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ORIGINAL ARTICLE

Clinical and genetic spectrum in Chinese families with Fabry disease: a single-centre case series

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Abstract

Aims Fabry disease (FD) is an X-linked genetic disease caused by mutations in the *GLA* gene that leads to deficient activity of lysosomal enzymes, accumulation of globotriaosylceramide in multi-organ systems, and variant clinical manifestations. We aimed to detail the clinical and genetic spectrum of FD in Chinese families.

Methods and results Five male probands with unexplained left ventricular hypertrophy and their family members were investigated. Genetic screening was available in 11 subjects of the 5 families, 10 of whom proved to be carriers of either *GLA* gene mutation, including 3 previous reported missense mutations (c.128G > A, c.811G > A, c.950T > C), 1 novel missense mutation (c.37G > C), and 1 novel deletion mutation (c.1241delT). A total of 17 patients were definitely or possibly diagnosed of FD, given their clinical manifestations and hereditary nature of FD. Echocardiography demonstrated normal cardiac structure and function in six female patients. Electrocardiographic pre-excitation occurred in 80% (4/5) of men and 16.7% (1/6) of women. Six patients (6/14, 42.9%) had chronic kidney disease with decreased renal function and all were male (6/7, 85.7%). Six patients presented with acroparesthesia, hypohidrosis, or both. Three female patients and two male patients experienced sudden death, and one male patient with the mutation (c.128G > A) died of progressive heart failure, between 41 and 66 years of age.

Conclusions We reported five unrelated families of FD with different *GLA* mutations. Clinical manifestations were highly heterogeneous between male and female patients even within the same family. Female patients showed relatively low risks of structural heart disease and renal insufficiency. However, the long-term outcomes might be adverse in both sexes. Our study underlines the importance of molecular screening of the *GLA* gene for early identification and clinical decision making in patients with FD.

Keywords Fabry disease; *GLA* gene; Left ventricular hypertrophy; Renal insufficiency

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Introduction

Fabry disease (FD, OMIM #301500) is a rare X-linked genetic disease caused by mutations in the *GLA* gene that encodes α-galactosidase A (α-Gal A). FD is an inborn lysosomal storage disease, and its incidence ranges from 1/40 000 to 1/117 000 in the general population.[1] The deficient α-Gal A leads to intra-lysosomal accumulation of glycosphingolipids in multiple organs, causing variant clinical symptoms of different systems, including peripheral and automatic neuropathy, cerebrovascular and cardiovascular disease, renal disease, and ocular disease.[2] According to differences in residual α-Gal A activity and clinical manifestations, FD is categorized into severe, early onset 'classical type' and mild, late onset 'non-classical type'. Cardiac involvement of FD typically manifests as a hypertrophic phenotype; therefore, it is often misdiagnosed as hypertrophic cardiomyopathy (HCM). The reported prevalence of FD is up to 12% in European and American patients diagnosed with HCM.[3,4] In the present study, we detail the clinical phenotypes of five different

Chinese families with FD caused by two novel mutations and three previous reported missense mutations.

Methods

Study subjects

Five unrelated male probands (43 to 63 years of age at presentation) with unexplained left ventricular hypertrophy and their family members were enrolled in our study. All subjects were evaluated on the basis of medical history, physical examination, laboratory tests, 12-lead electrocardiogram (ECG), and transthoracic echocardiography if possible. The study was approved by the ethics committees of Guangdong Provincial People's Hospital and performed in accordance with the Declaration of Helsinki. Informed and written consent was obtained from all the study subjects.

Molecular genetic analysis

Genomic DNA was extracted from peripheral blood lymphocytes using a commercial kit (QIAGEN Co., Ltd., CA, USA) for genetic screening with next-generation sequencing. All sequencing and genetic analyses have been detailed in our previous study.[5] In brief, genetic screening was available in 11 subjects and performed at presentation between the ages of 12 and 63 years, 10 of whom proved to be carriers of either *GLA* gene mutation. Candidate variants in five probands were identified by the next-generation sequencing and further validated by direct Sanger sequencing. Their family members only underwent direct Sanger sequencing to confirm the identified mutations. Seven patients probably carried the *GLA* mutation, given their clinical manifestations and hereditary nature of FD. A total of 17 patients was proved or likely diagnosed of FD.

Histological analysis

The proband in Family A underwent endomyocardial biopsy because of refractory and progressive heart failure. Cardiac tissue specimens were biopsied from the right interventricular septum via the right internal jugular vein. Specimens were fixed in 10% formalin for staining with haematoxylin and eosin (H&E) and Masson's trichrome, or in 2.5% glutaraldehyde for transmission electron microscopy (JEM1400-Plus, JEOL Ltd., Tokyo, Japan) and toluidine blue staining.

Results

GLA mutations in probands

Four missense mutations and one deletion mutation in *GLA* were identified in five probands (*Figure 1*). A missense mutation consisting of a G-to-A transition in Exon 1 (c.128G > A) was found in Family A, leading to the substitution of an aspartic acid for glycine at Residue 43 (p.Gly43Asp). A novel single-base deletion mutation in Exon 7 (c.1241delT) was identified in Family B, which predicted a frameshift mutation and a putatively truncated protein (p.Leu414fsX4). A missense mutation consisting of a G-to-A transition in Exon 6 (c.811G > A) was found in Family C, leading to the substitution of a serine for glycine at Residue 271 (p.Gly271Ser). Another missense mutation consisting of a T-to-C transition in Exon 6 (c.950T > C) was identified in Family D, predicting the substitution of a threonine for isoleucine at Residue 317 (p.Ile317Thr). A novel missense mutation consisting of a G-to-C transition in Exon 1 (c.37G > C) was found in Family E, leading to the substitution of a proline for alanine at Residue 13 (p.Ala13Pro). This proband had significantly elevated levels of lyso-GL-3 (19.22 ng/mL, normal range: <1.11 ng/mL).

Clinical features in probands

Clinical recognition in four patients occurred by virtue of cardiac symptoms (exertional dyspnoea, palpitation, and chest pain) and in one patient due to renal insufficiency. Four of them presented with acroparesthesia, two with hypohidrosis and four were diagnosed with Stage IV or V chronic kidney disease. The onset of symptoms occurred between the ages of 20 and 55 years. One patient was referred to our hospital because of a non-ST-elevation myocardial infarction. He underwent percutaneous coronary intervention of the occluded left circumflex artery. Two patients developed atrial fibrillation and/or atrial flutter and one of them also experienced aborted cardiac arrest due to ventricular tachyarrhythmia. One patient received an implantable cardioverter-defibrillator due to bradycardia and HCM at the age of 59 years.

The surface 12-lead ECGs were strikingly abnormal in all probands. The QRS morphology of lead V1 was an R pattern in two patients and rS in the remaining patients. Four patients had ventricular pre-excitation patterns with short PR intervals, initial QRS slurring (delta waves), or both (*Figure 2*). All these patients showed markedly increased standard and/or precordial lead voltages with deep negative T-waves. The electrophysiological study in a proband with electrocardiographic pre-excitation excluded the presence of an atrioventricular accessory pathway. The details of electrophysiological study are provided in the Supporting Information.

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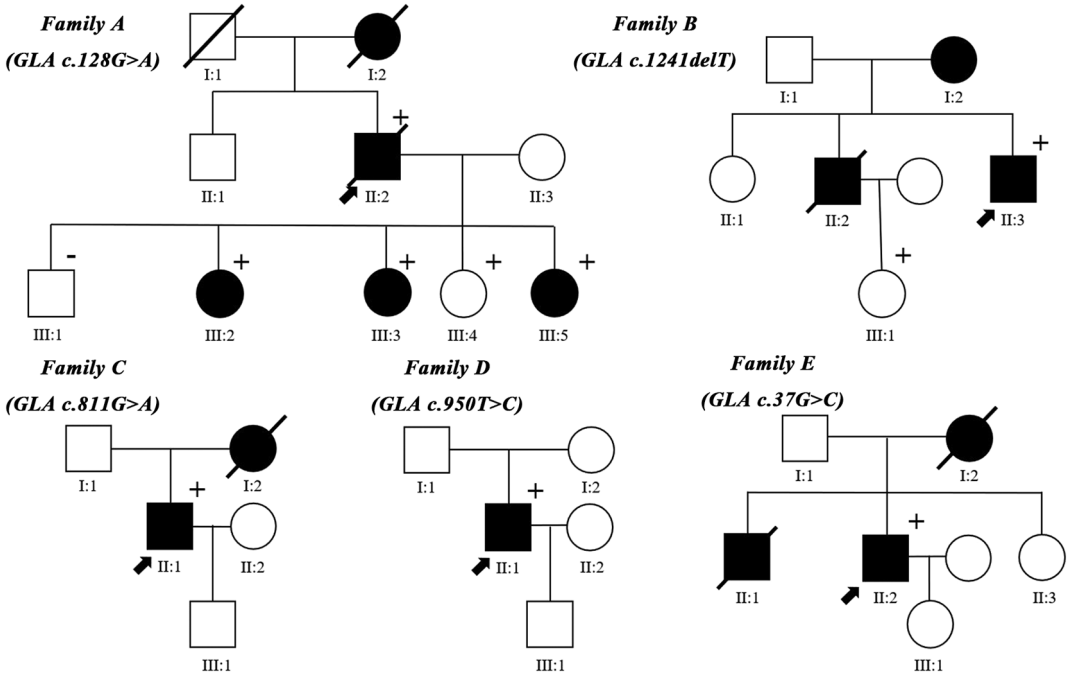
Figure 1 Family pedigree of the *GLA* mutant carrier in five families. Squares represent male individuals; circles represent female individuals; slashes represent deceased individuals; filled black shapes represent clinically affected family members; and arrows represent probands. Mutation carriers are labelled with a plus (+) sign, and non-carriers with a minus (−) sign.



Echocardiography showed left ventricular hypertrophy and diastolic dysfunction in all five probands (*Figure 3*, *Table 1*). The maximum septal wall thickness was 16–23 mm. The left ventricle tended to thin and dilate in one patient over 2 years of follow-up. Cardiac function progressively deteriorated in two patients with reduced left ventricular ejection fraction (40–45%) during the follow-up period, one of whom died of heart failure at the age of 66 years while awaiting heart transplantation. Left ventricular outflow tract obstruction was present in one patient (Valsalva-induced pressure gradient, 74 mmHg). He underwent alcohol septal ablation to relieve the symptoms.

Figure 2 Electrocardiogram of patient II:1 in Family D presented short PR (116 ms) intervals, positive delta waves in V1–2, and negative delta waves in leads I and V3–6 during sinus rhythm.

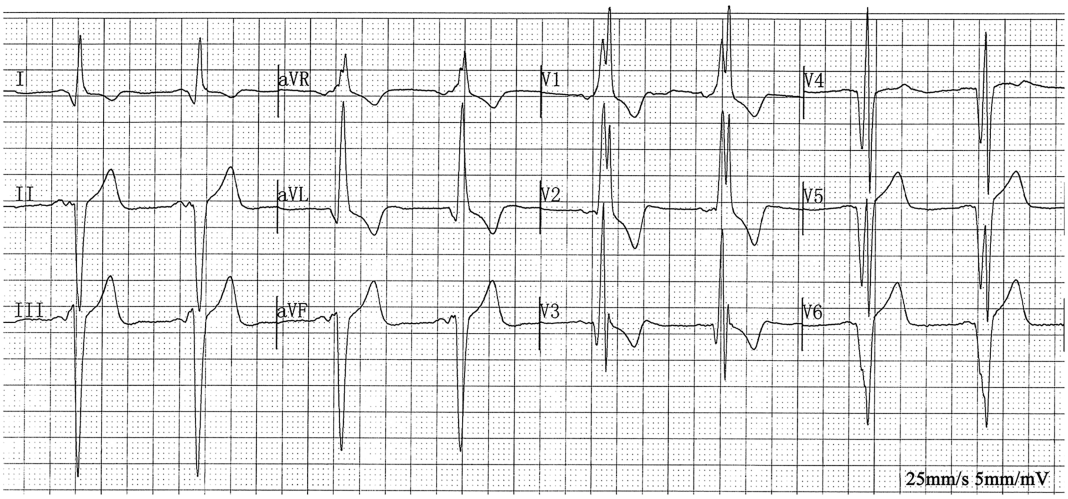


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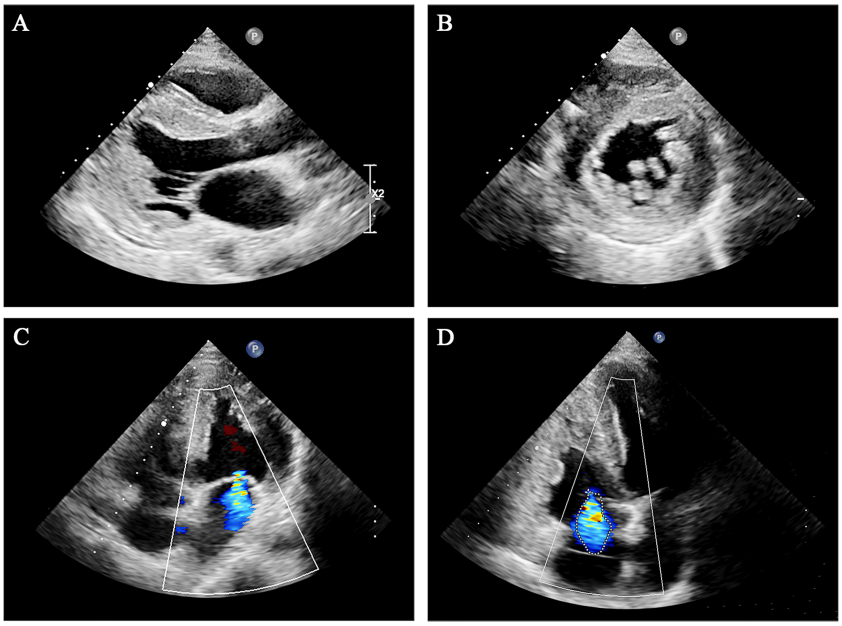
Figure 3 Echocardiogram of patient II:2 in Family E revealed left ventricular hypertrophy and moderate mitral and tricuspid regurgitation.



Moderate to severe mitral and tricuspid valve regurgitation was present in two patients (*Figure 3*). Cardiac magnetic resonance imaging of the proband in Family A demonstrated delayed gadolinium enhancement in the inferolateral wall of the left ventricle, suggesting potential myocardial fibrosis (*Figure 4*).

GLA mutations and clinical features in family members

In Family A, DNA was available from five offspring of the proband. All four daughters were carriers of the mutation. One daughter (III/2) complained of acroparesthesia for several years and another (III/5) had recurrent dizziness. Three daughters experienced episodes of syncope. Except for the daughter (III/5) presenting with short PR intervals (110 ms), ECGs and echocardiograms in mutation-positive family members were normal. The mother (I/2) of the proband experienced sudden death at the age of 60 years. She probably carried the *GLA* mutation, given that her son was clinically and genetically affected.

In Family B, DNA was also available from the proband's niece (III/1). She was heterozygous for the same mutation and had elevated lyso-GL-3 level (6.71 ng/mL, normal range: $<$1.11 ng/mL) but was asymptomatic and presented with normal cardiac examination and renal function at the age of 12 years. The mother (I/2) of the proband complained of exertional dyspnoea. His brother (II/2) was diagnosed with nephritis in the third decade with hypohidrosis and recurrent oedema. He died suddenly at the age of 41 years. The mutation was therefore inferred in subjects I/2 and II/2 of Family B, given their clinical manifestations and X-linked hereditary nature of this disease.

In Family C, the mother (I/2) of the proband had a history of asthma. She presented with exertional dyspnoea in the fifth decade of her life and suffered sudden death at the age of 60 years. In Family E, the mother (I/2) of the proband experienced sudden death at the age of 60 years. His brother (II/1) was diagnosed with end-stage renal failure at the age of 50 years with need of dialysis and died suddenly at the age of 53 years. The proband's daughter (III/1) was asymptomatic and had normal ECGs and echocardiograms. She should be a carrier given X-linked hereditary pattern of FD. However, she refused to perform genetic screening and assess plasma lyso-GL-3 levels. The clinical characteristics of these patients were detailed in *Table 1*.

Histological analysis

The proband of Family A underwent endomyocardial biopsy for pathological examination. Light microscopy revealed mild disarray of myocardial fibres with prominent cardiomyocyte atrophy and focal interstitial fibrosis [*Figure 5(A)* and *5(B)*]. Toluidine blue staining revealed diffusively distributed glycosphingolipid vacuoles in cardiomyocytes [*Figure 5(C)* and *5(D)*]. Transmission electron microscopy showed prominent myofibrillar dissolution with excess accumulation of

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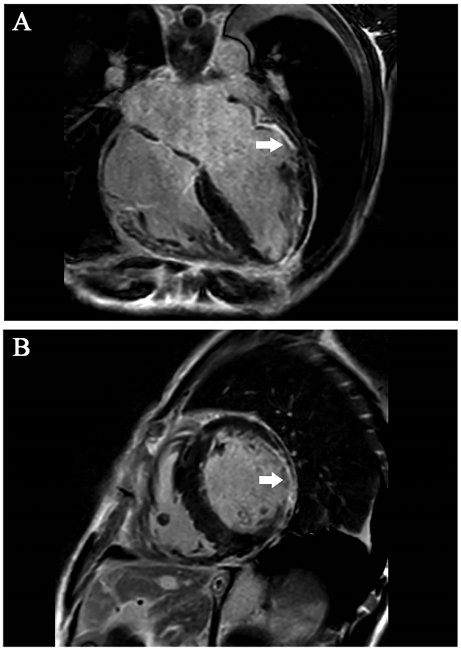
Table 1 Clinical and demographic findings in 16 patients with Fabry diseases

Family	Subject	Age (years)/ gender	Genetically affected	Clinical presentations	CKD/ stages	Echocardiogram						Arrhythmia	FU/age (years)	Death/age (years)
						IVS, mm	LVPW, mm	LVDd, mm	MR_2 cm^2	TR_2 cm^2	LVEF, %			
A	I:2	NA/F	NA	SD	NA	NA	NA	NA	NA	NA	NA	NA	—	+/60
A	II:2	63/M	+	Oedema, HF, acroparesthesia, hypohidrosis	+/IV	19 14	9.4 5	50 59	7.9 9.5	8.4 8.9	54 (63 years) 40 (64 years)	VP, AFL/AF, VT, SSS	3/66	+/66
A	III:2	33/F	+	Syncope, acroparesthesia	—	8.2	7.4	43	—	—	73	—	3/36	—
A	III:3	31/F	+	Syncope	—	10.3	7.2	43	—	—	67	—	3/34	—
A	III:4	30/F	+	—	—	8.6	8	41	—	—	77	—	3/33	—
A	III:5	29/F	+	Syncope	—	9.5	6.5	42	—	—	70	VP	3/32	—
B	I:2	73/F	NA	Exertional dyspnoea	—	NA	NA	NA	NA	NA	NA	NA	1/74	—
B	II:2	NA/M	NA	SD, oedema, hypohidrosis	+/V	NA	NA	NA	NA	NA	NA	NA	—	+/41
B	II:3	43/M	+	Oedema, acroparesthesia, hypohidrosis	+/V	17	17	51	—	—	71	—	3/46	—
B	III:1	12/F	+	—	—	7	7	46	—	—	60	—	1/13	—
C	I:2	NA/F	NA	SD, exertional dyspnoea	NA	NA	NA	NA	NA	NA	NA	NA	—	+/63
C	II:1	63/M	+	Acroparesthesia, ACS	+/V	22	16	44	2.2	—	67	VP	1/64	—
D	II:1	51/M	+	Exertional dyspnoea	—	23	22	36	3.9	—	58	VP	2/53	—
E	I:2	NA/F	NA	SD, stroke	NA	NA	NA	NA	NA	NA	NA	NA	—	+/61
E	II:1	NA/M	NA	SD	+/V	NA	NA	NA	NA	NA	NA	NA	—	+/53
E	II:2	63/M	+	Exertional dyspnoea, HF, syncope, oedema, acroparesthesia, angiokeratomas	+/V	15 16	15 13	48 50	— 5.2	— 5.5	54 (48 years) 45 (63 years)	VP, AFL/AF, SSS, AVB	—	—
E	III:1	36/F	NA	—	—	8	8	43	1.8	—	72	—	1/37	—

ACS, acute coronary syndrome; AFL/AF, atrial flutter/atrial fibrillation; AVB, atrioventricular block; CKD, chronic kidney disease; F, female; FU, follow-up; HF, heart failure; IVS, intra-ventricular septum; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall; M, male; MR, mitral regurgitation; NA, not available; SD, sudden death; SSS, sick sinus syndrome; TR, tricuspid regurgitation; VP, ventricular pre-excitation patterns with short PR intervals, initial QRS slurring (delta waves), or both; VT, ventricular tachycardia.

Figure 4 Late gadolinium enhancement of the proband in Family A. Cardiac magnetic resonance imaging revealed defect of perfusion and prominent delayed gadolinium enhancement in inferolateral segment. Arrow indicates delayed gadolinium enhancement.



amorphous vacuoles and central vacuolar degeneration of myocytes called 'zebra bodies' [*Figure 5(E)* and *5(F)*].

Discussion

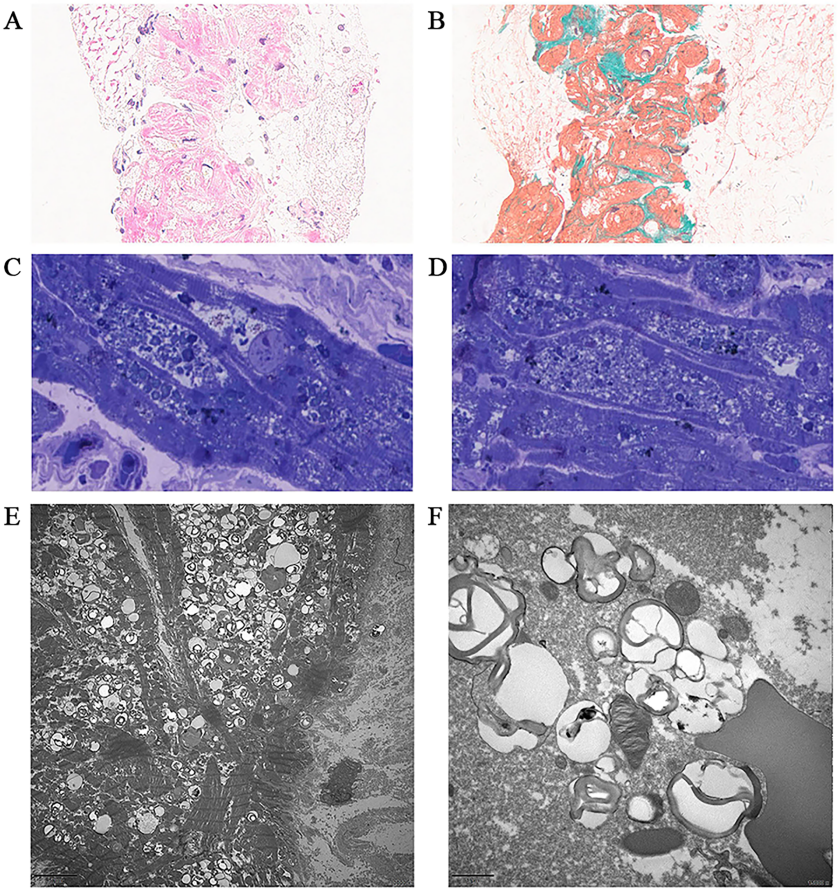
This study has several important findings relevant to the clinical management of FD. First, we expanded the phenotypic and genetic spectrum of *GLA*-related disorders. We identified five *GLA* mutations in five unrelated families, including three previously reported missense mutations (c.128G > A, c.811G > A, and c.950 T > C), a novel missense mutation (c.37G > C), and a novel deletion mutation (c.1241delT). Although three missense mutations have been reported previously in genetic studies, neither a detailed description of the clinical characteristics nor phenotypes of family members associated with these mutants were available.[4,6–9] Second, phenotypic expression of FD was highly heterogeneous in Chinese families. Male patients demonstrated significantly cardiac structural and electrocardiographic abnormalities and renal involvement. Third, female patients were less likely than male patients to develop severe disorders; however, regular cardiac evaluations were still critical because of potential risk of sudden death. Fourth, our study highlighted the importance of genetic screening of the *GLA* gene for early identification of patients with FD.

The clinical manifestations of our patients demonstrated high heterogeneity even within family members carrying the same *GLA* mutation. Male patients with FD presented with 100% penetrance in our study, whereas female patients show incomplete penetrance with variable expressivity from asymptomatic to severe. Five male probands demonstrated a high prevalence of left ventricular hypertrophy (5/5, 100%), whereas six female patients who underwent echocardiography demonstrated normal cardiac structure and function. Electrocardiographic pre-excitation occurred in 80% (4/5) of men and 16.7% (1/6) of women. Six patients (6/14, 42.9%) had reduced renal function and all were men (6/7, 85.7%). The potential mechanism for this phenotypic difference may be associated with the X-linked nature of inheritance and skewed X-chromosome inactivation.[10]

Of the 17 patients definitely or possibly diagnosed with of FD, 3 female patients (subject I/2 in Family A, subject I/2 in Family C, and subject I/2 in Family E) and 2 male patients (subject II/2 in Family B and subject II/1 in Family E) died suddenly from unknown causes and 1 male patient (subject II/2 in Family A) died of progressive heart failure, by 41 to 66 years of age. Although female patients were affected less severely than male patients, our data suggested that FD could also lead to sudden death in female patients, suggestive of the importance of regular cardiology evaluations and long-term follow-up in these patients.

Electrocardiographic abnormalities typically present with short PR intervals and later atrioventricular block in patients with FD.[11,12] In our study, electrocardiographic pre-excitation was present in four male probands and one heterozygous female. An electrophysiology study of the proband in Family A ruled out the presence of atrioventricular accessory pathways, which was consistent with published data.[13] The previous study indicated that the short PR interval in FD can result from accelerated conduction in the atrioventricular node. However, enhanced atrioventricular node conduction cannot explain the presence of QRS slurring mimicking ventricular pre-excitation. Our recent study on Danon disease, another lysosomal storage disorder, proved that ventricular pre-excitation was because of the presence of fasciculoventricular connections, rather than abnormal atrioventricular bypass tracts or accelerated atrioventricular node conduction.[5,14] Both FD and Danon disease are caused by lysosomal dysfunction as a consequence of deficiency of a single enzyme or lysosome-associated membrane protein.[15] Therefore, we speculate that a similar mechanism with Danon disease may also be responsible for the electrocardiographic abnormalities in patients with FD. Previous cardiac histopathology of FD verified that all cardiac tissues, including the

Figure 5 Histopathological analysis of cardiac tissue obtained from the proband in Family A. (A) The specimens of ventricular myocardium showed mild disarray of myocardial fibres with cardiomyocytes atrophy and intracellular vacuolation (haematoxylin and eosin staining). (B) Masson's trichrome staining showed focal interstitial fibrosis. (C, D) Toluidine blue staining revealed the accumulation of metachromatic substance in the cytoplasm of cardiomyocytes. (E) Electron microscopy demonstrated prominent myofibrillar dissolution with excess accumulation of amorphous vacuoles (bar = 5 μm). (F) Electron microscopy presented some central vacuolar degeneration of myocytes called 'zebra bodies' (bar = 1 μm).



conducting system, were involved and contained glycosphingolipid deposits,[16] suggestive of pre-excited ECG caused by fasciculoventricular connections possible because of the disruption of the His bundle and Purkinje fibre insulation. Additionally, the high incidence of progression from short PR intervals to atrioventricular block in patients with FD also supports that the ventricular pre-excitation pattern is related to a completely infranodal connection in accordance with the fasciculoventricular pathway.[12]

Early identification of FD is extremely important for patient care because rapid clinical deterioration leads to cardiac death.[17,18] Clinical heterogeneity, rarity of the disease, and early cardiac presentation similar to HCM increase the risk of delayed diagnosis of FD. Our cases suggest that extracardiac manifestations, especially renal insufficiency, provide important clues to further distinguish left ventricular hypertrophy associated with *GLA* mutations from those caused by defects in other disease-causing genes in males.

Limitations and future perspectives

In the present study, not all family members underwent molecular screening for the *GLA* gene, and seven patients were diagnosed with FD on the basis of their clinical manifestations and X-linked hereditary nature of this disease. Only one proband and one female patient checked their lyso-GL-3 levels in our study. The post-mortem examination was not performed in the cases of sudden death; therefore, a definite relationship between sudden death and FD was not established in these cases. None of the patients received enzyme replacement therapy with recombinant α-Gal A. On the one hand, it was commercially not available before in China. On the other hand, the delayed diagnosis of FD in our probands made them miss the best time for specific therapy of FD cardiomyopathy. Future multicentre or national studies are needed to obtain the clinical and genetic characteristics of FD patients in China as well as their response to specific therapy.

Conclusions

We described five unrelated families with *GLA* mutations that cause FD. The clinical manifestations were highly heterogeneous even within the same family. Male patients demonstrated a high prevalence of left ventricular hypertrophy and renal dysfunction, whereas female patients showed relatively low risks for structural heart disease and kidney failure. Our study underlines the importance of molecular screening of the *GLA* gene for early identification and clinical decision making in patients with FD.

Acknowledgements

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Conflict of interest

All authors report no conflicts.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Tracings obtained from the electrophysiological study of the proband in Family A. Atrial pacing demonstrated no change in the degree of ventricular pre-excitation and QRS morphologies, suggestive of antegrade conduction via atrioventricular node rather than atrioventricular accessory pathway. Ventricular pacing demonstrated 2:1 and concentric VA conduction.

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