest that individuals carrying the *p.G183D* variant face a high risk of renal dysfunction, potentially leading to early onset of end-stage kidney disease. Cerebrovascular complications represent the primary central nervous system manifestation in FD patients [19]. Five of the seven patients exhibited varying degrees of stroke or transient ischemic attack (TIA), highlighting the impact of the *p.G183D* variant on cerebrovascular function in FD patients. The study also observed minimal involvement of other organs, such as the digestive system, eyes, ears, and other functions, which may be linked to the low incidence of previously mentioned clinical manifestations and the study's limited sample size.

4.3. The impact of p.G183D variant on the structure and function of the cardiac

Currently, it is known that metabolic substrates of α-Gal A and their derivatives are capable of accumulating in various cell types within the cardiac tissue. This accumulation in myocardial cells can result in the development of LVH and diastolic dysfunction. Furthermore, when stored in endothelial and smooth muscle cells, it can lead to vascular structural abnormalities and myocardial ischemia. Additionally, accumulation in the conduction system may result in conduction block, atrial fibrillation, and ventricular arrhythmias [20]. Cardiac involvement in FD is noted in 60% of male patients and 50% of female patients, with LVH being a prominent indicator [20].

This study offers a comprehensive description of cardiac involvement in patients carrying the *p.G183D* variant, considering various aspects. The description encompasses clinical manifestations, hematological investigations, ECG, UCG, and CMR. The findings of the study indicate that all nine patients demonstrated varying degrees of cardiac involvement, including sinus bradycardia in three cases, left ventricular high voltage on ECG, and LVH on UCG across all nine patients. These results suggest a significant impact of the *p.G183D* variant on the cardiac structure of patients. Additionally, in conjunction with existing data, ECG emerges as a valuable tool for assessing early cardiac involvement in patients with FD, warranting further investigation. Moreover, certain abnormalities in laboratory parameters (such as troponin I, CK-MB, and NT-proBNP) in some patients are hypothesized to be linked to renal dysfunction.

In summary, our results highlight that the *p.G183D* variant may lead to structural and functional impairment in various organs, with a notable impact on the heart, kidneys, and nervous system. While additional research is required to establish a direct link between these phenotypes and the *p.G183D* gene variant, we advocate for enhanced monitoring and prompt initiation of targeted interventions for patients with FD harboring the *p.G183D* mutation in routine clinical practice.

5. Conclusions

Our findings demonstrate that the *p.G183D* variant may lead to structural and/or functional impairment in various organs, especially affecting the heart, kidneys, and nervous system.

6. Limitations

The study has some limitations. Firstly, it was not possible to screen the entire high-risk population for family lineage, primarily due to reasons such as patient refusal or unavailability. Consequently, there is missing information regarding some family members. Secondly, while CMR is essential for assessing cardiac involvement in FD patients, not all individuals underwent CMR with LGE, mainly due to cost constraints and renal dysfunction.

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CRediT authorship contribution statement

Zhiquan Liu: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Qi Wang:** Investigation, Data curation. **Dongmei Yang:** Investigation, Data curation. **Kui Mao:** Investigation. **Guohong Wu:** Investigation. **Xueping Wei:** Investigation. **Hao Su:** Investigation, Data curation. **Kangyu Chen:** Writing – review & editing, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101102.

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