**Case Report**

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# A novel *GLA* mutation in a Korean boy with an early cardiac manifestation of Fabry disease

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Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by the deficiency of α-galactosidase A. Patients with classical FD present acroparesthesia, hypohidrosis, cornea verticillata, disseminated angiokeratoma, and microalbuminuria in childhood, and develop life-threatening renal, cardiac, and cerebrovascular complications typically after the fourth decade of life. To date, more than 700 mutations responsible for FD have been identified in the human *GLA* gene. Herein, we report a novel *GLA* mutation, c.1117_1141del25 (p.Gly373Profs*10), identified in an 11-year-old Korean boy with FD presenting early cardiac and neurologic manifestation and in other affected family members. The boy had acroparesthesia, hypohidrosis, cornea verticillata, and left ventricular hypertrophy. His mother and sister also had acroparesthesia. Two males on the mother's side had similar pain and died of unknown causes. The plasma α-galactosidase A activity (4.1 nmol/hr/mg protein) of the patient was markedly lower than the mean value of the controls. The plasma level of globotriaosylsphingosine was elevated in the patient and all the carriers. We concluded the novel *GLA* mutation c.1117_1141del25 is a pathogenic mutation for FD, probably related to the early cardiac manifestation of FD.

**Key words:** Fabry disease, Lysosomal storage diseases, α-Galactosidase.

## Introduction

Fabry disease (FD; OMIM: 301500) is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene, which encodes the lysosomal hydrolase α-galactosidase A. The deficiency of this enzyme causes the progressive accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) in the lysosomes of various cells, subsequently leading to significant cellular dysfunction and organ damage. Patients with classical FD often present with characteristic features such as acroparesthesia, hypohidrosis, cornea verticillata, disseminated angiokeratoma, and microalbuminuria during early childhood and adolescence. In later stages, they may develop progressive kidney disease, hypertrophic cardiomyopathy, and cerebrovascular disease, which eventually lead to significant morbidity and mortality [1-4]. In contrast, patients with non-classical FD tend to present mild symptoms, occasionally limited to heart or kidney conditions [5]. Therefore, the diagnosis of FD is often delayed or missed completely because of the wide variety of symptoms [6]. The average delay from the onset of symptoms to diagnosis is more than a decade [6]. The introduction of enzyme replacement therapy (ERT) may make it possible to halt or even reverse

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the progress of symptoms before irreversible organ damage occurs [7]. Thus, early diagnosis of FD before the development of organ dysfunction is very important in improving a patient's outcome and quality of life.

Herein, we report the identification of a novel *GLA* mutation, c.1117_1141del25, in a Korean family with FD experiencing predominantly cardiac and neurologic symptoms.

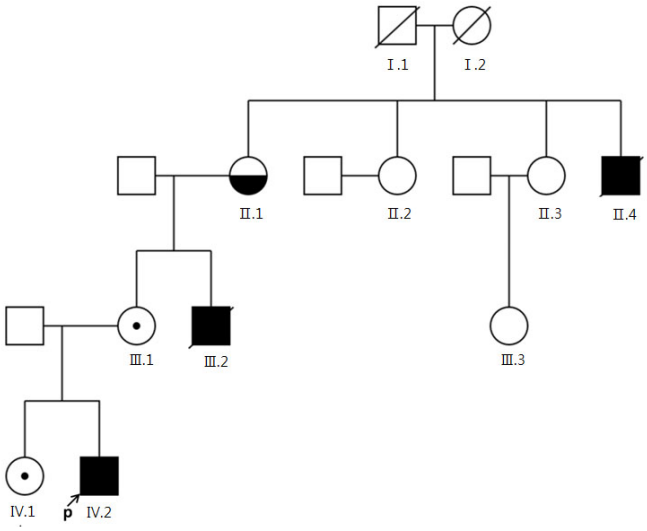


**Fig. 1.** Pedigree of the family harboring the c.1117_1141del25 *GLA* gene mutation. The squares and circles indicate males and females, respectively. The arrow indicates the proband. The shaded squares indicate affected males. The circles with dots indicate heterozygous females. The black and white circle indicates the suspected female carrier. A slash through a circle or a square indicates a deceased individual.

## Case

An 11-year-old boy was referred to our pediatric neurology clinic because of chronic pain with acute exacerbation on both fingertips and toes and fever for 2 days. He had symmetric burning or stabbing pain in his distal extremities, which waxed and waned over the past 3 years. His pain was aggravated by heat and cold exposure or physical activities. He also presented with anhidrosis and fatigue. His perinatal history was uneventful. His mother's uncle (II.4) and his uncle (III.2) experienced similar pain in their childhood and adolescence and died of unknown causes in their mid-twenties (Fig. 1). His grandmother (II.1) also had similar pain and mitral valve replacement in her fifties, and has had repeated episodes of stroke thereafter. His mother (III.1) and sister (IV.1) have similar, but mild pain. On physical examination, no skin lesion such as angiokeratoma was seen, but cornea verticillata was observed in an ophthalmologic examination. His neurologic examination findings were normal except for heat or cold intolerance on his hands and feet. The findings of nerve conduction studies and electromyography were unremarkable, but autonomic sweating response was absent on the quantitative sudomotor axon reflex test. His echocardiogram showed an increased thickness of the interventricular septum (11.1 mm; Z-score, 2.65) and left ventricular (LV) posterior wall (8.8 mm; Z-score, 2.19), suggestive of left ventricular hypertrophy (LVH) in the M-mode measurements (LV mass index, 120 g/m$^2$) (Fig. 2A). An electrocardiogram revealed a sinus rhythm with signs of LVH, tall R-waves in the $V_5$-$V_6$ leads, and deep S-waves in the $V_2$ lead (Fig. 2B).

On the basis of the clinical and laboratory findings, along with

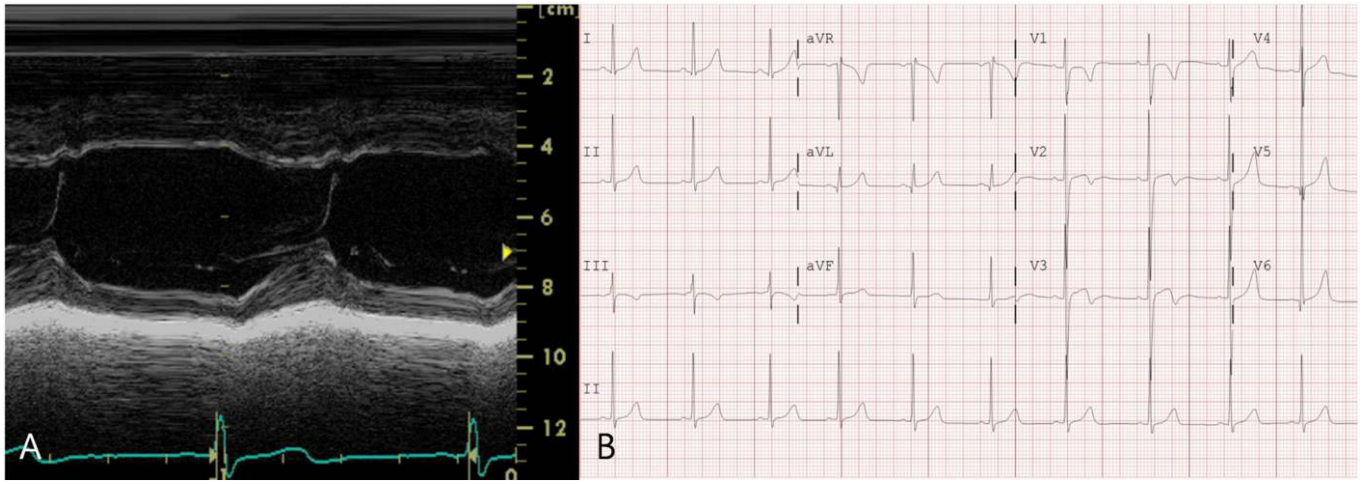


**Fig. 2.** (A) Echocardiogram of the proband shows the presence of left ventricular hypertrophy (LVH). (B) The electrocardiogram of the proband reveals a sinus rhythm with signs of LVH, tall R-waves in the $V_5$-$V_6$ leads, and deep S-waves in the $V_2$ lead.

the family history, we suspected the patient had FD. Accordingly, we tested α-galactosidase A enzyme activities and performed DNA sequencing of the *GLA* gene using serum samples collected from the patient, his mother, and sister. The patient's GLA enzyme activity in blood leukocytes was markedly lower than the mean value of the controls (4.1 nmol/hr/mg protein vs. 72.9 nmol/hr/mg protein). The cutoff value that indicates below-normal α-galactosidase A enzyme activity in plasma is 35 nmol/hr/mg protein. α-Galactosidase A enzyme activities in his mother and sister were 50.1 and 54.3 nmol/hr/mg protein, respectively, which were within the normal limit (normal controls, 103 nmol/hr/mg protein). DNA sequencing of the *GLA* gene revealed that the patient, his mother, and sister carried a novel mutation, c.1117_1141del25 (p.Gly373Profs*10), in exon 7 (Fig. 3). The levels of plasma lyso-Gb3 were increased in all affected family members, especially in the male patient (Table 1).

After identifying the *GLA* mutation, all affected female carriers revisited our clinics for detailed assessments including car-

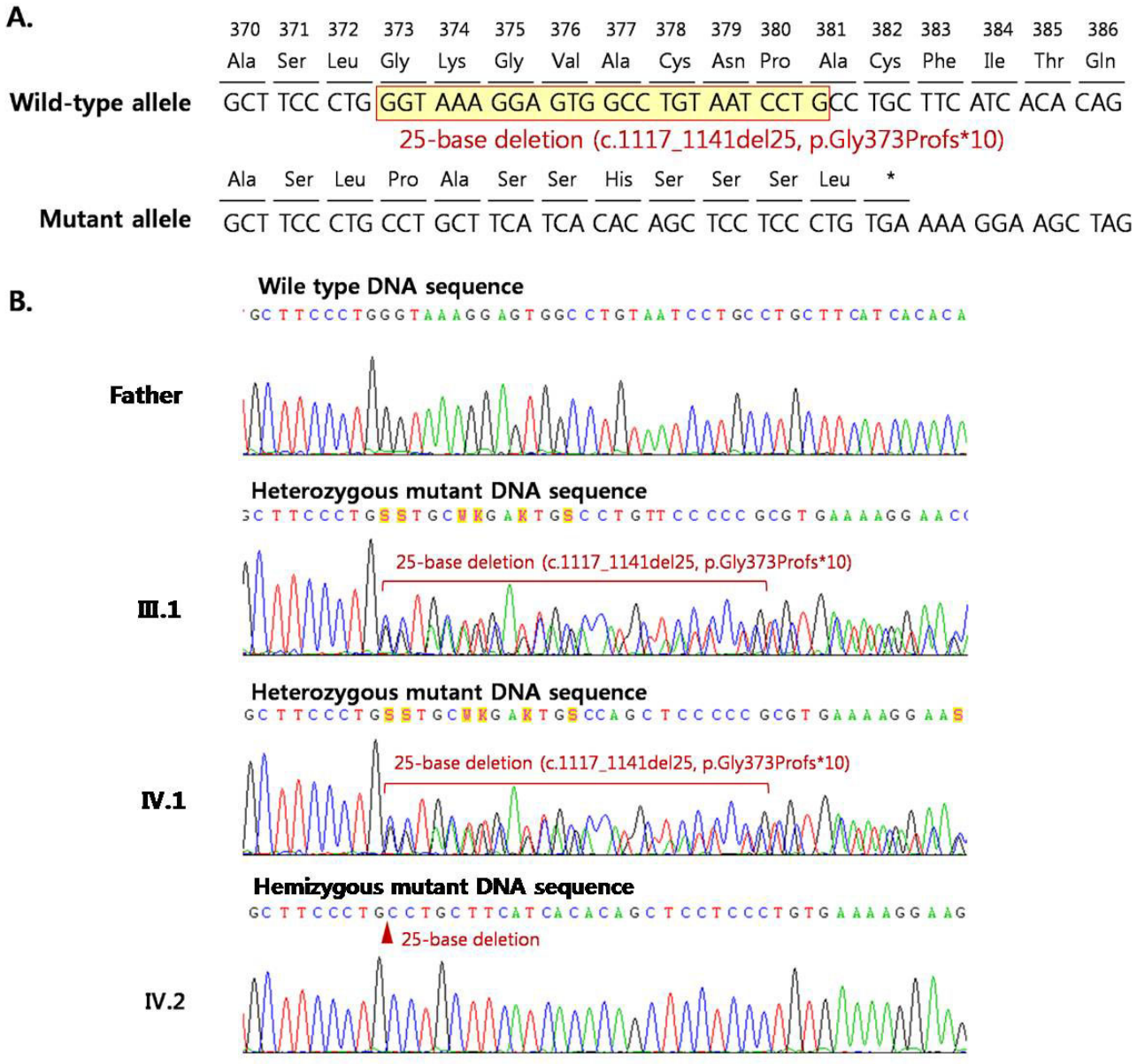


**Fig. 3.** (A) The DNA and corresponding amino acid sequences of the wild-type and mutant *GLA* alleles are shown. The 25-base deletion at nucleotide 1117-1141 shifts the frame, leading to premature termination at amino acid 382 in exon 7. (B) Representative chromatograms of polymerase chain reaction, fragments showing the presence of the 25-base deletion in the index patient (IV.2) and two female carriers (III.1 and IV.1), but not in the unaffected father.

**Table 1.** Clinical features of the affected family members described in this case report

| Patient | Sex/ age (yr) | Nervous system | Cardiovascular system | Nephrology system | Other symptoms | GLA enzyme activity (nmol/hr/mg protein)[a] | Gb3 level (μg/mL)[b] | Lyso-Gb3 level (ng/mL)[c] |
|---|---|---|---|---|---|---|---|---|
| IV.2 | M/11 | Neuropathic pain, anhidrosis | Left ventricular hypertrophy (LV mass index: 120 g/m$^2$) | eGFR 110 mL/min/1.73 m$^2$<br>Microalbuminuria (–)<br>Biopsy: zebra body in podocyte and epithelial cell | Cornea verticillata | 4.1 | 23.6 | 95.4 |
| IV.1 | F/13 | Neuropathic pain | Mitral valve prolapse | eGFR 145 mL/min/1.73 m$^2$<br>Microalbuminuria (–) | Cornea verticillata | 54.3 | 7.5 | 1.86 |
| III.1 | F/45 | Neuropathic pain, hypohidrosis | Unremarkable | eGFR 97 mL/min/1.73 m$^2$<br>Microalbuminuria (+)<br>(48 mg/g creatinine) | Cornea verticillata | 50.1 | 7.7 | 4.44 |

GLA, α-galactosidase A; Gb3, globotriaosylceramide; lyso-Gb3, globotriaosylsphingosine; LV, left ventricular; eGFR, estimated glomerular filtration rate. Normal range: [a]>35.0 nmol/hr/mg protein; [b]3.9-9.9 μg/mL; [c]≤1.74 ng/mL.

diologic, nephrologic, dermatologic, ophthalmologic, and neurologic assessments, as well as auditory function. Both of them showed normal electrocardiogram result without sign of cardiac rhythm disturbance. On echocardiogram, his sister showed mitral valve prolapse. His mother had mild microalbuminuria (48 mg/g creatinine). Both of them showed cornea verticillata in their ophthalmologic examinations.

The patient's urine test showed no significant microalbuminuria (7.8 μg/min), but a renal biopsy was performed to evaluate the presence of organ involvement before ERT. In the light microscopy, the glomeruli are diffusely enlarged. No glomerular sclerosis, crescent formation, chronic tubulointerstitial changes were observed. Electron microscopy revealed diffuse deposits of zebra bodies in podocytes and tubular epithelial cells with diffuse thickening of glomerular basement membrane and focal foot processes effacement (Fig. 4). The patient has started ERT with agalsidase beta 1.0 mg/kg every 2 weeks and supportive pain management, while his mother and sister have been examined the symptoms and signs of Fabry's disease on a regular basis without starting ERT.

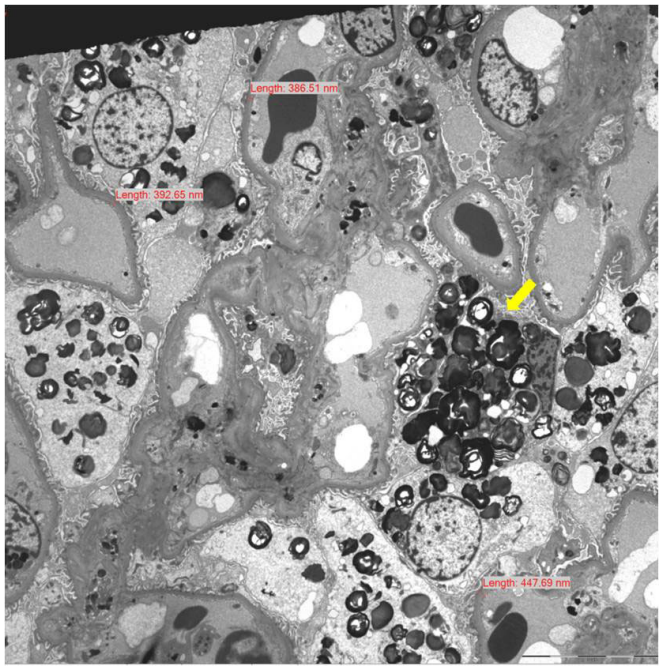


**Fig. 4.** Electron microsopy of renal biopsy showing multi-lamellated myelin figures, so-called zebra bodies in patient's podocyte and epithelial cell (arrow). Also, diffuse thickening of glomerular basement membrane and focal foot processes effacement were observed (×5,000).

## Discussion

We identified a novel *GLA* mutation (c.1117_1141del25) in a Korean family with FD. The presence of LVH, chronic neuropathic pain, cornea verticillata, and a strong family history raised the suspicion of FD and led to an excellent diagnosis in the proband.

FD is a devastating, progressive metabolic disorder caused by a defect in α-galactosidase A activity, and it has an incidence rate of 1 in 40,000 to 118,000 live births for males. The α-galactosidase A enzyme defect leads to the systemic accumulation of Gb3 and lyso-Gb3 inside the lysosomes of vascular endothelial cells, renal epithelial cells, myocardial cells, and neurons of the dorsal root ganglia and autonomic nervous system, resulting in a variety of multi-organ dysfunctions [8]. In classical FD, cardiac manifestation such as LVH arises typically during the fourth to seventh decades of life and at a later age in females than in males [9]. The proband in our report presented LVH at an earlier age than that seen in classical FD [10]. This suggests the novel *GLA* mutation (c.1117_1141del25) may be related to the early onset and severe cardiac phenotype of FD.

As in the present patient, pain is one of the earliest and predominant clinical symptoms of FD, affecting 60-70% of male

and 40-60% of female patients [3,4]. Neuropathic pain and heat and cold intolerance often begin at an average age of 6 to 8 years in males and, generally, a few years later in females than in males [6,11]. Typically, pain in FD manifests as episodes of burning, stabbing, or shooting pain that begins in the distal extremities with various triggering factors such as physical exercise, thermal stimuli, and fever [4]. Therefore, unexplained neuropathic pain in pediatric patients should alert the physician to the possibility of FD.

As FD is an X-linked genetic disorder, in the past, females were generally considered symptomatic carriers. Nevertheless, in recent years, it is widely accepted that heterozygous female carriers could develop mild to severe clinical manifestations of FD [6,12]. Females with FD can show wide variations in α-galactosidase A activity, ranging from severely deficient to normal levels possibly depending on random X-chromosome inactivation [13,14]. Although the progression of FD is slower and variable in female carriers, regular monitoring for signs and symptoms of FD is needed to recognize candidates for ERT. Plasma lyso-Gb3 level appears a useful biomarker for therapeutic evaluation and monitoring, particularly in females with normal and/or borderline α-galactosidase A activity [15,16]. Consistent with this findings, the two affected heterozygous females in our report, presenting mild symptom of FD, had normal α-galactosidase A activities, normal Gb3 level, and increased serum lyso-Gb3 levels.

Recently, more than 700 mutations in the *GLA* gene have been identified as pathogenic variants of FD. However, the diagnosis of FD is often difficult in several subjects because they have a *GLA* genetic variant of unknown significance. According to the current recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, multiple lines of evidence could be used to characterize the novel *GLA* mutation (c.1117_1141del25) as "pathogenic" for FD [17]. First, this mutation causes a frameshift leading to protein truncation by introducing a premature stop codon at position 382, which is assumed to disrupt *GLA* gene function. Second, the observation of the markedly decreased GLA enzyme level in the affected male carrier and the increased lyso-Gb3 levels in all the mutation carriers provides evidence for a damaging effect on the GLA enzyme. Third, the mutation is absent among the controls in the Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium. Furthermore, a different amino acid change occurring at p.Gly373 (p.Gly373Ser, pGly373Arg, or p.Gly373Asp) has previously been determined to be pathogenic for FD. Lastly, this novel *GLA* mutation was observed to segregate with the phenotype suggestive of FD in all affected family members.

In summary, we identified a novel *GLA* mutation (c.1117_1141del25) in a Korean family with FD. Particularly, the cardiac manifestation was detected early on in this patient, and this phenotype may be related to the novel *GLA* mutation. Our report may help accumulate knowledge about the correlation between the genotype and phenotype in FD.

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