Clinical characteristics and mutation spectrum of *GLA* in Korean patients with Fabry disease by a nationwide survey

Underdiagnosis of late-onset phenotype

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Abstract

Fabry disease is a rare X-linked lysosomal storage disorder caused by an α-galactosidase A deficiency. The progressive accumulation of globotriaosylceramide (GL-3) results in life-threatening complications, including renal, cardiac, and cerebrovascular diseases. This study investigated the phenotypic and molecular spectra of *GLA* mutations in Korean patients with Fabry disease using a nationwide survey.

This study included 94 patients from 46 independent pedigrees: 38 adult males, 46 symptomatic females, and 10 pediatric males. Each diagnosis was based on an enzyme assay and *GLA* gene mutation analysis.

The mean age at presentation was 24 years (range, 5–65 years); however, the diagnoses were delayed by 21 ± 19 years after the onset of symptoms. Those patients with late-onset Fabry disease were diagnosed by family screening or milder symptoms at a later age. Forty different mutations were identified: 20 missense (50%), 10 nonsense (25%), 8 frameshift (20%), and 2 splice site (5%) mutations. Five of them were novel. IVS4+919G>A (c.936+919 G>A) was not detected among the 6505 alleles via newborn screening using dried blood spots. Enzyme replacement therapy (ERT) was performed in all the males and pediatric patients, whereas 75% of the symptomatic females underwent ERT for 4.2 ± 3.6 years.

This study described the demographic data, wide clinical spectrum of phenotypes, and *GLA* mutation spectrum of Fabry disease in Korea. Most of the patients had classical Fabry disease, with a 4 times higher incidence than that of late-onset Fabry disease, indicating an underdiagnosis of mild, late-onset Fabry disease.

Abbreviations: ERT = enzyme replacement therapy, GL-3 = globotriaosylceramide, PCR = polymerase chain reaction.

Keywords: α-galactosidase A, enzyme replacement therapy, Fabry disease, *GLA*, globotriaosylceramide

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1. Introduction

Fabry disease (OMIM #301500) is a rare, X-linked lysosomal storage disorder caused by an α-galactosidase A deficiency.[1] The progressive systemic deposition of globotriaosylceramide (GL-3) in multiple organs results in proteinuria, which is often the first sign of renal involvement, episodic crises of severe pain in the extremities (acroparesthesia), hypo- or anhidrosis, corneal opacity, angiokeratoma, and/or stroke.[2]

Since the initial description of Fabry disease in 1898, several studies have described its clinical presentation and the natural course of Fabry disease in a large number of patients across all age groups based on the Fabry Registry.[3–5] The natural course of untreated Fabry disease is complicated by renal, cardiac, and cerebrovascular diseases. Prior to the advent of enzyme replacement therapy (ERT),[6,7] death was usually caused by serious complications such as chronic renal failure or stroke, in the fourth or fifth decades of life in affected males. In contrast, heterozygous females experience a wide spectrum of pheno-types, ranging from asymptomatic or mild forms to severe complications that are similar to those of classically affected males.[8]

Since the introduction of recombinant human α-galactosidase A treatment in 2001,[9,10] several clinical studies have shown that ERT has beneficial effects on renal, cardiac, and neurologic complications.[7,11–13] Thus, ERT is now considered to be the standard treatment for symptomatic male and female patients with Fabry disease.[8]

Since ERT has been fully subsidized in Korea since 2003 by the national insurance program, with special funding for orphan diseases, our group has reported the short-term and long-term efficacy of ERT in patients with Fabry disease based on a small number of patients at a single institute in Korea.[14,15] However, there is no nationwide data available on the baseline clinical characteristics, molecular spectrum of the GLA gene mutations, and effects of ERT in a large cohort of patients in Korea. Thus, this study was performed to determine the baseline demographic profiles, clinical characteristics, and GLA mutation spectrum in patients with Fabry disease in Korea by using a nationwide survey.

2. Methods

2.1. Subjects

This study included 94 patients from 46 independent families: 38 adult males (≥18 years of age, 40.4%), 46 symptomatic females (48.9%), and 10 pediatric males (10.6%). Eighty patients (85.1%) had family members with Fabry disease, whereas 10 patients (10.6%) had sporadic occurrences. Information on the family history was not available for the remaining 4 patients (4.3%).

The following clinical data were collected using question-naires (Supplementary data 1, http://links.lww.com/MD/B803): age at onset of symptoms, age at diagnosis, presenting features, biochemical findings, genotypes, and ERT efficacy. From March 2015 through October 2015, the questionnaires were sent to the physicians in 20 academic medical centers who were caring for patients with Fabry disease. Physicians from 17 centers responded to this nationwide survey. The study protocol was approved by the Institutional Review Board of the Asan Medical Center. Written informed consent was obtained from all the subjects or from their parents.

2.2. Biochemical tests and molecular analysis of the GLA gene

All the patients were diagnosed based on an assay of α-galactosidase A activity in the serum (male patients) and a mutation analysis of the GLA gene (both male and female patients), which were performed in a central core laboratory in at the Asan Medical Center in Seoul, Korea. The α-galactosidase A activity was measured via fluorometric assay using 4-methyl-umbelliferyl-α-D-galactoside as previously described.[14]

For the mutation analysis of the GLA gene, genomic DNA was isolated from the peripheral blood leukocytes. Seven coding exons and the exon–intron boundaries of the GLA were amplified by the polymerase chain reaction (PCR) with 7 sets of primers. After the PCR amplification, the PCR products were purified and sequenced directly using an ABI3130x1 Genetic Analyzer (Applied Biosystems, Foster City, CA).

The in silico prediction of the novel sequence variants was performed using PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), Sorting Intolerant From Tolerant (SIFT) (http://sift.jcvi.org/), Mutation Taster (http://www.mutationtaster.org/), Muta-tion Assessor (http://www.ngrl.org.uk/Manchester-/page/muta tion-assessor), and PMut (http://mmb.pcb.ub.es/PMut/) for the missense variants, and EX-SKIP (http://ex-skip.img.cas.cz/) for the splice site variants.

2.3. Newborn screening for the IVS4+919G>A (c.936 +919G>A) mutation using dried blood spots (DBSs)

We screened for the presence of the IVS4+919G>A mutation in 6505 alleles from 2249 male (2249 alleles) and 2128 female (4256 alleles) newborns using the genomic DNA extracted from DBSs. The intron 4 amplification was performed using the following primers: 5′-AGCTCCACACTATTTGGAAG-TATTTGT-3′ and 5′-GGTCCCTGCCCTCATGAAAC-3′. The IVS4+919G>A variant genotyping was performed using the Custom TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA). The PCR was carried out using the Chromo 4TM Four-Color Real-Time System (MJ Research, Watertown, MA). Finally, the data analysis for the allelic discrimination was conducted using the MJ Opticon MonitorTM analysis software (version 3.1; MJ Research, Watertown, MA).

3. Results

3.1. Baseline clinical characteristics of the Fabry disease patients

With regard to the patients that participated in our study, the mean age at the onset of symptoms was 24±18 years old (range, 5–65 years); however, the mean age at the diagnosis was 36±16 years old (range, 8–72 years). The mean interval between the onset and the diagnosis was 21±19 years (range, 0–42 years), excluding those cases identified by familial screening (Table 1).

All the adult males had typical manifestations at presentation. The most common presenting symptoms included hypo- or anhidrosis (73.5%), corneal clouding (73.0%), and acropar-esthesia (72.2%). Eight of the 38 (21.1%) adult male patients were classified as late-onset phenotypes and were diagnosed by family screening or hypertrophic cardiomyopathy (37.5%) at 48.0±7.5 years of age (range, 38–58 years) (Table 2, Fig. 1). In contrast, the adult male patients with the classical phenotype were diagnosed at 17.6±14.1 years of age (range, 5–49 years);

Table 1

Demographic profiles and biochemical findings in patients with Fabry disease.

	Adult males (N = 38)	Pediatric males (N = 10)	Females (N = 46)
Age at presentation, years, range	22.8 ± 17.4 (5–58)	10.4 ± 3.2 (5–13)	39.8 ± 17.3 (11–65)
Age at diagnosis, years, range	34.6 ± 12.2 (18–58)	13.0 ± 2.7 (8–17)	42.2 ± 15.0 (14–72)
Interval between presentation and diagnosis*, years, range	9.6 ± 10.2 (0–34)	1.5 ± 2.9 (0–9)	2.1 ± 7.4 (0–42)
Percent of median value of normal GLA activity, 45–86 nmol/hr/mg protein of WBCs	1.4 ± 2.0% (0.0–6.8%)	0.2 ± 0.6% (0.0–1.7%)	18.1 ± 22.4% (0.2–65.7%)
Serum GL-3, μg/mL, normal range < 4.7	15.2 ± 8.2 (0.3–36)	21.0 ± 13.2 (9–47)	10.2 ± 5.6 (4.3–25)
Urine GL-3, μg/mg Cr, normal range, 0.01–0.9	3.6 ± 3.9 (0.1–15)	6.4 ± 3.0 (0.1–10)	1.0 ± 1.6 (0.1–5.1)
Mean age at ERT initiation, years, range	36.2 ± 12.3 (19–59)	13.8 ± 2.5 (8–17)	45.1 ± 15.5 (14–72)
Duration of ERT, years, range	5.5 ± 3.9 (0–12)	5.2 ± 2.5 (1–10)	2.8 ± 3.0 (0–12)

ERT = enzyme replacement therapy, GL-3 = globotriaosylceramide, GLA = α-galactosidase A, WBCs = white blood cells.
* Symptomatic patients only.

6.9% of them manifested hypertrophic cardiomyopathy. All 10 of the pediatric males were diagnosed by family member screening, and all of them had acroparesthesia; the youngest one manifested symptoms at the age of 5 years old.

Renal involvement, such as proteinuria or chronic renal failure, was noted in 51.3% of the patients. Three of the males underwent a kidney transplantation before the diagnosis, whereas 2 of the males had chronic renal failure and were undergoing peritoneal or hemodialysis. The urinary protein excretion and serum creatinine levels were normal in all the pediatric patients. Sixteen of the male patients (13 adults and 3 pediatric patients) and 7 of the symptomatic female patients underwent kidney biopsies before the administration of ERT. All the adult male and symptomatic female patients demonstrated varying degrees of glomerulosclerosis with interstitial fibrosis or tubular atrophy, as seen on light microscopy (LM). The accumulation of GL-3 was observed in the endothelial cells, and mesangial cells, and podocytes on electron microscopy (EM) (Table 3). Interestingly, 8 of the patients exhibited complement 3 deposits in the mesangium via immunofluorescence. Moreover, the normoproteinuric female and male patients began to show abnormal pathological findings, such as mild glomerulosclerosis via LM or electron-dense deposits on EM.

Twelve of the patients manifested cardiac arrhythmias, including sinus bradycardia, Wolff–Parkinson–White syndrome, atrioventricular block, and bundle branch block.

3.2. GLA gene mutation spectrum and genotype-phenotype correlations

Forty different mutations were identified in the 94 patients (46 pedigrees) with Fabry disease that participated in this study: 20 missense (50%), 10 nonsense (25%), 8 frameshift (20%), and 2 splice site (5%) mutations (Fig. 2). All 48 males were hemizygous and all 46 symptomatic females were heterozygous for the GLA mutations. Five of them were novel: p.Y86H, p.G274R, p.L310V, c.639+5G>A (IVS4+5G>A), and p.

V316fs*1 [c.947_948ins(47)]. The novel missense and splice site variants were not detected in the ExAC browser (http://exac.broadinstitute.org/) and were predicted to be damaging by ≥3 prediction programs for the missense variants and EX-SKIP for the splice site variant (Supplementary data 2, http://links.lww.com/MD/B804).

The GLA mutations were dispersed throughout all the coding regions, except exon 4 (Fig. 2). All the truncating (nonsense and frameshift) and most of the missense mutations (16/20, 80%) were associated with classical Fabry disease. Those patients with 1 of the 4 missense mutations (p.I91T, p.F113L, p.R301Q, and p.L310V) or a novel splice site variant (c.639+5G>A) presented with late-onset Fabry disease (Fig. 2). Of these, the p.I91T, p.F113L, and p.R301Q mutations were already identified in those patients with the mild cardiac phenotype.[16,17]

Since a previous newborn screening identified a surprisingly high frequency for the IVS4+919G>A (c.936+919 G>A) mutation in Taiwanese males (~1 in 1250),[18] we screened for this mutation in 6505 alleles from 2249 males (2249 alleles) and 2128 females (4256 alleles) using genomic DNA extracted from DBSs. However, the frequency of the IVS4+919G>A mutation was 0% of the 6505 alleles in our Korean population.

3.3. Efficacy of enzyme replacement therapy

All the adult male and pediatric patients received ERT, as had 34 of the symptomatic female patients (73.9%) (Table 1). The mean age at ERT initiation was 36.2, 13.8, and 45.1 years old in the adult males, pediatric males, and symptomatic females, respectively. ERT was delayed for 13.4, 3.4, and 5.3 years after the

Table 2

Clinical phenotype of adult male patients with Fabry disease.

	Classical	Late onset variant
Number of patients	30 (78.9%)	8 (21.1%)
Age at presentation, years, range	17.6 ± 14.1 (5–49)	48.0 ± 7.5 (38–58)
Residual enzyme activity, %	1.0 ± 1.7	2.4 ± 2.5
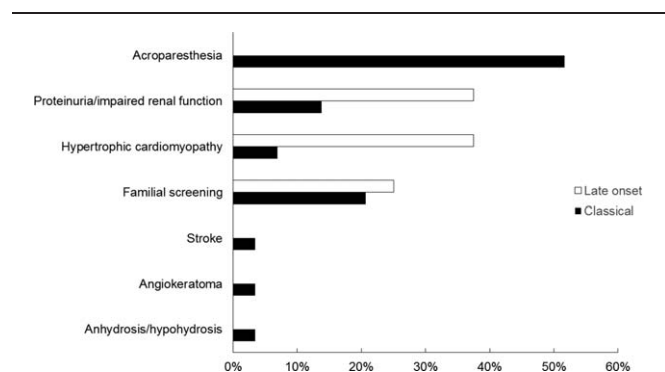
Figure 1. Presenting manifestation of adult male patients with classical and late-onset Fabry disease.

Table 3

Baseline renal biopsy pathological findings in patients with Fabry disease.

	Adult males (N=13)	Pediatric males (N=3)	Females (N=7)
Proteinuria	939±819 (64–2368) mg/day	94–106 mg/m²/day	553±563 (47–1447) mg/day
CKD stage	1 (N=11), 3 (N=1), 4 (N=1)	1 (N=3)	1 (N=4), 2 (N=1), 3 (N=2)
GL-3 deposit	Endothelial (N=8), mesangial (N=10), epithelial (N=7)	Endothelial (N=0), mesangial (N=2), epithelial (N=0)	Endothelial (N=2), mesangial (N=4), epithelial (N=1)
Global sclerosis, %	N=10, 21±26% (1–83%)	N=1, 33%	N=3, 19–50%
FSGS	4.5–67% (N=4)	N=0	3–25% (N=4)
Interstitial fibrosis, N	9	0	7
Tubular atrophy, N	7	0	6

CKD = chronic kidney disease, FSGS = focal segmental glomerulosclerosis, GL-3 = globotriaosylceramide.

onset of symptoms in the adult males, pediatric males, and symptomatic females, respectively.

Angiotensin-converting enzyme inhibitors or angiotensin receptors blocker were administered in 24 of the adult male patients (63.2%) and 8 of the female patients (17.4%) with overt proteinuria (>300 mg/day) before the administration of ERT. The renal function remained stable during the ERT in most of the adult males, but deteriorated in 2 of the patients who harbored 2 different truncating mutations (p.R342* and p.T412Sfs*37). In 3 of the male patients who had already received kidney transplants before the ERT, the serum creatinine levels and amount of proteinuria were stable during the ERT. When we evaluated the renal outcomes of those patients who received ERT for more than 5 years, the age at diagnosis, amount of proteinuria, and glomerular filtration rate before ERT were the most important factors affecting the renal outcomes.[15]

4. Discussion

This study described the demographic data, baseline clinical features, and *GLA* mutation spectrum of 94 patients with Fabry disease in Korea. Most of these patients exhibited classical Fabry disease and exhibited typical the clinical features, including renal, cardiac, and neurological complications.

The intervals between the mean age at onset and mean age at diagnosis were 9.6, 1.5, and 2.1 years in the adult males, pediatric males, and symptomatic females, respectively. Both the nonspecific nature of the early symptoms of Fabry disease and the lack of

recognition of the constellation of clinical features by the general physician could contribute to a delayed diagnosis.[3] The risks of a delayed or overlooked diagnosis have been confirmed in other surveys and lead to serious morbidity.[4]

Fabry disease has been regarded as a rare lysosomal storage disease with an incidence rate of 1 in 40,000 to 1 in 117,000 live births.[19] However, newborn screening results have shown a relatively high incidence, ranging from 1 in 1250 to 1 in 4600, with 6–7 times more late-onset patients than those with classical Fabry disease.[18,20] In contrast, our survey demonstrated an approximately 4 times higher incidence of classical than late-onset Fabry disease, indicating the underdiagnosis of the late-onset type. Moreover, when extrapolating less than 100 identified patients from the 50 million people in South Korea, Fabry disease is certainly being underdiagnosed, particularly the mild, late-onset type. Interestingly, Fabry disease was detected in only 1 additional family member following the diagnosis of a proband, which is a much lower incidence than that of a previous report in which the average number was 5.[21] This could have been due, in part, to the incomplete analysis of the family pedigree (lack of a genetic counseling system), or to cultural issues, such as refusing further family evaluations for fear of stigmatization.

Using enzyme assays or genotyping, several studies have undertaken mass screenings for Fabry disease in newborns or high-risk groups, such as hemodialysis patients with chronic renal failure, patients with left ventricular hypertrophy of unknown etiology, or patients with familial Mediterranean fever.[20,22–24] These types of screenings have also been done in
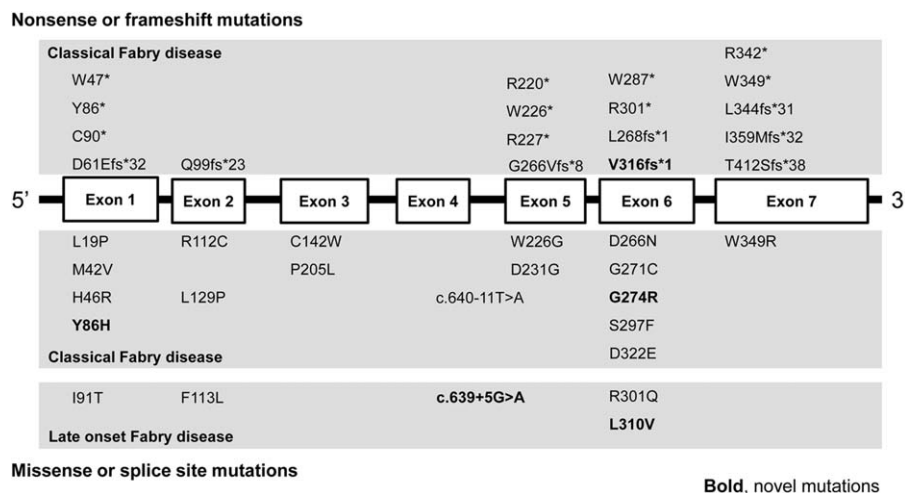
Figure 2. *GLA* gene mutations in Korean patients with Fabry disease. We identified 40 mutations. Five of them were novel mutations.

Korea.[25] However, newborn screening for Fabry disease has not yet been initiated and remains an ongoing pilot study. The IVS4 +919G>A (c.936+919G>A) mutation was initially discovered in Japanese patients with the late-onset cardiac phenotype, with ~10% residual α-galactosidase A activity in the patients' lymphoblasts.[26] This mutation is highly prevalent in Taiwanese newborns, with an incidence ranging from 1 in 875 to 1 in 1460.[18,27] However, the present study revealed that this mutation seems to be extremely rare in the Korean population, suggesting the possibility of a Southern origin of an ancient mutation.

Our group previously reported the short and long-term effects of ERT in patients with Fabry disease, focusing on renal and cardiac outcomes.[14,15] The renal pathological findings were recorded in those patients whose renal function was significantly deteriorated. Of note, complement 3 was often deposited in certain patients with Fabry disease before the ERT, indicating the constitutional activation of the complement system at the baseline. Overall, the renal functions remained stable during the ERT in most patients. However, in some of the adult males with overt proteinuria, a significant deterioration in the renal function was noted, despite the use of ERT.[15] This aggravation of renal function was inversely correlated with the age at the start of the ERT and the initial amount of protein excretion. These results indicate that early diagnosis and treatment are critical to improving a patients' prognosis. Finally, cardiac involvement in Fabry disease includes left ventricular hypertrophy, angina, myocardial infarction, and arrhythmia.[2,28] The beneficial effects of ERT include reducing the left ventricular mass.[11]

This study had several limitations. Since it was a voluntary observational survey using questionnaires, the clinical data may have been subject to ascertainment and recall bias. However, this analysis contributes to the recognition of the wide spectrum of clinical manifestations of Fabry disease affecting the pediatric age group and females.

In conclusion, this study described a nationwide survey of the demographic data, clinical spectrum of phenotypes, and the molecular characteristics of Fabry disease in Korea. Most of the patients exhibited classical Fabry disease, with a 4 times higher incidence than that of late-onset phenotype, indicating an underdiagnosis of mild, late-onset type. In addition, the IVS4 +919G>A (c.936+919 G>A) mutation, which is highly prevalent in Taiwanese males, was extremely rare based on mutation screening in Korean newborn.

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