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CASE REPORT

GLA and MYH7 Double Mutation Causing Fabry Disease with Familial Hypertrophic Cardiomyopathy: A Case Report

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Purpose: To explore clinical manifestations and treatment strategies in a patient with dual GLA and MYH7 mutations causing Fabry disease (FD) and hypertrophic cardiomyopathy (HCM), emphasizing the value of comprehensive genetic testing in complex cardiomyopathies.

Patients and Methods: We studied a 40-year-old Han Chinese woman with FD and familial HCM due to GLA and MYH7 mutations. Diagnosis involved echocardiography, electrocardiography, cardiac MRI, genetic sequencing, and α-galactosidase A activity assays. Treatment included pharmacotherapy (rivaroxaban, sacubitril/valsartan, bisoprolol, spironolactone, torasemide), agalsidase α enzyme replacement, and surgery for left ventricular outflow tract obstruction.

Results: The patient had severe left ventricular hypertrophy (interventricular septum 35 mm) and significant obstruction (LVOTG 121 mmHg). After 3 months, the 6-minute walk test distance increased from 132 to 369 meters, NT-proBNP levels dropped from 2164 to 1911 pg/mL, and the KCCQ score rose from 30.9 to 85.5, indicating improved quality of life.

Conclusion: Comprehensive genetic testing is crucial for diagnosing complex cardiomyopathies. A multidisciplinary approach effectively improves symptoms and quality of life in patients with dual genetic mutations.

Keywords: Fabry disease, hypertrophic cardiomyopathy, MYH7 gene, GLA gene, enzyme replacement therapy, double mutation

Introduction

Left ventricular hypertrophy (LVH) is a frequent clinical manifestation with diverse etiologies, posing significant diagnostic challenges. Fabry disease, an X-linked lysosomal storage disorder caused by GLA gene mutations, results in α-galactosidase A deficiency. The subsequent accumulation of globotriaosylceramide (Gb-3) and lyso-Gb3 across multiple organs leads to progressive pathology and potentially fatal complications. Cardiac involvement is prominent in Fabry disease, contributing significantly to mortality, with 30–60% of patients developing LVH. MYH7 gene mutations are a primary cause of familial hypertrophic cardiomyopathy, affecting myocardial structure and electrical conduction. The coexistence of these conditions may exacerbate organ damage, although such cases are rarely documented. We present a case of left ventricular hypertrophy with pathogenic variants in both GLA and MYH7 genes, highlighting the clinical complexity of overlapping rare genetic disorders and the necessity for precision medicine approaches. This case underscores the diagnostic and therapeutic challenges in managing patients with concurrent "metabolic" and "structural" cardiomyopathies.

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Case Description

Patient Presentation

A 40-year-old Han Chinese woman presented with recurrent chest tightness and shortness of breath for over 20 years, which had recently worsened with bilateral lower extremity edema for 1 week. Initial echocardiography revealed hypertrophic obstructive cardiomyopathy, characterized by an interventricular septum (IVS) thickness of 32 mm, a left ventricular posterior wall (LVPW) thickness of 9 mm, and a left ventricular outflow tract gradient (LVOTG) of 121 mmHg. These findings were accompanied by left ventricular outflow obstruction and positive systolic anterior motion (SAM). Laboratory tests showed elevated cardiac troponin I (cTnI) at 0.12 μg/L (reference range: 0–0.06 μg/L) and N-terminal pro-brain natriuretic peptide (NT-proBNP) at 1844 pg/mL (reference range: 0–125 pg/mL). In June 2014, the patient underwent alcohol septal ablation of the second septal branch. Post-procedure, the LVOTG decreased to a nadir of 38 mmHg. She was prescribed a regimen including spironolactone 20 mg, perindopril 4 mg, and sustained-release diltiazem 90 mg, each taken once daily. However, despite this therapeutic approach, her symptoms persisted. In July 2023, a repeat echocardiography demonstrated disease progression, with the IVS thickness increasing to 35 mm, LVPW measuring 10 mm, LVOTG rising to 96 mmHg, and SAM remaining evident. Electrocardiography revealed atrial fibrillation. She subsequently underwent left ventricular outflow tract relief surgery at Shanghai Jiao Tong University Affiliated Renji Hospital, without pathological examination. Post-surgery, her LVOTG decreased to 17 mmHg. Her medication regimen was modified to include rivaroxaban 20 mg daily for anticoagulation, sacubitril/valsartan 50 mg twice daily, bisoprolol 2.5 mg daily, spironolactone 20 mg daily, and torasemide 5 mg daily. Despite these interventions, in June 2024, she experienced clinical deterioration, with worsening chest tightness, dyspnea, and bilateral lower extremity edema. No history of hypertension or valvular disease was documented. Her medical history was notable for the absence of hypertension or valvular disease. Family history revealed muscle hypertrophy in her mother, two maternal aunts.

Physical Examination

The blood pressure of patient was 98/53 mmHg, the heart border was enlarged to the left, and rate and rhythm were irregular due to atrial fibrillation. Bilateral lower extremity edema was observed; however, there were no signs of angiokeratomas or other dermatological manifestations.

Diagnosis Process

After hospitalization, the patient completed relevant tests. cTnI was (0.15 μg/L; reference range: 0–0.03) and NT-Pro-BNP (2164.1 pg/mL; reference range: 0–125). Complete blood count, C-reactive protein (CRP), and urinalysis were unremarkable. Coagulation studies showed prothrombin time (PT) 14.0 s (reference range: 22.3–32.5), International Normalized Ratio (INR) 1.23, and activated partial thromboplastin time (APTT) 37.0 s (reference range: 22.3–32.5). Lactate dehydrogenase was elevated at 263 U/L (reference range: 103–227). Electrocardiogram (Figure 1) indicated atrial fibrillation with complete left bundle branch block. Cardiac ultrasound (Figure 2) showed left atrium (LA) 48 mm, IVS 20 mm, LVPW 10 mm, E/e' 8, left ventricular ejection fraction (LVEF) 64%, LVOTG 2 mmHg; These measurements indicated asymmetric left ventricular hypertrophy, characterized by disproportionate papillary muscle hypertrophy and reduced strain in the mid-inferolateral wall segment. Cardiac MR demonstrated hypertrophic cardiomyopathy (Figure 3), myocardial fibrosis (Figure 3). These images were consistent with FD. Finally, α-Gal A activity at 1.3 μmol/L/h (reference range: 2.20–17.65 μmol/L/h), lyso-GL-3 1.09 ng/mL (reference value: <1.11ng/mL) and GLA gene mutation (Figure 4) located in the chrX:100654735,c.640–801G > A confirmed the diagnosis: FD. Considering the X-linked inheritance pattern of Fabry disease, we performed family screening and identified GLA mutations in the patient's mother, maternal grandmother, and one maternal uncle. Notably, two maternal aunts and one of their offspring did not carry the GLA mutation but instead harbored a MYH7 mutation—specifically c.2141T>C (p.Leu714Pro) (Figure 5). This heterozygous variant is associated with familial hypertrophic cardiomyopathy type 1 (autosomal dominant, disease-causing) but has uncertain clinical significance. The comprehensive genetic investigation ultimately revealed that the patient, her mother, maternal grandmother, and one maternal uncle all carried the GLA mutation, while two maternal

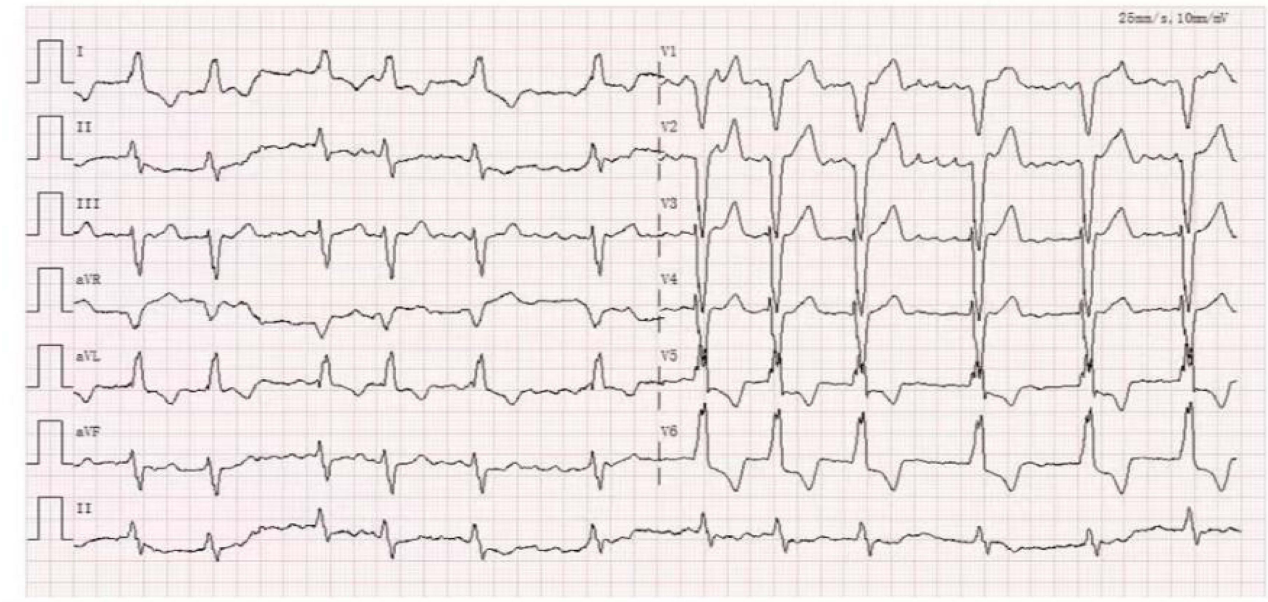

Figure 1 Electrocardiography confirmed atrial fibrillation with complete left bundle branch block.

aunts and one of their offspring carried the MYH7 mutation. Most significantly, both the patient and her mother harbored dual mutations affecting both GLA and MYH7, an exceptionally rare genetic phenomenon. The complete family pedigree (Figure 6).

Our multidisciplinary team developed an individualized treatment approach that included general management (limitation of strenuous physical activity, close monitoring of cardiac rhythm, heart rate, and blood pressure), pharmacological therapy (rivaroxaban 20 mg daily for anticoagulation, sacubitril/valsartan 50 mg twice daily, bisoprolol 2.5 mg daily, spironolactone 20 mg daily, and torasemide 5 mg daily), and enzyme replacement therapy with agalsidase α concentrate at 0.2 mg/kg body weight, administered intravenously every two weeks. After 3 months of follow-up, the patient's symptoms of chest tightness and shortness of breath improved, and her exercise tolerance increased. Her functional capacity, as objectively measured by the 6-minute walk test (6MWT), increased from 132 meters to 369 meters. Hemodynamic parameters stabilized, with blood pressure readings between 90–102/60–70 mmHg and heart rate controlled at 60–70 beats per minute. NT-proBNP levels decreased from 2164 pg/mL to 1911 pg/mL. Her Kansas City Cardiomyopathy Questionnaire (KCCQ) score, a validated measure of heart failure symptoms and their impact on quality of life, improved markedly from 30.9 to 85.5.

Discussion

This case highlights the diagnostic and therapeutic challenges of dual genetic mutations in GLA and MYH7 causing Fabry disease and hypertrophic cardiomyopathy (HCM). The patient's early-onset and severe phenotype (IVS 35 mm, LVOTG 121 mmHg) suggest a potential synergistic effect of the "double-hit" mechanism, where metabolic dysfunction from GLA mutation and structural abnormality from MYH7 mutation converge to exacerbate cardiac pathology.

FD is a rare lysosomal storage disorder caused by mutations in the GLA gene. The global prevalence of Fabry disease is estimated to be between 1 in 40,000 and 1 in 170,000.[1] When GLA mutations reduce or eliminate α-galactosidase A (α-Gal A) activity, metabolic substrates such as globotriaosylceramide (Gb3) and lyso-Gb3 accumulate across various organs and tissues, triggering a cascade of multi-organ dysfunction.[2,3] This disease affects multiple systems, including the heart (ventricular hypertrophy, arrhythmias, valvular regurgitation, heart failure), nervous system (neuropathic pain, such as acroparesthesia, stroke, white matter lesions, hypohidrosis, or hearing impairment), kidneys (proteinuria, renal insufficiency), skin (angiokeratomas), digestive tract (diarrhea, constipation, postprandial abdominal pain), eyes (corneal opacity, retinal vascular lesions, cataracts), and others. The clinical diagnosis of Fabry disease primarily relies on clinical

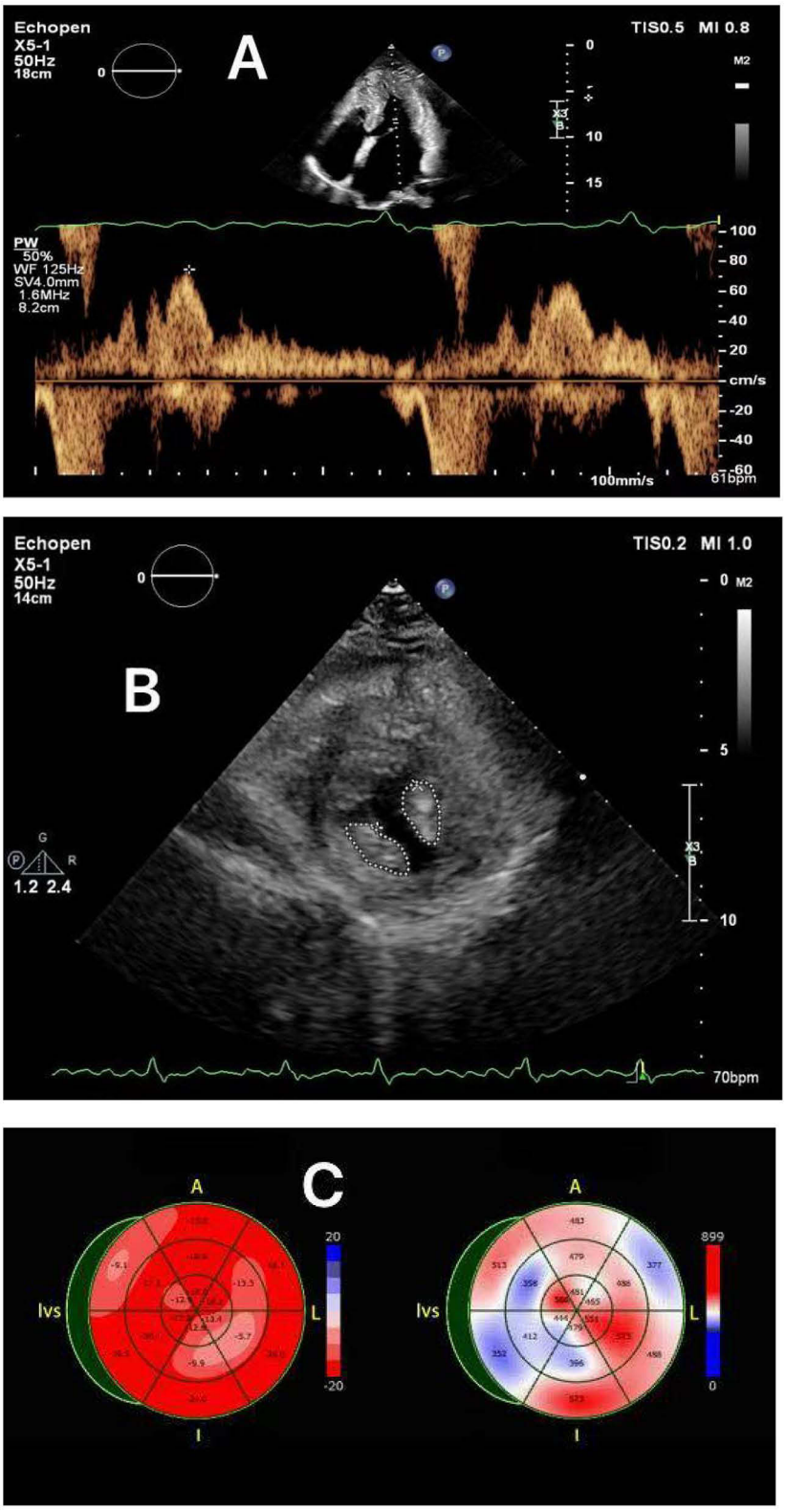

Figure 2 Doppler echocardiography confirmed LVOTG 2 mmHg (**A**) and asymmetric left ventricular hypertrophy with disproportionate papillary muscle hypertrophy (**B**) and reduced strain in the mid-inferolateral wall segment (**C**).

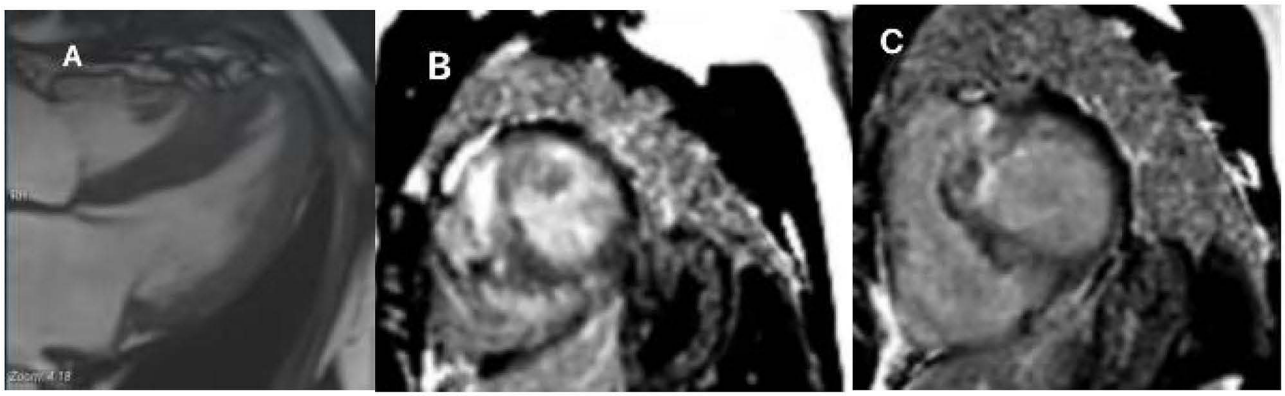

Figure 3 Cardiac Magnetic Resonance Imaging, specifically the cine sequence four-chamber view, revealed diffuse left ventricular myocardial thickening most pronounced in the interventricular septum (**A**). Late gadolinium enhancement (LGE) was evident throughout the proximal, middle, and distal interventricular septum, adjacent anterior wall (**B**), and anterior papillary muscle (**C**).

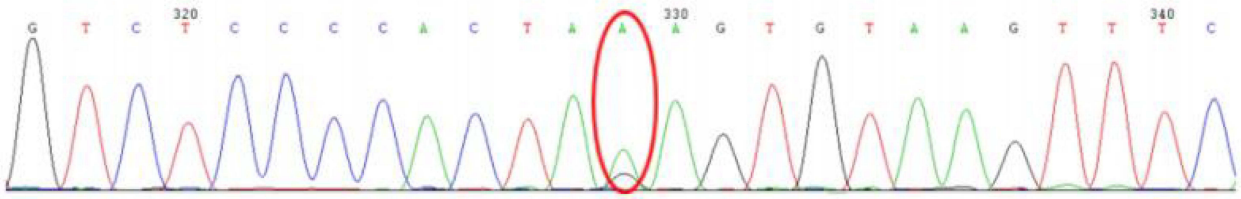

Figure 4 Gene sequencing identified a GLA gene mutation (chrX:100654735,c.640–801G > A). The red oval highlights the mutation site.

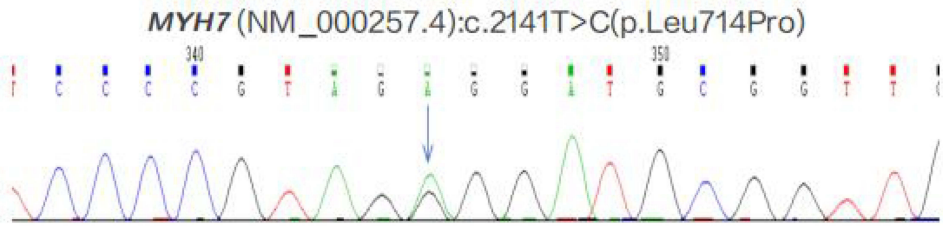

Figure 5 Gene sequencing identified MYH7 gene mutation (NM_000257.4):c.2141T>C (p.Leu714Pro).

presentation, biochemical tests, specific enzyme assays, genetic testing, and histopathology of affected organs.[4] Fabry disease can be classified into classic or late-onset phenotypes. Classic cases are characterized by absent or severely diminished α-galactosidase A activity, leading to rapid disease progression with multi-system involvement. In contrast, late-onset phenotypes, often caused by missense variants such as c.640–801G>A (in Taiwan calls IVS4+919G>A), present with a more chronic clinical course, predominantly affecting the heart (cardiac variant). These patients typically have residual enzyme activity and may be asymptomatic or exhibit subtle clinical manifestations during childhood and adolescence.[5] Current guidelines highlight that the predominant etiology of HCM involves genetic variants affecting sarcomeric proteins, with MYH7 being one of the most frequently mutated genes.[6,7]

The coexistence of GLA IVS4+919G>A and MYH7 p.Leu714Pro mutations in our proband likely created a detrimental synergy. The GLA mutation leads to sphingolipid accumulation, disrupting lysosomal function and impairing cellular energy metabolism via the lysosomal-mitochondrial axis.[2,8] Concurrently, the MYH7 p.Leu714Pro mutation, located in the highly conserved ATP-binding pocket of the myosin head, is predicted to compromise myofilament sliding efficiency and increase myocardial stiffness.[6,9] This "metabolic-structural" double burden may explain the accelerated disease progression and severe LVOT obstruction observed, consistent with reports that double

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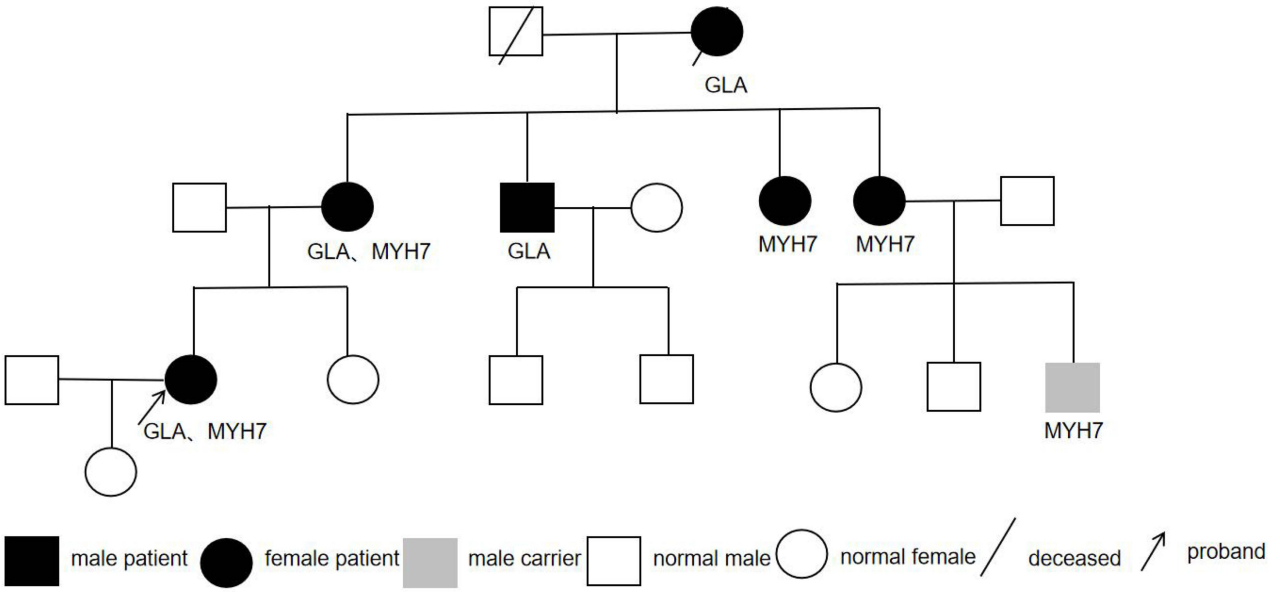

Figure 6 Pedigree of a family with HCM mutation.

mutation carriers often exhibit more severe phenotypes than single heterozygotes.[10,11] For instance, Zhao et al reported that families with TNN/MYH7 double mutations had a 26% greater interventricular septal thickness than single mutation families.[11] The variable penetrance observed within this family (eg, some mutation carriers were asymptomatic) underscores the influence of genetic modifiers and environmental factors, a phenomenon also noted in other inherited cardiac conditions.[12] Further family studies with expanded genotyping could help elucidate these modifying factors.

Our treatment strategy was meticulously designed following a hierarchy of clinical priorities, guided by the 2023 ESC Cardiomyopathy Guidelines[3] and the 2024 TSOC Fabry Disease Consensus.[5] The decision to prioritize surgical relief of the severe LVOT obstruction before initiating enzyme replacement therapy (ERT) was driven by the imperative to first address the immediate life-threatening hemodynamic compromise, a principle clearly outlined in guideline recommendations for managing significant obstruction.[13] Initiating ERT in the face of such a severe mechanical impediment would not have yielded prompt symptomatic relief. The rationale for employing standard-dose agalsidase α, despite near-normal lyso-Gb3 levels, was grounded in the presence of substantial replacement fibrosis on CMR—an objective marker of irreversible Fabry cardiomyopathy—and the patient's specific GLA mutation, an approach substantiated by outcome studies in analogous Asian cohorts.[14] Our pharmacotherapy was deliberately selected to target the dual pathophysiology: sacubitril/valsartan was utilized to address both Fabry-related myocardial fibrosis and HCM-impaired diastolic function,[2,15] while low-dose bisoprolol was chosen to control atrial fibrillation without augmenting the dynamic outflow tract obstruction, a critical precaution in HCM management.[16] The marked clinical improvement following this combined, pathophysiology-driven approach suggests a potential for synergistic benefit, warranting further investigation in larger cohorts.[17]

A key limitation of this study is the focus on a single proband and her family. While the familial genetic data is informative, a broader analysis of genotype-phenotype correlations in double mutation carriers is needed. Furthermore, the pathophysiological interplay between these two mutations warrants deeper investigation through basic science studies.

Conclusion

This case underscores that in patients presenting with early, severe hypertrophy and a complex family history, comprehensive genetic testing is essential for an accurate diagnosis. The coexistence of FD and HCM mutations may lead to a synergistic worsening of the clinical phenotype. A multidisciplinary treatment strategy, addressing both the metabolic and structural aspects of the disease, can significantly improve patient outcomes. This case also highlights the

critical importance of thorough family screening and long-term follow-up to fully understand the penetrance and expressivity of such rare double mutations.

Informed Consent

Institutional approval was not required by the Ethics Committee of The First Hospital of Putian City to publish this case details. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The patient's identity and medical information have been fully protected.

Disclosure

The authors report no conflicts of interest in this work.

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