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RESEARCH ARTICLE

Correlation of enzyme activities and genotype with clinical manifestations in Chinese patients of different sexes with classical and late-onset Fabry disease

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Abstract **Fabry disease, a rare genetic disorder affecting multiple organs, has understudied correlations among enzyme activity, genotype, and clinical manifestations in patients of different sexes with classical and late-onset phenotypes. In this study, clinical data, α-Gal A activity, and *GLA* gene test results of 311 patients, who were categorized by classical and late-onset phenotypes, ⩽5% and > 5% of the normal mean value of enzyme activity, and truncated and nontruncated mutation groups, were collected. The common clinical manifestations of Fabry disease included acroparesthesia, hypohidrosis/anhidrosis, neuropsychiatric system, and renal and cardiovascular involvement. Multiorgan involvement was higher in males and classical phenotype patients. In both sexes, classical patients commonly presented with acroparesthesia and multiorgan involvement, whereas late-onset patients showed renal, neuropsychiatric, and cardiovascular involvement. Male and classical patients had lower enzyme activity than female and late-onset patients, respectively. Classical males with enzyme activity of ⩽5% of the normal mean level showed higher multiorgan involvement frequency than those with enzyme activity of > 5%, whereas no significant difference was observed among females. Ninety-five gene mutation sites were detected, with significant phenotype heterogeneity in patients with the same mutation. No significant difference in enzyme activity or clinical manifestations was observed between truncated and nontruncated mutations. Overall, male patients with Fabry disease, regardless of classical or late-onset phenotype, have a higher frequency of multiple-organ involvement and lower α-Gal A activity than female patients. α-Gal A activity was closely correlated with clinical symptoms in males but weakly correlated with clinical manifestations in females. The clinical manifestations of patients with the same mutation are heterogeneous, and the correlation between gene mutation and enzyme activity or clinical manifestation is weak.**

Keywords Fabry disease; α-galactosidase A; *GLA*; classical phenotype; male

Introduction

Fabry disease is a rare X-linked hereditary lysosomal storage disease caused by mutations in the *GLA* gene located at Xq22.1. These mutations result in a decrease or complete loss of α-galactosidase A (α-Gal A) activity. Subsequently, the enzyme metabolism substrate globotriaosylceramide (Gb3) and its deacylated derivative globotriaosylsphingosine (Lyso-Gb3) progressively accumulate in the lysosomes of multiple-organ tissues, causing multi-organ lesions and corresponding clinical manifestations [1–4].

Fabry disease is divided into classical and late-onset phenotypes. Classical patients have markedly reduced or absent enzyme activity, whereas late-onset patients have partially decreased activity. Classical patients often have multi-organ involvement compared with late-onset patients [5]. As Fabry disease is an X-linked hereditary disorder, males have an early onset and more severe clinical manifestations than females [6–9]. Male patients often develop the disease during childhood or

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adolescence and exhibit classical manifestations involving multiple systems [10]. By contrast, most female patients have a later onset with limited organ involvement, primarily affecting the kidneys and heart. Their clinical manifestations are relatively subtle, and they are at risk of premature death caused by renal failure and cardiovascular complications [11]. Despite relevant reports [5,8–10,12–14] on the differences in clinical manifestations between classical and late-onset patients or between sexes, those studies have focused on European and American populations. Large-scale studies on Fabry disease among Chinese patients are currently lacking. In addition, previous studies mostly grouped patients based on sex or phenotype without comparing the clinical manifestations of patients of different sexes within the classical and late-onset Fabry disease groups. In this study, we analyzed organ involvement in a large sample of male and female Chinese patients with classical and late-onset Fabry disease and revealed differences in the clinical manifestations of patients with Fabry disease with different sexes and phenotypes.

The α-Gal A activity is used for diagnosing and evaluating Fabry disease, with a threshold level of α-Gal A activity below 30%–35% of the normal mean level indicating clinically significant disease [6]. Clinically, most males have a remarkable decrease or complete loss of enzyme activity. In general, classical male patients have α-Gal A activity as low as 1%–5% of the normal mean level, with a higher incidence of multiorgan involvement compared with females [5,15–17]. However, enzyme activity in females can be normal or partially decreased, leading to a range of clinical manifestations from asymptomatic to severe classical presentation. Enzyme activity-based diagnosis has limitations in females [18,19]. Previous studies focused on enzyme activities in European and American populations, with limited large-scale clinical studies on the correlation between enzyme activities and clinical manifestations in Chinese patients with Fabry disease. Furthermore, previous studies mainly compared enzyme activities between males and females or between classical and late-onset patients, without detailed investigation of organ involvement in patients of different sexes with different enzyme activities. The correlation between enzyme activities and clinical manifestations remains unclear [15,20]. In this study, the cutoff for enzyme activity between classical and late-onset Fabry disease was defined as 5% of the normal mean level [5], and the relationship among different sexes, enzyme activities, and clinical manifestations of classical and late-onset Fabry disease was explored using a large sample size, providing insights into the correlation between enzyme activities and organ involvement in patients with classical and late-onset Fabry disease of different sexes.

The mutation of the *GLA* gene encoding α-Gal A is considered as the gold standard for the diagnosis of Fabry disease [21]. More than 1000 mutations in the *GLA* gene have been identified to date, most of which are missense or nonsense mutations [22,23]. Different *GLA* mutations may also be related to the degree of α-Gal A activity loss, and great differences in clinical manifestations are observed [24]. Few clinical reports have been found on the correlation between Fabry disease caused by different mutation types (such as truncated and nontruncated mutations) and enzyme activity or clinical manifestation, and no relevant study on the relationship between gene mutations and enzyme activity or clinical manifestation has been conducted in patients of different sexes with classical and late-onset phenotype. This study aimed to clarify the relationship among genotype, enzyme activity, and clinical manifestation by analyzing the correlation among gene mutations, enzyme activities, and clinical manifestations in male and female Chinese patients with classical and late-onset Fabry disease.

This study is the largest clinical study of Fabry disease in China. Furthermore, this study aimed to improve our understanding of Fabry disease by exploring the clinical manifestations of 311 patients of different sexes with classical and late-onset phenotypes, the correlation between different enzyme activities and clinical manifestations of 170 patients, the correlation between gene variants and enzyme activities, and the clinical manifestations of 163 patients.

Materials and methods

Study population

The medical records of 311 patients with Fabry disease diagnosed between June 2012 and May 2022 from outpatients, previously hospitalized patients and the National Rare Diseases Registry System of China were collected. To enhance the completeness and accuracy of the data, a questionnaire survey was conducted on patients in April 2022, and statistical analysis was conducted on the basis of the data of the questionnaire survey. The inclusion criteria for these patients were based on expert consensus recommendations for Fabry disease diagnosis [25,26], including typical clinical symptoms, family history, laboratory examination results (*GLA* gene analysis and α-Gal A activity), and pathological changes in biopsy samples. This clinical study was reviewed and approved by the Medical Ethics Committee of the Chinese PLA General Hospital (approval number: 2012-001), and it was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided a written informed consent. For minors, parents/legal guardians were

informed, and their parents/legal guardians signed the informed consent instead.

Clinical data collection

Clinical data included general information (sex, age, family history, etc.). Clinical symptoms of various involved systems included the urinary system, cardiovascular system, neuropsychiatric system, digestive system, eye system, ear system, and laboratory results. α-Galactosidase A activity was detected in venous blood samples by using the dried blood spot or peripheral blood fluorescent substrate methods, and *GLA* gene analysis was performed by next-generation sequencing.

Clinical grouping

Patients with Fabry disease were divided into classical and late-onset phenotypes in accordance with the criteria of Fabry disease in the *Journal of the American Society of Nephrology* [5]. For males, classical phenotype required a *GLA* mutation, α-Gal A activity of ⩽5% of the mean value of the normal reference range, and the presence of characteristic manifestations (neuropathic pain, angiokeratoma, and corneal opacity). Males not meeting these criteria were classified as late-onset. Female patients were considered as classical if they had *GLA* mutations and characteristic manifestations, whereas those without manifestations were considered as late-onset.

Patients were grouped by sex and classified as classical or late-onset based on *GLA* gene mutation, α-Gal A activity (males), and organ involvement. Enzyme activity levels were divided into ⩽5% and > 5% of the normal mean. Patients were also divided into truncated mutation (including nonsense, frameshift mutations, and fragment deletions) and nontruncated mutation (missense mutations) groups based on gene mutation results.

Statistical analysis

Statistical analysis software SPSS 26.0 was used for data analysis, and GraphPad Prism 9.3.0 was used for mapping. Measurement data conforming to a normal distribution were expressed as the mean ± standard deviation, and an independent sample *t*-test was used to compare the differences between two groups. Measurement data that did not conform to a normal distribution were expressed as the median (interquartile range; M (P25, P75)). Differences were compared using the rank sum test and Kruskal–Wallis test with K independent samples. Enumeration data were expressed as percentages (%), and differences between two groups were compared by using the χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Frequency of clinical manifestations between male and female patients with Fabry disease

A total of 311 patients with Fabry disease were enrolled, including 200 males (64.31%) and 111 females (35.69%). Patients were also divided into classical (237 cases, 76.21%) and late-onset phenotypes (74 cases, 23.79%).

Statistical analysis of clinical manifestations of all patients (Table 1) showed that with regard to organ system involvement, acroparesthesia (66.56%) was the most common manifestation, followed by hypohidrosis/anhidrosis (62.70%), neuropsychiatric system (58.20%), renal (57.88%), and cardiovascular involvement (54.66%).

Among specific symptoms, acroparesthesia was the most common (66.56%), followed by hypohidrosis/anhidrosis (62.70%), proteinuria (51.13%), and angiokeratomas (45.98%).

The comparison of clinical manifestations between male and female patients showed that the incidence of acroparesthesia; hypohidrosis/anhidrosis; renal, cardiovascular, digestive, and respiratory system involvement; angiokeratomas; and eye and ear involvement was significantly higher in male patients than in female patients ($P < 0.05$).

Frequency and comparison of clinical manifestations of patients of different sexes with classical and late-onset Fabry disease

As shown in Table 2, in male and female classical patients, the most common clinical manifestation was acroparesthesia, accompanied with multi-organ involvement, such as hypohidrosis/anhidrosis, angiokeratoma, and renal involvement. The frequency of multi-organ involvement (such as acroparesthesia; hypohidrosis/anhidrosis; angiokeratoma; renal, neuropsychiatric, and cardiovascular system involvement; and eye and ear involvement) was significantly higher in classical male patients than in classical female patients ($P < 0.05$).

Patients with late-onset Fabry disease mainly exhibit renal, cardiovascular, and neuropsychiatric system involvement. The frequency of renal involvement in male patients with late-onset Fabry disease was significantly higher than that in female patients with late-onset Fabry disease ($P < 0.05$). Other organ involvement was slightly more common in males with late-onset Fabry disease than in females, but no significant difference was observed.

Furthermore, classical male patients have a higher frequency of multiorgan involvement (such as acroparesthesia, hypohidrosis/anhidrosis, angiokeratoma, and neuropsychiatric and cardiovascular system involvement) than male patients with late-onset Fabry disease.

Table 1 Comparison of clinical manifestations between male and female patients with Fabry disease (*n*/*N* (%))

	All patients (*N* = 311)	Males (*n* = 200)	Females (*n* = 111)	*P* value
Acroparesthesia (limb pain)	207/311 (66.56)	159/200 (79.50)	48/111 (43.24)	< 0.001
Anhidrosis or hypohidrosis	195/311 (62.70)	155/200 (77.50)	40/111 (36.04)	< 0.001
Neuropsychiatric involvement	181/311 (58.20)	121/200 (60.50)	60/111 (54.05)	0.270
Decreased attention	117/311 (37.62)	84/200 (42.00)	33/111 (29.73)	0.032
Anxiety and depression	93/311 (29.90)	67/200 (33.50)	26/111 (23.42)	0.063
Dizziness	97/311 (31.19)	63/200 (31.50)	34/111 (30.63)	0.874
Headache	6/311 (1.93)	6/200 (3.00)	0/111	0.065
Syncope	24/311 (7.12)	16/200 (8.00)	8/111 (7.21)	0.802
Cerebral infarction	33/311 (10.61)	26/200 (13.00)	7/111 (6.31)	0.066
Cerebral hemorrhage	14/311 (4.50)	9/200 (4.50)	5/111 (4.50)	0.999
Renal involvement	180/311 (57.88)	147/200 (73.50)	33/111 (29.73)	< 0.001
Proteinuria	159/311 (51.13)	130/200 (65.00)	29/111 (26.13)	< 0.001
Increased serum creatinine	92/311 (29.58)	85/200 (42.50)	7/111 (6.31)	< 0.001
Cardiovascular involvement	170/311 (54.66)	127/200 (63.50)	43/111 (38.74)	< 0.001
Palpitation	80/311 (25.72)	56/200 (28.00)	24/111 (21.62)	0.218
Chest tightness	26/311 (8.36)	20/200 (10.00)	6/111 (5.41)	0.161
Chest pain	14/311 (4.50)	11/200 (5.50)	3/111 (2.70)	0.254
Hypertension	52/311 (16.72)	43/200 (21.50)	9/111 (8.11)	0.002
Left ventricular hypertrophy	94/311 (30.22)	77/200 (38.50)	17/111 (15.32)	< 0.001
Valve disease	43/311 (13.83)	32/200 (16.00)	11/111 (9.91)	0.136
Abnormal electrocardiogram	64/311 (20.58)	40/200 (20.00)	24/111 (21.62)	0.735
Digestive system involvement	166/311 (53.38)	121/200 (60.50)	45/111 (40.54)	0.001
Nausea and vomiting	68/311 (21.86)	50/200 (25.00)	18/111 (16.22)	0.073
Stomachache	63/311 (20.26)	45/200 (22.50)	18/111 (16.22)	0.187
Diarrhea	119/311 (38.26)	100/200 (50.00)	19/111 (17.12)	< 0.001
Constipation	38/311 (12.22)	21/200 (10.50)	17/111 (15.32)	0.241
Ear involvement	163/311 (52.41)	123/200 (61.50)	40/111 (36.04)	< 0.001
Tinnitus	124/311 (39.87)	97/200 (48.50)	27/111 (24.32)	< 0.001
Deafness	14/311 (4.50)	13/200 (6.50)	1/111 (0.90)	0.023
Hearing loss	125/311 (40.19)	95/200 (47.50)	30/111 (27.03)	< 0.001
Eye involvement	155/311 (49.84)	119/200 (59.50)	36/111 (32.43)	< 0.001
Vision loss	113/311 (36.33)	87/200 (43.50)	26/111 (23.42)	< 0.001
Corneal vortex opacity	71/311 (22.83)	57/200 (28.50)	14/111 (12.61)	0.001
Retinal vascular tortuosity	39/311 (12.54)	31/200 (15.50)	8/111 (7.21)	0.034
Conjunctival vascular tortuosity	27/311 (8.68)	21/200 (10.50)	6/111 (5.41)	0.126
Posterior capsular opacification	26/311 (8.36)	18/200 (9.00)	8/111 (7.21)	0.584
Angiokeratomas	143/311 (45.98)	122/200 (61.00)	21/111 (18.92)	< 0.001
Osteoporosis	46/311 (14.79)	33/200 (16.50)	13/111 (11.71)	0.254
Respiratory system involvement	45/311 (14.47)	36/200 (18.00)	9/111 (8.11)	0.018
Dyspnea	17/311 (5.47)	13/200 (6.50)	4/111 (3.60)	0.282
Chronic bronchitis	27/311 (8.68)	20/200 (10.00)	7/111 (6.31)	0.268
COPD	9/311 (2.89)	9/200 (4.50)	0/111	0.023
Bronchial asthma	3/311 (0.96)	3/200 (1.50)	0/111	0.195

Abbreviations: COPD, chronic obstructive pulmonary disease.

Table 2 Frequency and comparison of clinical manifestations of patients of different sexes with classical and late-onset Fabry disease (*n*/*N* (%))

	Classical phenotype (*N* = 237)				Late-onset phenotype (*N* = 74)			
	All patients	Males (*n* = 171)	Females (*n* = 66)	*P* value	All patients	Males (*n* = 28)	Females (*n* = 46)	*P* value
Acroparesthesia (limb pain)	207/237 (87.34)	159/171 (92.98)	48/66 (72.73)	< 0.001	0/74[a]	0/28[b]	0/46[c]	–
Anhidrosis or hypohidrosis	180/237 (75.95)	149/171 (87.13)	31/66 (46.97)	< 0.001	15/74 (20.27)[a]	6/28 (21.43)[b]	9/46 (19.57)[c]	0.847
Neuropsychiatric involvement	155/237 (65.40)	112/171 (65.50)	43/66 (65.15)	0.960	26/74 (35.14)[a]	9/28 (32.14)[b]	17/46 (36.96)[c]	0.674
Decreased attention	98/237 (41.35)	76/171 (44.44)	22/66 (33.33)	0.119	19/74 (25.68)[a]	8/28 (28.57)	11/46 (23.91)	0.656
Anxiety and depression	86/237 (36.29)	65/171 (38.01)	21/66 (31.82)	0.374	7/74 (9.46)[a]	2/28 (7.14)[b]	5/46 (10.87)[c]	0.5951
Dizziness	89/237 (37.55)	62/171 (36.26)	27/66 (40.91)	0.507	8/74 (10.81)[a]	1/28 (3.57)[b]	7/46 (15.22)[c]	0.118
Headache	6/237 (2.53)	6/171 (3.51)	0/66	0.123	0/74	0/28	0/46	–
Syncope	24/237 (10.13)	16/171 (9.36)	8/66 (12.12)	0.527	0/74[a]	0/28	0/46[c]	–
Cerebral infarction	33/237 (13.92)	26/171 (15.20)	7/66 (10.61)	0.359	0/74[a]	0/28[b]	0/46[c]	–
Cerebral hemorrhage	13/237 (5.49)	9/171 (5.26)	4/66 (6.06)	0.809	1/74 (1.35)	0/28	1/46 (2.17)	0.432
Renal involvement	149/237 (62.87)	128/171 (74.85)	21/66 (31.82)	< 0.001	31/74 (41.89)[a]	19/28 (67.86)	12/46 (26.09)	< 0.001
Proteinuria	129/237 (54.43)	111/171 (64.91)	18/66 (27.27)	< 0.001	30/74 (40.54)[a]	19/28 (67.86)	11/46 (23.91)	< 0.001
Increased serum creatinine	82/237 (34.60)	79/171 (46.20)	3/66 (4.55)	< 0.001	10/74 (13.51)[a]	6/28 (21.43)	4/46 (8.70)	0.120
Cardiovascular involvement	145/237 (61.18)	116/171 (67.84)	29/66 (43.94)	0.001	25/74 (33.78)[a]	11/28 (39.29)[b]	14/46 (30.43)	0.435
Palpitation	72/237 (30.38)	54/171 (31.58)	18/66 (27.27)	0.518	8/74 (10.81)[a]	2/28 (7.14)[b]	6/46 (13.04)	0.428
Chest tightness	24/237 (10.13)	20/171 (11.70)	4/66 (6.06)	0.197	2/74 (2.70)[a]	0/28	2/46 (4.35)	0.263
Chest pain	13/237 (5.49)	11/171 (6.43)	2/66 (3.03)	0.302	1/74 (1.35)	0/28	1/46 (2.17)	0.432
Hypertension	47/237 (19.83)	40/171 (23.39)	7/66 (10.61)	0.027	5/74 (6.76)[a]	3/28 (10.71)	2/46 (4.35)	0.290
Left ventricular hypertrophy	81/237 (34.18)	70/171 (40.94)	11/66 (16.67)	< 0.001	13/74 (17.57)[a]	7/28 (25.00)	6/46 (13.04)	0.190
Valve disease	38/237 (16.03)	29/171 (16.96)	9/66 (56.25)	0.532	5/74 (6.76)[a]	3/28 (10.71)	2/46 (4.35)	0.290
Abnormal electrocardiogram	55/237 (23.21)	38/171 (22.22)	17/66 (25.76)	0.563	9/74 (12.16)[a]	2/28 (7.14)	7/46 (15.22)	0.303
Digestive system involvement	154/237 (64.98)	116/171 (67.84)	38/66 (57.58)	0.138	12/74 (16.22)[a]	5/28 (17.86)[b]	7/46 (15.22)[c]	0.765
Nausea and vomiting	64/237 (27.00)	49/171 (28.65)	15/66 (22.73)	0.357	4/74 (5.41)[a]	1/28 (3.57)[b]	3/46 (6.52)[c]	0.586
Stomachache	59/237 (24.89)	43/171 (25.15)	16/66 (24.24)	0.885	4/74 (5.41)[a]	2/28 (7.14)[b]	2/46 (4.35)[c]	0.606
Diarrhea	113/237 (47.68)	96/171 (56.14)	17/66 (25.76)	< 0.001	6/74 (8.11)[a]	4/28 (14.29)[b]	2/46 (4.35)[c]	0.129
Constipation	35/237 (14.77)	19/171 (11.11)	16/66 (24.24)	0.011	3/74 (4.05)[a]	2/28 (7.14)	1/46 (2.17)[c]	0.293
Ear involvement	145/237 (61.18)	116/171 (67.84)	29/66 (43.94)	0.001	18/74 (24.32)[a]	7/28 (25.00)[b]	11/46 (23.91)[c]	0.916
Tinnitus	115/237 (48.52)	93/171 (54.39)	22/66 (33.33)	0.004	9/74 (12.16)[a]	4/28 (14.29)[b]	5/46 (10.87)[c]	0.663
Deafness	13/237 (5.49)	12/171 (7.02)	1/66 (1.52)	0.095	1/74 (1.35)	1/28 (3.57)	0/46	0.197
Hearing loss	109/237 (45.99)	88/171 (51.46)	21/66 (31.82)	0.007	16/74 (21.62)[a]	7/28 (25.00)[b]	9/46 (19.57)	0.582
Eye involvement	144/237 (60.76)	116/171 (67.84)	28/66 (42.42)	< 0.001	11/74 (14.86)[a]	3/28 (10.71)[b]	8/46 (17.39)[c]	0.434
Vision loss	103/237 (43.46)	85/171 (49.71)	18/66 (27.27)	0.002	10/74 (13.51)[a]	2/28 (7.14)[b]	8/46 (17.39)	0.211
Corneal vortex opacity	71/237 (29.96)	57/171 (33.33)	14/66 (21.21)	0.068	0/74[a]	0/28[b]	0/46[c]	–
Retinal vascular tortuosity	37/237 (15.61)	30/171 (17.54)	7/66 (10.61)	0.187	2/74 (2.70)[a]	1/28 (3.57)	1/46 (2.17)	0.719
Conjunctival vascular tortuosity	26/237 (10.97)	21/171 (12.28)	5/66 (7.58)	0.299	1/74 (1.35)[a]	0/28[b]	1/46 (2.17)	0.432
Posterior capsular opacification	26/237 (10.97)	18/171 (10.53)	8/66 (12.12)	0.725	0/74[a]	0/28	0/46[c]	–
Angiokeratomas	143/237 (60.34)	122/171 (71.35)	21/66 (31.82)	< 0.001	0/74[a]	0/28[b]	0/46[c]	–
Osteoporosis	44/237 (18.57)	32/171 (18.71)	12/66 (18.18)	0.925	2/74 (2.70)[a]	1/28 (3.57)[b]	1/46 (2.17)[c]	0.719
Respiratory system involvement	43/237 (18.14)	35/171 (20.47)	8/66 (12.12)	0135	2/74 (2.70)[a]	1/28 (3.57)[b]	1/46 (2.17)	0.719
Dyspnea	17/237 (7.17)	13/171 (7.60)	4/66 (6.06)	0.680	0/74[a]	0/28	0/46	–
Chronic bronchitis	25/237 (10.55)	19/171 (11.11)	6/66 (9.09)	0.650	2/74 (2.70)[a]	1/28 (3.57)	1/46 (2.17)	0.719
COPD	9/237 (3.80)	9/171 (5.26)	0/66	0.057	0/74	0/28	0/46	–

(*Continued*)

	Classical phenotype (N = 237)				Late-onset phenotype (N = 74)			
	All patients	Males (n = 171)	Females (n = 66)	P value	All patients	Males (n = 28)	Females (n = 46)	P value
Bronchial asthma	3/237 (1.27)	3/171 (1.75)	0/66	0.279	0/74	0/28	0/46	–

Note: COPD, chronic obstructive pulmonary disease; [a]the difference between patients with late-onset and patients with classical type was statistically significant ($P < 0.05$); [b]the difference between male patients with late-onset and male patients with classical type was statistically significant ($P < 0.05$); [c]the difference between female patients with late-onset and female patients with classical type was statistically significant ($P < 0.05$).

Similarly, classical female patients have a higher frequency of multiple-organ involvement (such as acroparesthesia, hypohidrosis/anhidrosis, angiokeratoma, and neuropsychiatric and digestive system involvement) than female patients with late-onset Fabry disease ($P < 0.05$).

Relationship between α-Gal A activity and clinical manifestations of patients of different sexes with classical and late-onset Fabry disease

Analysis of α-Gal A activity in patients with Fabry disease revealed that the average α-Gal A activity was 0.30 (0.25, 1.38) μmol/L/h (dry blood spot) and 0.70 (0.35, 14.59) nmol/g/min (fluorescent substrate method). Males had significantly lower enzyme activity than females (0.29 (0.22, 0.35) vs. 3.57 (1.53, 5.15) μmol/L/h (dry blood spot); 0.40 (0.20, 0.70) vs. 25.35 (16.05, 35.78) nmol/g/min (fluorescent substrate method), $P < 0.05$), and classical patients had lower activity than late-onset patients (0.29 (0.20, 0.36) vs. 2.90 (0.89, 4.66) μmol/L/h (dry blood spot); 0.52 (0.30, 11.54) vs. 4.45 (0.85, 24.33) nmol/g/min (fluorescent substrate method)).

Patients were divided into ⩽5% and > 5% of the normal mean value of enzyme activity, and the enzyme activity of classical male patients was ⩽ 5% of the normal mean value (Table 3). Among the patients, those with enzyme activity of ⩽5% of the normal mean value of enzyme activity had a significantly higher frequency of acroparesthesia, hypohidrosis/anhidrosis, angiokeratoma, renal involvement (proteinuria, increased serum creatinine), diarrhea, eye involvement (vision loss, corneal vortex opacity), and ear involvement (tinnitus, deafness, and hearing loss) than those with > 5% of the normal mean value of enzyme activity ($P < 0.05$).

Among classical patients, those with enzyme activity of ⩽5% of the normal mean value had a significantly higher frequency of acroparesthesia, hypohidrosis/anhidrosis, angiokeratoma, and renal involvement (proteinuria, increased serum creatinine) than those with enzyme activity of > 5% ($P < 0.05$). Considering that the sample size of patients with late-onset Fabry disease was small, when the patients were dispersed into different enzyme activity groups, the sample size in each group was even smaller, and the results were not statistically significant.

In male patients, the incidence of acroparesthesia, hypohidrosis/anhidrosis, angiokeratoma, eye involvement (vision loss), and ear involvement (tinnitus, hearing loss) in patients with enzyme activity of ⩽5% of the normal mean value was significantly higher than that in patients with enzyme activity of > 5% ($P < 0.05$).

In female patients, no significant difference in organ involvement was observed between patients with enzyme activity of ⩽5% of the normal mean and those with enzyme activity of > 5%, and the correlation between enzyme activity and clinical manifestation was weak.

GLA gene mutation detection in Fabry disease patients

The *GLA* gene mutation results of 163 patients were examined in this study, and 95 different mutation sites were detected. Exon 5 had the highest proportion of mutations (30/163, 18.40%), and missense mutations (61.96%) were the most common mutation type, followed by nonsense mutations (16.56%), frameshift mutations (13.50%), splicing mutations (4.91%), and large-fragment deletions (3.07%; Fig. 1).

Moreover, the same mutation, c.334C>T, p.R112C (exon 2), was found in nine patients from six unrelated families, with a frequency of 5.52% (9/163). This

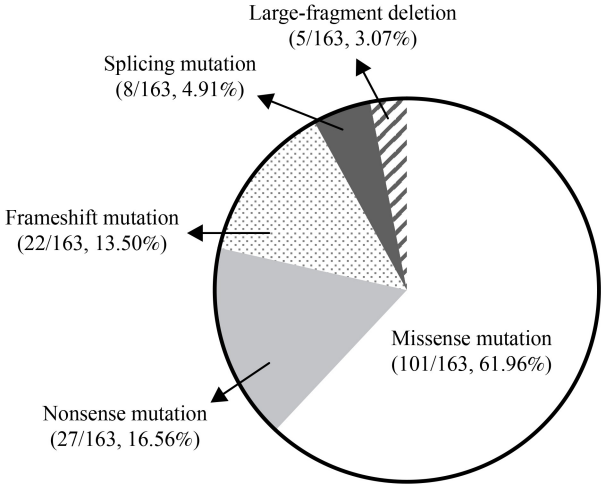

Fig. 1 Summary of *GLA* gene mutation types. Among the *GLA* gene mutations, missense mutations accounted for the largest proportion (61.96%), followed by nonsense mutations (16.56%), frameshift mutations (13.50%), splicing mutations (4.91%), and large-fragment deletion (3.07%).

Table 3 Comparison of clinical manifestations in patients with Fabry disease with different enzyme activities and sexes (*n*/*N* (%))

	Enzyme activity ⩽ 5% of normal mean				Enzyme activity > 5% of normal mean			
	All patients (*N* = 118)	Males (*n* = 111)	Females (*n* = 7)	*P* value	All patients (*N* = 52)	Males (*n* = 14)	Females (*n* = 38)	*P* value
Acroparesthesia (limb pain)	105/118 (88.98)	101/111 (90.99)	4/7 (57.14)	0.006	26/52 (50.00)[a]	8/14 (57.14)[b]	18/38 (47.37)	0.532
Anhidrosis or hypohidrosis	95/118 (80.51)	91/111 (81.98)	4/7 (57.14)	0.108	18/52 (34.62)[a]	6/14 (42.86)[b]	12/38 (31.58)	0.448
Angiokeratomas	82/118 (69.49)	78/111 (70.27)	4/7 (57.14)	0.464	10/52 (19.23)[a]	3/14 (21.43)[b]	7/38 (18.42)[c]	0.807
Renal involvement	87/118 (73.73)	85/111 (76.58)	2/7 (28.57)	0.005	24/52 (46.15)[a]	9/14 (64.29)	15/38 (39.47)	0.111
Proteinuria	78/118 (66.10)	76/111 (68.47)	2/7 (28.57)	0.031	20/52 (38.46)[a]	8/14 (57.14)	12/38 (31.58)	0.093
Increased serum creatinine	54/118 (45.76)	53/111 (47.75)	1/7 (14.28)	0.085	9/52 (17.31)	4/14 (28.57)	5/38 (13.16)	0.193
Cardiovascular involvement	85/118 (72.03)	80/111 (72.07)	5/7 (71.43)	0.971	31/52 (59.62)	8/14 (57.14)	23/38 (60.53)	0.825
Palpitation	45/118 (38.14)	41/111 (36.94)	4/7 (57.14)	0.286	15/52(28.85)	1/14 (7.14)[b]	14/38 (36.84)	0.036
Chest tightness	18/118 (15.25)	17/111 (15.32)	1/7 (14.28)	0.941	4/52 (7.69)	0/14	4/38 (10.53)	0.206
Chest pain	11/118 (9.32)	10/111 (9.01)	1/7 (14.28)	0.641	2/52 (3.85)	0/14	2/38 (5.26)	0.381
Left ventricular hypertrophy	50/118 (42.37)	48/111 (43.24)	2/7 (28.57)	0.446	14/52 (26.92)	5/14 (35.71)	9/38 (23.68)	0.386
Valve disease	25/118 (21.19)	23/111 (20.72)	2/7 (28.57)	0.662	10/52 (19.23)	3/14 (21.43)	7/38 (18.42)	0.807
Abnormal electrocardiogram	31/118 (26.27)	29/111 (26.13)	3/7 (42.86)	0.334	14/52 (26.92)	2/14 (14.29)	12/38 (31.58)	0.212
Neuropsychiatric involvement	80/118 (67.80)	76/111 (68.46)	4/7 (57.14)	0.534	31/52 (59.62)	7/14 (50.00)	24/38 (63.16)	0.391
Decreased attention	53/118 (44.92)	50/111 (45.05)	3/7 (42.86)	0.910	18/52 (34.62)	4/14 (28.57)	14/38 (36.84)	0.578
Anxiety and depression	47/118 (39.83)	44/111 (39.64)	3/7 (42.86)	0.866	13/52 (25.00)	3/14 (21.43)	10/38 (26.32)	0.718
Dizziness	46/118 (38.98)	45/111 (40.54)	1/7 (14.28)	0.167	19/52 (36.54)	3/14 (21.43)	16/38 (42.11)	0.170
Headache	4/118 (3.39)	4/111 (3.60)	0/7	0.609	0/52	0/14	0/38	–
Cerebral infarction	17/118 (14.41)	17/111 (15.32)	0/7	0.263	6/52 (11.54)	2/14 (14.29)	4/38 (10.53)	0.707
Cerebral hemorrhage	5/118 (4.24)	5/111 (4.50)	0/7	0.566	1/52 (1.92)	0/14	1/38 (2.63)	0.540
Digestive system involvement	79/118 (66.95)	75/111 (67.57)	4/7 (57.14)	0.570	28/52 (53.85)	7/14 (50.00)	21/38 (55.26)	0.736
Nausea and vomiting	35/118 (29.66)	34/111 (30.63)	1/7 (14.28)	0.358	10/52 (19.23)	3/14 (21.43)	7/38 (18.42)	0.807
Stomachache	31/118 (26.27)	29/111 (26.13)	2/7 (28.57)	0.887	10/52 (19.23)	2/14 (14.28)	8/38 (21.05)	0.583
Diarrhea	67/118 (56.78)	65/111 (58.56)	2/7 (28.57)	0.120	18/52 (34.62)[a]	6/14 (42.86)	12/38 (31.58)	0.448
Constipation	16/118 (13.56)	14/111 (12.61)	2/7 (28.57)	0.232	9/52 (17.31)	0/14	9/38(23.68)	0.045
Eye involvement	89/118 (75.42)	86/111 (77.48)	3/7 (42.86)	0.039	27/52 (51.92)[a]	6/14 (42.86)[b]	21/38 (55.26)	0.427
Vision loss	66/118 (55.93)	63/111 (56.76)	3/7 (42.86)	0.472	17/52 (32.69)[a]	4/14 (28.57)[b]	13/38 (34.21)	0.701
Corneal vortex opacity	44/118 (37.29)	44/111 (39.64)	0/7	0.035	11/52 (21.15)[a]	2/14 (14.29)	9/38(23.68)	0.462
Retinal vascular tortuosity	24/118 (20.34)	23/111 (20.72)	1/7 (14.28)	0.682	7/52 (13.46)	1/14 (7.14)	6/38 (15.79)	0.418
Conjunctival vascular tortuosity	19/118 (16.10)	19/111 (17.12)	0/7	0.232	5/52 (9.62)	0/14	5/38 (13.16)	0.153
Posterior capsular opacification	15/118 (12.71)	15/111 (13.51)	0/7	0.298	7/52 (13.46)	1/14 (7.14)	6/38 (15.79)	0.418
Ear involvement	79/118 (66.95)	76/111 (68.47)	3/7 (42.86)	0.162	25/52 (48.08)[a]	5/14 (35.71)[b]	20/38 (52.63)	0.279
Tinnitus	68/118 (57.63)	66/111 (59.46)	2/7 (28.57)	0.109	21/52 (40.38)[a]	4/14 (28.57)[b]	17/38 (44.74)	0.292
Deafness	13/118 (11.02)	12/111 (10.08)	1/7 (14.28)	0.776	0/52[a]	0/14	0/38[c]	–
Hearing loss	55/118 (46.61)	53/111 (47.75)	2/7 (28.57)	0.324	16/52 (30.77)	2/14 (14.29)[b]	14/38 (36.84)	0.118
Respiratory system involvement	26/118 (22.03)	25/111 (22.52)	1/7 (14.28)	0.610	10/52 (19.23)	4/14 (28.57)	6/38 (15.79)	0.300
Dyspnea	11/118 (9.32)	10/111 (9.01)	1/7 (14.28)	0.641	5/52 (9.62)	2/14 (14.29)	3/38 (7.89)	0.488
Chronic bronchitis	16/118 (13.56)	16/111 (14.41)	0/7	0.280	6/52 (11.54)	1/14 (7.14)	5/38 (13.16)	0.547
COPD	5/118 (4.24)	5/111 (4.50)	0/7	0.566	1/52 (1.92)	1/14 (7.14)	0/38	0.096
Bronchial asthma	3/118 (2.54)	3/111 (2.70)	0/7	0.660	0/52	0/14	0/38	–
Osteoporosis	24/118 (20.34)	21/111 (18.92)	3/7 (42.86)	0.123	7/52 (13.46)	2/14 (14.29)	5/38 (13.16)	0.916

Note: COPD, chronic obstructive pulmonary disease; [a]the difference between patients with enzyme activity of > 5% of the normal mean and patients with enzyme activity of ⩽5% of the normal mean was statistically significant ($P < 0.05$); [b]the difference between male patients with enzyme activity of > 5% of the normal mean and male patients with enzyme activity of ⩽5% of the normal mean was statistically significant ($P < 0.05$); [c]the difference between female patients with enzyme activity of > 5% of the normal mean and female patients with enzyme activity of ⩽5% of the normal mean was statistically significant ($P < 0.05$).

mutation was predicted to be pathogenic by PolyPhen-2, Mutation Taster, PROVEAN, and SIFT analysis. The clinical manifestations of nine patients from six families were analyzed (Table 4). A significant heterogeneity in the clinical manifestations of Fabry disease was found among different families and within the same family. In Pedigree 1 and Pedigree 3, organ involvement in males was more evident than that in females. In Pedigree 2, organ involvement in older patients was more evident than that in younger patients.

Relationship between *GLA* gene mutation and enzyme activities of patients of different sexes with classical and late-onset Fabry disease

Based on the type of gene mutations, patients were divided into the truncated mutation (62 cases) and nontruncated mutation (101 cases) groups.

The enzyme activity of patients in the truncated mutation group was slightly lower than those in the nontruncated mutation group (0.31 (0.14, 0.37) vs. 0.36 (0.24, 1.65) μmol/L/h (dried blood spot), 0.40 (0.20, 8.73) vs. 0.90 (0.40, 21.03) nmol/g/min (fluorescent substrate method)), but the difference was not statistically significant.

Further analysis showed no significant difference in enzyme activity between truncated and nontruncated mutations in male and female patients with classical and late-onset phenotypes (data not shown).

In addition, the enzyme activity of missense mutations was slightly higher than that of other mutation types (nonsense, frameshift, splicing mutation, and large-

Table 4 Summary of clinical manifestations of nine patients with Fabry disease from six families with the same mutation site

	Case 1.1	Case 1.2	Case 2.1	Case 2.2	Case 3.1	Case 3.2	Case 4	Case 5	Case 6
Sex	Male	Female	Male	Male	Female	Male	Male	Male	Male
Age (year)	37	10	16	21	52	25	39	14	52
Initial manifestations	Acro	High Lyso-Gb3 concentrations	Acro	Acro	Acro	Acro	Acro	Acro	Acro
Angiokeratomas	+	–	–	–	–	+	+	–	+
Anhidrosis or hypohidrosis	+	–	+	+	–	+	+	+	+
Proteinuria	–	–	–	+	–	+	+	–	+
Increased serum creatinine	–	–	–	–	–	–	+	–	+
Palpitation	+	–	–	–	–	–	+	–	–
Chest tightness	–	–	–	–	–	–	+	–	–
Chest pain	–	–	–	–	–	–	+	–	–
Left ventricular hypertrophy	+	–	–	–	–	–	+	–	+
Valve disease	+	–	–	–	–	–	+	–	–
Abnormal electrocardiogram	+	–	–	–	–	–	–	–	–
Nausea and vomiting	+	–	–	–	–	–	+	+	–
Stomachache	–	–	–	+	–	–	–	+	+
Diarrhea	+	–	–	+	+	+	+	–	–
Constipation	+	–	–	–	–	–	–	–	+
Vision loss	+	–	+	–	–	+	–	–	–
Corneal vortex opacity	+	–	–	–	–	–	–	–	–
Retinal vascular tortuosity	–	–	–	–	–	–	+	–	+
Conjunctival vascular tortuosity	–	–	–	–	–	+	+	–	–
Tinnitus	–	–	–	–	+	+	+	–	–
Deafness	–	–	–	–	–	–	+	–	–
Hearing loss	–	–	+	+	–	–	+	–	–
Chronic bronchitis	–	–	–	–	–	–	+	–	–
Osteoporosis	–	–	–	–	–	–	+	–	–
Enzyme activity	0.26 μmol/L/h	3.45 μmol/L/h	0	1.38 μmol/L/h	22.6 nmol/g/min	0	0	0	NA

Note: Acro, acroparesthesia (limb pain); NA, not available. "+" indicates the presence of the corresponding clinical symptom. "–" indicates the absence of the corresponding clinical symptom. Normal range of enzyme activity detection methods: dried blood spot, 2.4–17.65 μmol/L/h; fluorescent substrate method, 24.5–63.6 nmol/g/min.

fragment deletion), but the difference was not statistically significant.

Relationship between *GLA* gene mutations and clinical manifestations of patients of different sexes with classical and late-onset Fabry disease

The relationship between gene mutations and clinical manifestations of Fabry disease was analyzed (Table 5). The results indicated that among the patients, the frequency of eye involvement (posterior capsular opacification) and ear involvement (tinnitus, hearing loss) in patients with truncated mutations was higher than that in patients with nontruncated mutations ($P < 0.05$). Patients with truncated mutation patients also showed slightly higher rates of other organ involvement, although the difference was not statistically significant. Male patients with truncated mutations also had a higher frequency of eye involvement (vision loss, posterior capsular opacification) and ear involvement (tinnitus, hearing loss) than those with nontruncated mutations ($P < 0.05$). By contrast, no significant difference in the frequency of organ involvement was found between female patients with truncated mutation and female patients with nontruncated mutation.

In patients with truncated mutations, the frequency of multiorgan involvement (such as acroparesthesia, hypohidrosis/anhidrosis, angiokeratoma, renal involvement (proteinuria, increased serum creatinine), diarrhea, eye involvement (decreased vision), and ear involvement (tinnitus, hearing loss)) was significantly higher in male patients than in female patients. In patients with nontruncated mutations, the frequency of multiorgan involvement (such as acroparesthesia, hypohidrosis/anhidrosis, angiokeratoma, renal involvement (proteinuria, increased serum creatinine), and diarrhea) in male patients was significantly different from that in female patients ($P < 0.05$).

In this study, the relationship between gene mutations and clinical manifestations in classical and late-onset patients was further analyzed (Table S1). The results indicated no significant difference in the frequency of organ involvement between classical patients with truncated mutations and those with nontruncated mutations, regardless of sex. However, in patients with truncated and nontruncated mutations, the frequency of multiple-organ involvement in male patients was significantly higher than that in female patients ($P < 0.05$).

Discussion

This study is the largest clinical study of Fabry disease in China, and it has several noteworthy findings. First, the incidence of multi-organ involvement was significantly higher in male patients with a classical phenotype than in female patients with a late-onset phenotype. In both sexes, classical patients commonly presented with acroparesthesia and multiorgan involvement, whereas late-onset patients showed renal, neuropsychiatric, and cardiovascular system involvement. Second, male patients had lower enzyme activity than female patients, and classical patients had lower enzyme activity than late-onset patients. α-Gal A activity was closely correlated with clinical symptoms in males but weakly correlated with clinical manifestation in females. Third, missense mutation was the most common mutation in Fabry disease. The clinical manifestations of patients with the same mutation were heterogeneous, and the correlation between gene mutation and enzyme activity or clinical manifestation is weak. Previous studies focused on European and American populations, and most of them were grouped by sex or phenotype. Only few reports have been found on the correlation among sex, enzyme activity, gene mutation, and the clinical manifestation of classical and late-onset phenotypes. The correlation among enzyme activity, gene mutation, and clinical manifestations remains unclear [27]. Thus, this study aimed to explore the clinical manifestations, enzyme activity, and gene mutations of Chinese patients of different sexes with classical and late-onset Fabry disease, which will provide a comprehensive understanding of the disease.

This study showed that the common systemic involvement of patients with Fabry disease mainly included acroparesthesia, hypohidrosis/anhidrosis, neuropsychiatric, renal, and cardiovascular involvement. Among the specific clinical symptoms, limb pain was the most common symptom (66.56%), followed by hypohidrosis/anhidrosis (62.70%), proteinuria (51.13%), and angiokeratomas (45.98%). Based on the statistical analysis of the related symptoms of 1765 patients in the International Fabry Registry system [14], the incidences of limb pain and angiokeratomas were 54.1% and 45%, respectively; these findings are consistent with the results of this study. However, the incidence of proteinuria was only 17%, which was significantly lower than the value reported in this study. Most of the patients in this study were adults over 20 years of age who visited the nephrology department, whereas more than 40% of the patients in the International Fabry Registry were adolescents under 20 years of age. In addition, relevant studies have reported that ocular lesions are a common symptom of Fabry disease. Previous studies in Europe and the United States showed that a considerable proportion of patients with Fabry disease were diagnosed through ophthalmic examination, and almost all males and 70%–90% of females had ocular lesions of different degrees [28]. However, this study and a previous clinical study in Japan [29] showed that the incidence of ocular

Table 5 Relationship between *GLA* gene mutations and clinical manifestations of patients of different sexes with Fabry disease (*n*/*N* (%))

	Truncated mutation group				Nontruncated mutation group			
	All patients (*N* = 62)	Males (*n* = 42)	Females (*n* = 20)	*P* value	All patients (*N* = 101)	Males (*n* = 73)	Females (*n* = 28)	*P* value
Acroparesthesia (limb pain)	51/62 (82.26)	39/42 (92.86)	12/20 (60.00)	0.002	70/101 (69.31)	58/73 (79.45)	12/28 (42.86)	< 0.001
Anhidrosis or hypohidrosis	43/62 (69.35)	36/42 (85.71)	7/20 (35.00)	< 0.001	65/101 (66.33)	54/73 (73.97)	11/28 (39.29)	0.001
Angiokeratomas	33/62 (53.23)	29/42 (69.05)	4/20 (20.00)	< 0.001	43/101 (42.57)	38/73 (52.05)	5/28 (17.86)	0.002
Renal involvement	43/62 (69.35)	34/42 (80.95)	9/20 (45.00)	0.004	63/101 (62.38)	56/73 (76.71)	7/28 (25.00)	< 0.001
Proteinuria	37/62 (59.68)	29/42 (69.05)	8/20 (40.00)	0.029	57/101 (56.44)	51/73 (69.86)	6/28 (21.43)	< 0.001
Increased serum creatinine	26/62 (41.94)	22/42 (52.38)	4/20 (20.00)	0.016	32/101 (31.68)	31/73 (42.47)	1/28 (3.57)	< 0.001
Cardiovascular involvement	44/62 (70.97)	31/42 (73.81)	13/20 (65.00)	0.475	70/101 (69.30)	53/73 (72.60)	17/28 (60.71)	0.246
Palpitation	25/62 (40.32)	17/42 (40.48)	8/20 (40.00)	0.971	33/101 (32.67)	24/73 (32.88)	9/28 (32.14)	0.944
Chest tightness	9/62 (14.52)	7/42 (16.67)	2/20 (10.00)	0.486	10/101 (9.90)	6/73 (8.22)	4/28 (14.29)	0.361
Chest pain	4/62 (6.45)	3/42 (7.14)	1/20 (5.00)	0.748	6/101 (5.94)	4/73 (5.48)	2/28 (7.14)	0.752
Hypertension	14/62 (22.58)	11/42 (26.19)	3/20 (15.00)	0.325	25/101 (24.75)	21/73 (28.77)	4/28 (14.29)	0.131
Left ventricular hypertrophy	25/62 (40.32)	19/42 (45.24)	6/20 (30.00)	0.253	38/101 (37.62)	31/73 (42.47)	7/28 (25.00)	0.105
Valve disease	14/62 (22.58)	11/42 (26.19)	3/20 (15.00)	0.325	21/101 (20.79)	15/73 (20.55)	6/28 (21.43)	0.922
Abnormal electrocardiogram	18/62 (29.03)	11/42 (26.19)	7/20 (35.00)	0.475	25/101 (24.75)	16/73 (21.92)	9/28 (32.14)	0.286
Neuropsychiatric involvement	41/62 (66.13)	30/42 (71.43)	11/20 (55.00)	0.297	66/101 (65.35)	50/73 (68.49)	16/28 (57.14)	0.283
Decreased attention	23/62 (37.10)	18/42 (42.86)	5/20 (25.00)	0.174	45/101 (44.55)	35/73 (47.95)	10/28 (35.71)	0.268
Anxiety and depression	24/62 (38.71)	17/42 (40.48)	7/20 (35.00)	0.679	36/101 (35.64)	31/73 (42.47)	5/28 (17.86)	0.021
Dizziness	25/62 (40.32)	17/42 (40.48)	8/20 (40.00)	0.971	37/101 (36.64)	29/73 (39.73)	8/28 (28.57)	0.298
Headache	2/62 (3.23)	2/42 (4.76)	0/20	0.321	0/101	0/73	0/28	–
Cerebral infarction	11/62 (17.74)	8/42 (19.05)	3/20 (15.00)	0.697	11/101 (10.89)	10/73 (13.70)	1/28 (3.57)	0.144
Cerebral hemorrhage	3/62 (4.84)	2/42 (4.76)	1/20 (5.00)	0.967	4/101 (3.96)	4/73 (5.48)	0/28	0.206
Digestive system involvement	43/62 (69.35)	31/42 (73.81)	12/20 (60.00)	0.270	60/101 (59.41)	46/73 (63.01)	14/28 (50.00)	0.233
Nausea and vomiting	20/62 (32.26)	15/42 (35.71)	5/20 (25.00)	0.399	22/101 (21.78)	19/73 (26.03)	3/28 (10.71)	0.095
Stomachache	19/62 (30.65)	14/42 (33.33)	5/20 (25.00)	0.506	27/101 (26.73)	22/73 (30.14)	5/28 (17.86)	0.212
Diarrhea	30/62 (48.39)	24/42 (57.14)	6/20 (30.00)	0.046	46/101 (45.54)	40/73 (54.79)	6/28 (21.43)	0.003
Constipation	13/62 (20.97)	8/42 (19.05)	5/20 (25.00)	0.590	14/101 (13.86)	7/73 (9.60)	7/28 (25.00)	0.045
Eye involvement	46/62 (74.19)	35/42 (83.33)	11/20 (55.00)	0.017	64/101 (63.36)	49/73 (67.12)	15/28 (53.57)	0.206
Vision loss	36/62 (58.06)	28/42 (66.67)	8/20 (40.00)	0.047	43/101 (42.57)	33/73 (45.21)[b]	10/28 (35.71)	0.388
Corneal vortex opacity	23/62 (37.10)	18/42 (42.86)	5/20 (25.00)	0.174	28/101 (27.72)	22/73 (30.14)	6/28 (21.43)	0.381
Retinal vascular tortuosity	15/62 (24.19)	12/42 (28.57)	3/20 (15.00)	0.243	16/101 (15.84)	12/73 (16.44)	4/28 (14.29)	0.791
Conjunctival vascular tortuosity	12/62 (19.35)	9/42 (21.43)	3/20 (15.00)	0.549	11/101 (10.89)	8/73 (10.96)	3/28 (10.71)	0.972
Posterior capsular opacification	14/62 (22.58)	10/42 (23.81)	4/20 (20.00)	0.737	9/101 (8.91)[a]	6/73 (8.22)[b]	3/28 (10.71)	0.694
Ear involvement	42/62 (67.74)	34/42 (80.95)	8/20 (40.00)	0.001	52/101 (51.49)[a]	37/73 (50.68)[b]	15/28 (53.57)	0.795
Tinnitus	36/62 (58.06)	28/42 (66.67)	8/20 (40.00)	0.047	40/101 (39.60)[a]	28/73 (38.36)[b]	12/28 (42.86)	0.679
Deafness	4/62 (6.45)	4/42 (9.52)	0/20	0.154	7/101 (6.93)	7/73 (9.59)	0/28	0.089
Hearing loss	34/62 (54.84)	27/42 (64.29)	7/20 (35.00)	0.030	37/101 (36.63)[a]	28/73 (38.36)[b]	9/28 (32.14)	0.562
Respiratory system involvement	13/62 (20.97)	10/42 (23.81)	3/20 (15.00)	0.426	18/101 (17.82)	14/73 (19.17)	4/28 (14.29)	0.565
Dyspnea	7/62 (11.29)	6/42 (14.29)	1/20 (5.00)	0.280	5/101 (4.95)	3/73 (4.11)	2/28 (7.14)	0.529
Chronic bronchitis	7/62 (11.29)	4/42 (9.52)	3/20 (15.00)	0.524	11/101 (10.89)	9/73 (12.33)	3/28 (10.71)	0.822
COPD	2/62 (3.23)	2/42 (4.76)	0/20	0.321	4/101 (3.96)	4/73 (5.48)	0/28	0.206
Osteoporosis	13/62 (20.97)	10/42 (23.81)	3/20 (15.00)	0.426	20/101 (19.80)	13/73 (17.81)	7/28 (25.00)	0.417

Note: COPD, chronic obstructive pulmonary disease; [a]the difference between patients with nontruncated mutations and patients with truncated mutations was statistically significant ($P < 0.05$); [b]the difference between male patients with nontruncated mutations and male patients with truncated mutations was statistically significant ($P < 0.05$).

lesions in patients with Fabry disease was low. To determine whether this result is related to Asian ethnicity, genetic factors, or different cognition and emphasis on disease, conducting further research is necessary. In Chinese mainland, ophthalmic examinations of patients with Fabry disease are primarily conducted in larger centers, and the absence of ophthalmology in some multidisciplinary teams can lead to misdiagnosis. Therefore, enhancing the understanding and recognition of Fabry disease in various clinical departments is crucial.

Clinically, Fabry disease can be divided into classical and late-onset types [5]. In classical type, enzyme activity is absent or significantly decreased and more common in men, and it involves multiple organs. In late-onset type, enzyme activity is partially decreased or normal and more common in women. It also occurs in adulthood and often shows single-organ involvement. In this study, most classical patients were males (72.15%), whereas most late-onset patients were females (62.16%). Regardless of sex, classical patients commonly manifested acroparesthesia with multiple-organ involvement, whereas late-onset patients mainly showed renal, neuropsychiatric, and cardiovascular involvement. Classical patients had lower enzyme activity and a higher frequency of multi-organ involvement compared with late-onset patients, which are consistent with the known characteristics of Fabry disease [30]. Clinical analysis revealed more severe organ involvement and lower α-Gal A activity in males than in females [7]. Although Fabry disease primarily affects males because of its X-linked inheritance, female heterozygotes can also exhibit varying levels of enzyme activity and a range of clinical manifestations, from asymptomatic carriers to severe symptoms similar to males, even among female heterozygotes with the same *GLA* gene mutation site. Current research indicates that the heterogeneity in the clinical manifestation of females may be largely attributed to skewed X chromosome inactivation. In a female heterozygote, only one X chromosome is actively expressed in each somatic cell (the other X chromosome is condensed into chromatin, forming a Barr body, leading to gene function inhibition and impaired expression). If the active X chromosome in most somatic cells carries a mutated *GLA* gene, then the clinical presentation is more severe. Conversely, if the active X chromosome in most somatic cells carries a normal *GLA* gene, then the clinical presentation is milder. Therefore, clinical manifestations vary among female patients [18,31–36]. Apart from its association with skewed X chromosome inactivation, the heterogeneity in the clinical manifestation of females may also be influenced by factors such as environmental influences, blood type, epigenetics, and alterations of the molecular process. No direct correlation is found between enzyme activity levels and clinical manifestations in most women, and symptoms often appear later in life and progress slowly. Furthermore, age is closely related to organ involvement in patients with Fabry disease. Our research group has previously explored the initial manifestations and renal involvement of Chinese patients of different sexes and ages with classical and late-onset Fabry disease [37]. The research indicates that in male and female classical patients, the initial manifestations of the preschool and juvenile groups were mainly acroparesthesia, and the frequency of renal and cardiovascular involvement in the young group was higher than that in the preschool and juvenile groups, with cardiovascular involvement being more common in middle-aged/elderly patients. No evident renal involvement was observed in the preschool group, and renal involvement was most common in the young, middle-aged, and elderly groups. Proteinuria can appear in classical male patients as early as approximately 20 years, and renal insufficiency can occur at approximately 25 years. With age, over 50% of patients can experience varying degrees of proteinuria and renal insufficiency around the ages of 25 and 40 years, respectively.

α-Gal A is a homodimeric glycoprotein encoded by the *GLA* gene [38,39]. The threshold level of α-Gal A activity for clinically significant Fabry disease is below 30%–35% of the normal mean value [6,40]. Patients with classical Fabry disease typically have α-Gal A activity below 1%–5% of the normal mean value, whereas patients with late-onset Fabry disease have α-Gal A activity above 3% but mostly below 30% of the normal mean value [16,41,42]. In this study, group analysis was performed in patients with enzyme activity of below 5% of the mean value of normal enzyme activity. Classical male patients with enzyme activity of ⩽5% had a higher frequency of acroparesthesia and multi-organ involvement than those with enzyme activity of > 5%. A relationship is found between enzyme activity and organ involvement frequency, and male patients with lower enzyme activity may have more severe organ involvement [15]. In females, α-Gal A activity can be within normal limits, slightly decreased, or completely lost because of skewed X chromosome inactivation. Less than 50% of females in this study had enzyme activity below the lower limit of the normal value. No significant difference in organ involvement was found between females with enzyme activity of ⩽5% and those with enzyme activity of > 5%. The use of α-Gal A activity as a diagnostic marker for Fabry disease in women has been controversial. The Fabry Outcome Survey showed that nearly half of females with clinical symptoms of Fabry disease had α-Gal A activity within the normal range [43]. In addition, in female heterozygous patients, a low level of residual α-Gal activity is associated with more severe gene variants, indicating its role as a surrogate marker for higher disease severity and poorer outcomes [18,44]. However, further evaluation with a larger female

cohort is necessary to determine the reliability of residual α-Gal A activity in predicting clinical severity.

Fabry disease is primarily due to mutations in the *GLA* gene, and the detection of *GLA* gene mutations is the gold standard for diagnosis [45]. Most mutations are unique to each family or individual [46,47], and no obvious hotspot mutations have been identified. However, some studies have reported the same mutations in unrelated families, particularly mutations in CpG dinucleotides (CpG mutation hotspots) [48]. In this study, the highest number of gene mutation sites (18.40%) was found in exon 5 among 163 patients, and nine patients from six families were found to have the same missense mutation (c.334C>T), with a mutation frequency of 5.52%. This mutation was identified as a pathogenic mutation by online software pathogenicity prediction analysis. Previous studies have reported that the most common mutation in patients with Fabry disease in Europe and the United States was p.A143T, which is usually considered as a benign polymorphism and is detected in 64% of male newborns with Fabry disease [49]. Moreover, a hotspot mutation (IVS4+919G>A) associated with cardiac variants was reported in Taiwan, China, and the detection rate was as high as 83.3% in male neonates with Fabry disease [50,51]. However, no reports on hotspot mutations of Fabry disease have been found in Chinese mainland. Few studies have reported on a c.334C>T mutation, and whether it is a hotspot mutation of Fabry disease in Chinese mainland needs further study.

Few studies have been conducted on the correlation between the genotypes and enzyme activity or clinical manifestations in Fabry disease, but such a correlation remains unclear [47]. Based on previous reports, even patients with the same gene mutation within the same family have different clinical manifestations [52]. In this study, clinical manifestations of patients belonging to six families with the same mutation (c.334C>T) were analyzed. The results indicated that patients with the same mutation had lower α-Gal A activity compared with the normal range, but a significant variability was found in the affected organs. The heterogeneity in clinical manifestations among patients is influenced by factors such as gene mutations, enzyme activities, sex, age, clinical phenotype, blood type, skewed X chromosome inactivation (female heterozygotes), and environment. In this study, patients were divided into the truncated and nontruncated mutation groups. The results revealed no significant differences in enzyme activity and clinical manifestations between these groups in both sexes or between classical and late-onset patients. These findings indicate a relatively weak relationship among gene mutations in Fabry disease, enzyme activity, and clinical manifestations. Therefore, further research is necessary to determine the precise intrinsic relationship among genotype, enzyme activity, and clinical manifestations.

This study has certain limitations. First, most of the patients with Fabry disease, who were included in this study, were of classical type with more prominent subjective symptoms as the main clinical manifestations. Late-onset patients and those with abnormalities detected through specialized examinations such as ophthalmologic and otologic evaluations were relatively fewer. By contrast, research reports from Europe and the United States indicate a higher prevalence of late-onset patients [7]. Therefore, considerable attention should be paid to the screening and diagnosis of late-onset patients in the Chinese population to reduce missed diagnosis. Furthermore, among the 311 patients with Fabry disease in this study, only 67 had complete enzyme metabolism substrate concentrations of Gb3/Lyso-Gb3 (53 classical patients and 14 late-onset patients). Given the small sample size, this study did not delve further into the correlation among enzyme metabolism substrate concentrations and genotypes, enzyme activity, and clinical manifestations of patients with Fabry disease. In addition, clinical prognostic data of patients with Fabry disease were lacking in this study, highlighting the necessity for long-term clinical follow-up to comprehensively understand the progression of the disease, as well as the relationship among enzyme activity, gene mutations, and prognosis.

Conclusions

In this study, the correlation among Fabry disease gene mutations, enzyme activity, and clinical manifestations was systematically elucidated, contributing to an enhanced understanding of Fabry disease. The research findings indicate that male patients with Fabry disease, whether classic or late-onset, have a higher frequency of multi-organ involvement compared with female patients, with lower α-Gal A activity and a close relationship between enzyme activity and clinical manifestations. By contrast, the correlation between enzyme activity and clinical manifestations is weaker in female patients. Furthermore, patients with the same *GLA* gene mutation site exhibit heterogeneity in clinical manifestations, with a weaker correlation among gene mutations, enzyme activity, and clinical manifestations.

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Compliance with ethics guidelines

Conflicts of interest Wenkai Guo, Yuansheng Xie, Pengcheng Ji, Qinggang Li, Peng Wang, and Guangyan Cai have declared that no competing interest exists. Xiangmei Chen is a member of the Editorial Board of Frontiers of Medicine, who was excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by the other editors to minimise bias.

This clinical study was reviewed and approved by the Medical Ethics Committee of the Chinese PLA General Hospital (approval number: 2012-001), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All participants provided written informed consent. For minors, parents/legal guardians were informed, and their parents/legal guardians signed the informed consent instead.

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References

1. Fabry H. Angiokeratoma corporis diffusum—Fabry disease: historical review from the original description to the introduction of enzyme replacement therapy. Acta Paediatr 2002; 91(s439): 3–5
2. Zarate YA, Hopkin RJ. Fabry's disease. Lancet 2008; 372(9647): 1427–1435
3. Schiffmann R, Hughes DA, Linthorst GE, Ortiz A, Svarstad E, Warnock DG, West ML, Wanner C, Bichet DG, Christensen EI, Correa-Rotter R, Elliott PM, Feriozzi S, Fogo AB, Germain DP, Hollak CEM, Hopkin RJ, Johnson J, Kantola I, Kopp JB, Kröner J, Linhart A, Martins AM, Matern D, Mehta AB, Mignani R, Najafian B, Narita I, Nicholls K, Obrador GT, Oliveira JP, Pisani A, Politei J, Ramaswami U, Ries M, Terryn W, Tøndel C, Torra R, Vujkovac B, Waldek S, Walter J. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 2017; 91(2): 284–293
4. Wanner C, Arad M, Baron R, Burlina A, Elliott PM, Feldt-Rasmussen U, Fomin VV, Germain DP, Hughes DA, Jovanovic A, Kantola I, Linhart A, Mignani R, Monserrat L, Namdar M, Nowak A, Oliveira JP, Ortiz A, Pieroni M, Spada M, Tylki-Szymańska A, Tøndel C, Viana-Baptista M, Weidemann F, Hilz MJ. European expert consensus statement on therapeutic goals in Fabry disease. Mol Genet Metab 2018; 124(3): 189–203
5. Arends M, Wanner C, Hughes D, Mehta A, Oder D, Watkinson OT, Elliott PM, Linthorst GE, Wijburg FA, Biegstraaten M, Hollak CE. Characterization of classical and nonclassical Fabry disease: a multicenter study. J Am Soc Nephrol 2017; 28(5): 1631–1641
6. Schiffmann R, Fuller M, Clarke LA, Aerts JM. Is it Fabry disease? Genet Med 2016; 18(12): 1181–1185
7. Nowicki M, Bazan-Socha S, Blazejewska-Hyzorek B, Gellert R, Imiela J, Kaźmierczak J, Kłopotowski M, Oko-Sarnowska Z, Pawlaczyk K, Ponikowski P, Sławek J, Sykut-Cegielska J, Witkowski A, Zwolińska D. Enzyme replacement therapy in Fabry disease in Poland: a position statement. Pol Arch Intern Med 2020; 130(1): 91–97
8. Ortiz A, Cianciaruso B, Cizmarik M, Germain DP, Mignani R, Oliveira JP, Villalobos J, Vujkovac B, Waldek S, Wanner C, Warnock DG. End-stage renal disease in patients with Fabry disease: natural history data from the Fabry Registry. Nephrol Dial Transplant 2010; 25(3): 769–775
9. Hopkin RJ, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, Lemay R, Tylki-Szymanska A, Wilcox WR. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. Pediatr Res 2008; 64(5): 550–555
10. Ramaswami U, Whybra C, Parini R, Pintos-Morell G, Mehta A, Sunder-Plassmann G, Widmer U, Beck M. Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey. Acta Paediatr 2006; 95(1): 86–92
11. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, Eng C, Hopkin RJ, Laney D, Linhart A, Waldek S, Wallace E, Weidemann F, Wilcox WR. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab 2018; 123(4): 416–427
12. Wanner C, Oliveira JP, Ortiz A, Mauer M, Germain DP, Linthorst GE, Serra AL, Maródi L, Mignani R, Cianciaruso B, Vujkovac B, Lemay R, Beitner-Johnson D, Waldek S, Warnock DG. Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. Clin J Am Soc Nephrol 2010; 5(12): 2220–2228
13. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med 2009; 11(11): 790–796
14. Eng CM, Fletcher J, Wilcox WR, Waldek S, Scott CR, Sillence DO, Breunig F, Charrow J, Germain DP, Nicholls K, Banikazemi M. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. J Inherit Metab Dis 2007; 30(2): 184–192
15. Branton MH, Schiffmann R, Sabnis SG, Murray GJ, Quirk JM, Altarescu G, Goldfarb L, Brady RO, Balow J, Austin HA III, Kopp JB. Natural history of Fabry renal disease: influence of α-galactosidase A activity and genetic mutations on clinical course. Medicine (Baltimore) 2002; 81(2): 122–138
16. Mahmud HM. Fabry's disease—a comprehensive review on pathogenesis, diagnosis and treatment. J Pak Med Assoc 2014; 64(2): 189–194
17. Lenders M, Stappers F, Brand E. *In vitro* and *in vivo* amenability to migalastat in Fabry disease. Mol Ther Methods Clin Dev 2020; 19: 24–34
18. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, Jabbour F, Beldjord C, De Mazancourt P, Germain DP. X-chromosome inactivation in female patients with Fabry disease. Clin Genet 2016; 89(1): 44–54
19. Linthorst GE, Poorthuis BJ, Hollak CE. Enzyme activity for determination of presence of Fabry disease in women results in

40% false-negative results. J Am Coll Cardiol 2008; 51(21): 2082
20. Inoue T, Hattori K, Ihara K, Ishii A, Nakamura K, Hirose S. Newborn screening for Fabry disease in Japan: prevalence and genotypes of Fabry disease in a pilot study. J Hum Genet 2013; 58(8): 548–552
21. Vieitez I, Souto-Rodriguez O, Fernandez-Mosquera L, San Millan B, Teijeira S, Fernandez-Martin J, Martinez-Sanchez F, Aldamiz-Echevarria LJ, Lopez-Rodriguez M, Navarro C, Ortolano S. Fabry disease in the Spanish population: observational study with detection of 77 patients. Orphanet J Rare Dis 2018; 13(1): 52
22. Wu Y, Xia H, Yuan J, Xu H, Deng X, Liu J, Zhang H, Deng H. Identification of a missense mutation in the α-galactosidase A gene in a Chinese family with Fabry disease. Curr Genomics 2018; 19(1): 70–75
23. Delarosa-Rodríguez R, Santotoribio JD, Paula HA, González-Meneses A, García-Morillo S, Jiménez-Arriscado P, Guerrero JM, Macher HC. Accuracy diagnosis improvement of Fabry disease from dried blood spots: enzyme activity, lyso-Gb3 accumulation and GLA gene sequencing. Clin Genet 2021; 99(6): 761–771
24. Blaydon D, Hill J, Winchester B. Fabry disease: 20 novel GLA mutations in 35 families. Hum Mutat 2001; 18(5): 459
25. Gal A, Hughes DA, Winchester B. Toward a consensus in the laboratory diagnostics of Fabry disease—recommendations of a European expert group. J Inherit Metab Dis 2011; 34(2): 509–514
26. Ezgu F, Alpsoy E, Bicik Bahcebasi Z, Kasapcopur O, Palamar M, Onay H, Ozdemir BH, Topcuoglu MA, Tufekcioglu O. Expert opinion on the recognition, diagnosis and management of children and adults with Fabry disease: a multidisciplinary Turkey perspective. Orphanet J Rare Dis 2022; 17(1): 90
27. Lukas J, Giese AK, Markoff A, Grittner U, Kolodny E, Mascher H, Lackner KJ, Meyer W, Wree P, Saviouk V, Rolfs A. Functional characterisation of alpha-galactosidase a mutations as a basis for a new classification system in fabry disease. PLoS Genet 2013; 9(8): e1003632
28. Schiffmann R. Natural history of Fabry disease in males: preliminary observations. J Inherit Metab Dis 2001; 24(Suppl 2): 15–17
29. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, Yoshida A, Kuriyama M, Hayashibe H, Sakuraba H, Tanaka H. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med 1995; 333(5): 288–293
30. Wanner C, Ortiz A, Wilcox WR, Hopkin RJ, Johnson J, Ponce E, Ebels JT, Batista JL, Maski M, Politei JM, Martins AM, Banikazemi M, Linhart A, Mauer M, Oliveira JP, Weidemann F, Germain DP. Global reach of over 20 years of experience in the patient-centered Fabry Registry: advancement of Fabry disease expertise and dissemination of real-world evidence to the Fabry community. Mol Genet Metab 2023; 139(3): 107603
31. Redonnet-Vernhet I, Ploos van Amstel JK, Jansen RP, Wevers RA, Salvayre R, Levade T. Uneven X inactivation in a female monozygotic twin pair with Fabry disease and discordant expression of a novel mutation in the alpha-galactosidase A gene. J Med Genet 1996; 33(8): 682–688
32. Morrone A, Cavicchi C, Bardelli T, Antuzzi D, Parini R, Di Rocco M, Feriozzi S, Gabrielli O, Barone R, Pistone G, Spisni C, Ricci R, Zammarchi E. Fabry disease: molecular studies in Italian patients and X inactivation analysis in manifesting carriers. J Med Genet 2003; 40(8): e103
33. Dobrovolny R, Dvorakova L, Ledvinova J, Magage S, Bultas J, Lubanda JC, Elleder M, Karetova D, Pavlikova M, Hrebicek M. Relationship between X-inactivation and clinical involvement in Fabry heterozygotes. Eleven novel mutations in the alpha-galactosidase A gene in the Czech and Slovak population. J Mol Med (Berl) 2005; 83(8): 647–654
34. Bouwman MG, Rombach SM, Linthorst GE, Poorthuis BJHM, Lekanne Deprez RH, Aerts JMFG, Wijburg FA. Early cerebral manifestations in a young female with Fabry disease with skewed X-inactivation. Clin Genet 2011; 80(5): 500–502
35. Hossain MA, Wu C, Yanagisawa H, Miyajima T, Akiyama K, Eto Y. Future clinical and biochemical predictions of Fabry disease in females by methylation studies of the GLA gene. Mol Genet Metab Rep 2019; 20: 100497
36. Viggiano E, Politano L. X chromosome inactivation in carriers of Fabry disease: review and meta-analysis. Int J Mol Sci 2021; 22(14): 7663
37. Guo W, Xie Y, Ji P, Li S, Cai G, Chen X. The evolution of the initial manifestations and renal involvement of chinese patients with classical and late-onset Fabry disease at different sexes and ages. BMC Nephrol 2023; 24(1): 90
38. Guce AI, Clark NE, Salgado EN, Ivanen DR, Kulminskaya AA, Brumer H III, Garman SC. Catalytic mechanism of human α-galactosidase. J Biol Chem 2010; 285(6): 3625–3632
39. Garman SC, Garboczi DN. Structural basis of Fabry disease. Mol Genet Metab 2002; 77(1–2): 3–11
40. Ferreira S, Ortiz A, Germain DP, Viana-Baptista M, Caldeira-Gomes A, Camprecios M, Fenollar-Cortés M, Gallegos-Villalobos Á, Garcia D, García-Robles JA, Egido J, Gutiérrez-Rivas E, Herrero JA, Mas S, Oancea R, Péres P, Salazar-Martín LM, Solera-Garcia J, Alves H, Garman SC, Oliveira JP. The alpha-galactosidase A p.Arg118Cys variant does not cause a Fabry disease phenotype: data from individual patients and family studies. Mol Genet Metab 2015; 114(2): 248–258
41. Nakao S, Kodama C, Takenaka T, Tanaka A, Yasumoto Y, Yoshida A, Kanzaki T, Enriquez ALD, Eng CM, Tanaka H, Tei C, Desnick RJ. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. Kidney Int 2003; 64(3): 801–807
42. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, Rivera S, Deschênes G, Lacombe D. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet 2019; 96(2): 107–117
43. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004; 34(3): 236–242
44. Elstein D, Schachamorov E, Beeri R, Altarescu G. X-inactivation in Fabry disease. Gene 2012; 505(2): 266–268
45. Matsuzawa F, Aikawa S, Doi H, Okumiya T, Sakuraba H. Fabry disease: correlation between structural changes in alpha-galactosidase, and clinical and biochemical phenotypes. Hum Genet 2005; 117(4): 317–328
46. Filoni C, Caciotti A, Carraresi L, Cavicchi C, Parini R, Antuzzi D, Zampetti A, Feriozzi S, Poisetti P, Garman SC, Guerrini R, Zammarchi E, Donati MA, Morrone A. Functional studies of new

GLA gene mutations leading to conformational Fabry disease. Biochim Biophys Acta Mol Basis Dis 2010; 1802(2): 247–252

47. Pan X, Ouyang Y, Wang Z, Ren H, Shen P, Wang W, Xu Y, Ni L, Yu X, Chen X, Zhang W, Yang L, Li X, Xu J, Chen N. Genotype: a crucial but not unique factor affecting the clinical phenotypes in Fabry disease. PLoS One 2016; 11(8): e0161330
48. Germain DP, Shabbeer J, Cotigny S, Desnick RJ. Fabry disease: twenty novel α-galactosidase A mutations and genotype-phenotype correlations in classical and variant phenotypes. Mol Med 2002; 8(6): 306–312
49. Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, Schneider M, Grange DK, Nash C, Shryock H, Barnett R, Shao R, Basheeruddin K, Dizikes G. Newborn screening for lysosomal storage disorders in Illinois: the initial 15-month experience. J Pediatr 2017; 190: 130–135
50. Lin HY, Chong KW, Hsu JH, Yu HC, Shih CC, Huang CH, Lin SJ, Chen CH, Chiang CC, Ho HJ, Lee PC, Kao CH, Cheng KH, Hsueh C, Niu DM. High incidence of the cardiac variant of Fabry disease revealed by newborn screening in the Chinese Taiwan population. Circ Cardiovasc Genet 2009; 2(5): 450–456
51. Lu YH, Huang PH, Wang LY, Hsu TR, Li HY, Lee PC, Hsieh YP, Hung SC, Wang YC, Chang SK, Lee YT, Ho PH, Ho HC, Niu DM. Improvement in the sensitivity of newborn screening for Fabry disease among females through the use of a high-throughput and cost-effective method, DNA mass spectrometry. J Hum Genet 2018; 63(1): 1–8
52. Altarescu GM, Goldfarb LG, Park KY, Kaneski C, Jeffries N, Litvak S, Nagle JW, Schiffmann R. Identification of fifteen novel mutations and genotype-phenotype relationship in Fabry disease. Clin Genet 2001; 60(1): 46–51