World Journal of *Clinical Cases*

World J Clin Cases 2022 January 21; 10(3): 753-1139





Published by Baishideng Publishing Group Inc

W J C C World Journal of Clinical Cases

Contents

Thrice Monthly Volume 10 Number 3 January 21, 2022

OPINION REVIEW

753 Lung injury after cardiopulmonary bypass: Alternative treatment prospects Zheng XM, Yang Z, Yang GL, Huang Y, Peng JR, Wu MJ

REVIEW

762 Acute myocardial injury in patients with COVID-19: Possible mechanisms and clinical implications Rusu I, Turlacu M, Micheu MM

MINIREVIEWS

777 Anemia in cirrhosis: An underestimated entity Manrai M, Dawra S, Kapoor R, Srivastava S, Singh A

ORIGINAL ARTICLE

Retrospective Cohort Study

790 High tumor mutation burden indicates a poor prognosis in patients with intrahepatic cholangiocarcinoma Song JP, Liu XZ, Chen Q, Liu YF

Retrospective Study

802 Does delaying ureteral stent placement lead to higher rates of preoperative acute pyelonephritis during pregnancy?

He MM, Lin XT, Lei M, Xu XL, He ZH

- 811 Management of retroperitoneal sarcoma involving the iliac artery: Single-center surgical experience Li WX, Tong HX, Lv CT, Yang H, Zhao G, Lu WQ, Zhang Y
- 820 COVID-19 pandemic changed the management and outcomes of acute appendicitis in northern Beijing: A single-center study Zhang P, Zhang Q, Zhao HW
- 830 Laparoscopic approach for managing intussusception in children: Analysis of 65 cases Li SM, Wu XY, Luo CF, Yu LJ
- 840 Clinical features and risk factors of severely and critically ill patients with COVID-19 Chu X, Zhang GF, Zheng YK, Zhong YG, Wen L, Zeng P, Fu CY, Tong XL, Long YF, Li J, Liu YL, Chang ZG, Xi H
- Evaluating tumor-infiltrating lymphocytes in hepatocellular carcinoma using hematoxylin and eosin-856 stained tumor sections Du M, Cai YM, Yin YL, Xiao L, Ji Y



Contents

Clinical Trials Study

870 Role of carbon nanotracers in lymph node dissection of advanced gastric cancer and the selection of preoperative labeling time

Zhao K, Shan BQ, Gao YP, Xu JY

Observational Study

882 Craving variations in patients with substance use disorder and gambling during COVID-19 lockdown: The Italian experience

Alessi MC, Martinotti G, De Berardis D, Sociali A, Di Natale C, Sepede G, Cheffo DPR, Monti L, Casella P, Pettorruso M, Sensi S, Di Giannantonio M

891 Mesh safety in pelvic surgery: Our experience and outcome of biological mesh used in laparoscopic ventral mesh rectopexy

Tsiaousidou A, MacDonald L, Shalli K

899 Dynamic monitoring of carcinoembryonic antigen, CA19-9 and inflammation-based indices in patients with advanced colorectal cancer undergoing chemotherapy

Manojlovic N, Savic G, Nikolic B, Rancic N

919 Prevalence of depression and anxiety and associated factors among geriatric orthopedic trauma inpatients: A cross-sectional study

Chen JL, Luo R, Liu M

Randomized Controlled Trial

929 Efficacy of acupuncture at ghost points combined with fluoxetine in treating depression: A randomized study

Wang Y, Huang YW, Ablikim D, Lu Q, Zhang AJ, Dong YQ, Zeng FC, Xu JH, Wang W, Hu ZH

SYSTEMATIC REVIEWS

939 Atrial fibrillation burden and the risk of stroke: A systematic review and dose-response meta-analysis Yang SY, Huang M, Wang AL, Ge G, Ma M, Zhi H, Wang LN

META-ANALYSIS

954 Effectiveness of Maitland and Mulligan mobilization methods for adults with knee osteoarthritis: A systematic review and meta-analysis

Li LL, Hu XJ, Di YH, Jiao W

966 Patients with inflammatory bowel disease and post-inflammatory polyps have an increased risk of colorectal neoplasia: A meta-analysis

Shi JL, Lv YH, Huang J, Huang X, Liu Y

CASE REPORT

985 Intravascular fasciitis involving the external jugular vein and subclavian vein: A case report Meng XH, Liu YC, Xie LS, Huang CP, Xie XP, Fang X



_	World Journal of Clinical Cases
Conter	nts Thrice Monthly Volume 10 Number 3 January 21, 2022
992	Occurrence of human leukocyte antigen B51-related ankylosing spondylitis in a family: Two case reports
	Lim MJ, Noh E, Lee RW, Jung KH, Park W
1000	Multicentric recurrence of intraductal papillary neoplasm of bile duct after spontaneous detachment of primary tumor: A case report
	Fukuya H, Kuwano A, Nagasawa S, Morita Y, Tanaka K, Yada M, Masumoto A, Motomura K
1008	Case of primary extracranial meningioma of the maxillary sinus presenting as buccal swelling associated with headache: A case report
	Sigdel K, Ding ZF, Xie HX
1016	Pulmonary amyloidosis and multiple myeloma mimicking lymphoma in a patient with Sjogren's syndrome: A case report
	Kim J, Kim YS, Lee HJ, Park SG
1024	Concomitant Othello syndrome and impulse control disorders in a patient with Parkinson's disease: A case report
	Xu T, Li ZS, Fang W, Cao LX, Zhao GH
1032	Multiple endocrine neoplasia type 1 combined with thyroid neoplasm: A case report and review of literatures
	Xu JL, Dong S, Sun LL, Zhu JX, Liu J
1041	Full recovery from chronic headache and hypopituitarism caused by lymphocytic hypophysitis: A case report
	Yang MG, Cai HQ, Wang SS, Liu L, Wang CM
1050	Novel method of primary endoscopic realignment for high-grade posterior urethral injuries: A case report
	Ho CJ, Yang MH
1056	Congenital muscular dystrophy caused by <i>beta1,3-N-acetylgalactosaminyltransferase</i> 2 gene mutation: Two case reports
	Wu WJ, Sun SZ, Li BG
1067	Novel α-galactosidase A gene mutation in a Chinese Fabry disease family: A case report
	Fu AY, Jin QZ, Sun YX
1077	Cervical spondylotic myelopathy with syringomyelia presenting as hip Charcot neuroarthropathy: A case report and review of literature
	Lu Y, Xiang JY, Shi CY, Li JB, Gu HC, Liu C, Ye GY
1086	Bullectomy used to treat a patient with pulmonary vesicles related to COVID-19: A case report
	Tang HX, Zhang L, Wei YH, Li CS, Hu B, Zhao JP, Mokadam NA, Zhu H, Lin J, Tian SF, Zhou XF
1093	Epibulbar osseous choristoma: Two case reports
	Wang YC, Wang ZZ, You DB, Wang W
1099	Gastric submucosal lesion caused by an embedded fish bone: A case report
	Li J, Wang QQ, Xue S, Zhang YY, Xu QY, Zhang XH, Feng L



Conter	World Journal of Clinical Cases Thrice Monthly Volume 10 Number 3 January 21, 2022
1106	Metastasis to the thyroid gland from primary breast cancer presenting as diffuse goiter: A case report and review of literature
	Wen W, Jiang H, Wen HY, Peng YL
1116	New method to remove tibial intramedullary nail through original suprapatellar incision: A case report <i>He M, Li J</i>
1122	Recurrence of sigmoid colon cancer-derived anal metastasis: A case report and review of literature
	Meng LK, Zhu D, Zhang Y, Fang Y, Liu WZ, Zhang XQ, Zhu Y
1131	<i>Mycoplasma hominis</i> meningitis after operative neurosurgery: A case report and review of literature <i>Yang NL, Cai X, Que Q, Zhao H, Zhang KL, Lv S</i>



Contents

Thrice Monthly Volume 10 Number 3 January 21, 2022

ABOUT COVER

Editorial Board Member of World Journal of Clinical Cases, M Anwar Iqbal, PhD, Professor, Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY 14642, United States. anwar_iqbal@urmc.rochester.edu

AIMS AND SCOPE

The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ying-Yi Yuan, Production Department Director: Xiang Li, Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL	INSTRUCTIONS TO AUTHORS
World Journal of Clinical Cases	https://www.wignet.com/bpg/gerinfo/204
ISSN	GUIDELINES FOR ETHICS DOCUMENTS
ISSN 2307-8960 (online)	https://www.wjgnet.com/bpg/GerInfo/287
LAUNCH DATE	GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
April 16, 2013	https://www.wignet.com/bpg/gerinfo/240
FREQUENCY	PUBLICATION ETHICS
Thrice Monthly	https://www.wjgnet.com/bpg/GerInfo/288
EDITORS-IN-CHIEF Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku	PUBLICATION MISCONDUCT https://www.wjgnet.com/bpg/gerinfo/208
EDITORIAL BOARD MEMBERS	ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/2307-8960/editorialboard.htm	https://www.wjgnet.com/bpg/gerinfo/242
PUBLICATION DATE	STEPS FOR SUBMITTING MANUSCRIPTS
January 21, 2022	https://www.wjgnet.com/bpg/GerInfo/239
COPYRIGHT	ONLINE SUBMISSION
© 2022 Baishideng Publishing Group Inc	https://www.f6publishing.com

© 2022 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com



W J C C World Journal C Clinical Cases

World Journal of

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 January 21; 10(3): 1067-1076

DOI: 10.12998/wjcc.v10.i3.1067

ISSN 2307-8960 (online)

CASE REPORT

Novel α-galactosidase A gene mutation in a Chinese Fabry disease family: A case report

An-Yi Fu, Qi-Zhi Jin, Ya-Xun Sun

ORCID number: An-Yi Fu 0000-0003-3067-3161; Qi-Zhi Jin 0000-0002-1052-2377; Ya-Xun Sun 0000-0003-3184-5949.

Author contributions: Fu AY and Sun YX carried out the studies, participated in collecting the data, and drafted the manuscript; Fu AY and Jin QZ performed the statistical analysis and participated in its design; Sun YX and Jin QZ helped to draft the manuscript; all authors read and approved the final manuscript.

Informed consent statement:

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Supported by Key Research and Development Program of Zhejiang Province, No. 2019C03022.

Country/Territory of origin: China

Specialty type: Cardiac and

An-Yi Fu, Ya-Xun Sun, Department of Clinical Medicine, Zhejiang University, Hangzhou 310058, Zhejiang Province, China

An-Yi Fu, Qi-Zhi Jin, Department of Cardiology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Quzhou 325035, Zhejiang Province, China

Ya-Xun Sun, Department of Cardiology, Sir Run Run Shaw Hospital, Clinical Medicine of Zhejiang University, Hangzhou 310016, Zhejiang Province, China

Corresponding author: Ya-Xun Sun, MD, Doctor, Department of Cardiology, Sir Run Run Shaw Hospital, Clinical Medicine of Zhejiang University, No. 3 Qingchun East Road, Shangcheng District, Hangzhou 310016, Zhejiang Province, China. sunyaxun@zju.edu.cn

Abstract

BACKGROUND

Fabry disease (FD) is a rare X-linked lysosomal storage disease caused by a deficiency of the enzyme α -galactosidase A.

CASE SUMMARY

Herein, we analyzed a four-generation Chinese family. The proband is a 57-yearold woman who was diagnosed with left ventricular hypertrophy and atrial fibrillation 7 years ago. Echocardiography showed an end-diastolic diameter of the interventricular septum of 19.9 mm, left ventricular end-diastolic diameter of 63.1 mm, and moderate-to-severe mitral regurgitation. Cardiac magnetic resonance indicated an enlarged left heart and right atrium, decreased left ventricular systolic and diastolic function, a left ventricular ejection fraction of 20%, and thickening of the left ventricular septum. In March 2019, gene and enzyme activity tests confirmed the diagnosis of FD. Her son was diagnosed with FD after gene and enzyme activity assay, and was prescribed agalsidase- β for enzyme replacement therapy in July 2020. Two sisters of the proband were also diagnosed with FD by genetic testing. Both of them had a history of atrial fibrillation.

CONCLUSION

A novel mutation was identified in a Chinese family with FD, in which the male patient had a low level of enzyme activity, early-onset, and severe organ involvement. Comprehensive analysis of clinical phenotype genetic testing and enzyme activity testing helped in the diagnosis and treatment of this FD family.

Key Words: Lysosomal storage disease; Enzyme activity; Fabry disease; Frameshift



Cardiovascular Systems

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0 Grade B (Very good): 0 Grade C (Good): C Grade D (Fair): 0 Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: htt p://creativecommons.org/License s/by-nc/4.0/

Received: June 22, 2021 Peer-review started: June 22, 2021 First decision: July 26, 2021 Revised: August 9, 2021 Accepted: December 23, 2021 Article in press: December 23, 2021 Published online: January 21, 2022

P-Reviewer: Spinelli L S-Editor: Chang KL L-Editor: Wang TQ P-Editor: Chang KL



deletion; Whole exon sequencing; Case report

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by a deficiency of α -galactosidase A. We present herein a case of novel mutation (348delG:p.G116fs) in exon 2 in a Chinese FD family. Time delay in the diagnosis was 6 years. The proband died of respiratory circulatory failure. The son of the proband had a low level of enzyme activity, early-onset, and severe organ involvement. He was prescribed agalsidase- β for enzyme replacement therapy to delay progression of the disease. This case highlights that clinical phenotype, gene detection, and enzyme activity results should be analyzed comprehensively for patients suspected of having FD.

Citation: Fu AY, Jin QZ, Sun YX. Novel α-galactosidase A gene mutation in a Chinese Fabry disease family: A case report. *World J Clin Cases* 2022; 10(3): 1067-1076 **URL:** https://www.wjgnet.com/2307-8960/full/v10/i3/1067.htm **DOI:** https://dx.doi.org/10.12998/wjcc.v10.i3.1067

INTRODUCTION

Fabry disease (FD, OMIM 301500) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism caused by a deficient or absent lysosomal α -galactosidase A (α -GLA) activity[1]. The prevalence of FD was once believed to be very rare, occurring approximately in 1:50000 patients[2]. Substrates of this lysosomal enzyme accumulate, resulting in cellular dysfunction in multiple organs. FD is commonly known as a silent disease that appears later in life and could be easily misdiagnosed. Patients lacking α -GLA activity exhibit a 10-20 year shortened life span: Male patients with FD have a median survival of 57 years, and the median female survival is 72 years[3].

Classically affected FD males with no residual α -GLA activity, may display neurological (pain and acroparesthesia), cutaneous (angiokeratoma), renal (proteinuria and kidney failure), cardiovascular (cardiomyopathy, arrhythmia, and valvulopathy), cochleovestibular, and cerebrovascular (transient ischemic attacks and strokes) signs while heterozygous females have symptoms ranging from mild to severe[1]. Male patients are usually severely affected, while the clinical presentation in female patients may be more variable[4].

There are currently 967 known *GLA* mutations, including 671 missense/nonsense mutations, listed in the Human Gene Mutation Database[5]. The type of amino acid exchange domain in the α -GLA 3D-structure determines the disease severity and temporal course of clinical presentation. Patients with active site or buried mutations showed a severe phenotype with multi-organ involvement and early disease manifestation. Patients with certain mutations showed a milder phenotype with less organ impairment and later disease onset[6]. In male patients, the α -GLA enzyme activity is often significantly decreased, while about a third of female patients have enzymes within the normal range.

Enzyme replacement therapy (ERT) and chaperone therapy are currently considered the main targeted treatments for FD. As two representative drugs of enzyme replacement therapy, agalsidase- α and agalsidase- β have been shown to be clinically effective for patients with FD; yet, these are very expensive (approximately \$200000 per patient annually in China). Some patients with amenable *GLA* mutations have residual activity in α -GLA. In these patients, small molecular chaperones could promote enzyme stability and are clinically effective.

In the present study, we describe a novel frameshift mutation in *GLA* and different α -GLA enzymatic activity in a Chinese family in which both male and female members presented with left ventricular hypertrophy and atrial fibrillation.

Raisbideng® WJCC | https://www.wjgnet.com

CASE PRESENTATION

Chief complaints

The proband was a 57-year-old woman who has experienced paroxysmal chest tightness and shortness of breath for 7 years.

History of present illness

A 57-year-old woman was diagnosed with left ventricular hypertrophy and atrial fibrillation 7 years ago. Echocardiography showed an end-diastolic diameter of the interventricular septum of 19.9 mm, left ventricular end-diastolic diameter of 63.1 mm, moderate-to-severe mitral regurgitation, and a left ventricular ejection fraction (LVEF) of 45%. Cardiac magnetic resonance (CMR) indicated an enlarged left heart and right atrium, decreased left ventricular systolic and diastolic function, an LVEF of about 20%, and thickening of the left ventricular septum. In March 2019, gene and enzyme activity tests confirmed the diagnosis of FD. Her son was diagnosed with FD after gene and enzyme activity assay, and was prescribed agalsidase- $\boldsymbol{\beta}$ for enzyme replacement therapy in July 2020. Two sisters of the proband were also diagnosed with FD by genetic testing. Both of them had a history of atrial fibrillation.

History of past illness

The proband had a history of hypertension for more than 20 years.

Personal and family history

The proband did not have any significant personal history. Her father died of cardiomyopathy, while her mother died of colon cancer. Her son and two sisters were diagnosed with FD.

Physical examination

At the last admission, the proband's blood pressure was 99/65 mmHg. She was conscious, but presented with an appearance of weakness. Her tongue stuck out to the right. Her jugular vein was filling. Rales could be heard widely over both lung fields. The heart rate was 96 bpm. The intensity of the first heart sound was unequal. Systolic murmur (III/6) was identified in the apex of the heart. There was no edema in her lower limbs.

Laboratory examinations

Enzymatic measurement of \alpha-GLA: The enzyme activity of α -GLA was reduced to only 1.0 nmol/h/mg protein in the son of the proband, while a normal range was observed in all other family members (Table 1).

Clinical and biochemical studies: All of the patients in this family, whether hemizygous or heterozygote, had left ventricular hypertrophy. All female family members (II3, II5, and II7) had atrial fibrillation, except the propositus granddaughter (IV-1), who did not undergo inspection due to being only 2 years old. The levels of troponin I were all increased, and the ejection fraction was generally lower in female than male patients (III-2). Female heterozygotes suffered more severe cardiovascular damage while the kidney damage occurred earlier in males than in female family members. Stroke was more common in women, possibly due to atrial fibrillation and older age. At the same time, cutaneous and neuralgia manifestations were present in males of the same lineage, suggesting a wider range of glycosphingolipid deposition in the hemizygote and more involved organs (Table 1, Figure 1-5).

Gene expression: (1) Whole exome sequencing results: In this family, we found a frameshift mutation (348delG:p.G116fs) according to the guidelines for mutation nomenclature recommended by the Human Genome Variation Society (www. hgvs.org/mutnomen). The mutation occurred in the guanine deletion at position 348 of the GLA gene, resulting in a series of changes in the code of the 116th amino acid and its downstream (Figure 6). This mutation causes a change in the GLA protein domain (Figure 7)[7,8]; and (2) Conventional sequencing results: Sanger sequencing confirmed that the mutation occurred due to the guanine deletion in exon 2. Figure 8A shows the gene sequencing results of the proband (II-3). Adenine takes the place of guanine, thus causing a rearrangement of the subsequent amino acid sequence. The son of the proband (III-2) and the two sisters showed the same mutation (Figure 8B and C).

Fu A et al. A novel α-galactosidase A gene mutation

Table 1 Clinical fe	eatures				
Variables	II-3	II-5	II-7	II-1	III-2
Sex	Female	Female	Female	Male	Male
Age at diagnosis	56	52	47	63	22
Mutation	NM_000169.2:c.348delG:p.G116fs	NM_000169.2:c.348delG:p.G116fs	NM_000169.2:c.348delG:p.G116fs	-	NM_000169.2:c.348delG:p.G116fs
Genotype	Heterozygote	Heterozygote	Heterozygote	Wild Type	Hemizygote
Enzymatic activity (nmol/h/mg protein)	N/A	42	34	60	1
Cardiovascular sym	ptoms				
Heart rhythm	AF	AF	AF	SR	SR
LVPWD (mm)	9.6	9.9	13.4	9.8	14.5
IVST (mm)	16	15.8	14.5	9.8	17.4
EF (%)	28.1	58.3	55.6	67.3	61.5
hsTNI (ng/mL)	0.21	0.59	0.11	< 0.01	< 0.110
NT-proBNP (pg/mL)	> 25000	1124	3242	< 10	586
Kidney symptoms					
Serum creatinine(µmol/L)	258	57	63	N/A	344
Neuralgia	+	-	-	-	+
Neurological sympt	oms				
Neuropathic pain	-	-	-	-	+
Cerebrovascular involvement	+	+	-	-	-
Gastrointestinal syn	nptoms				
Nausea	+	-	-	-	-
Abdominal Pain	+	-	-	-	-
Chronic diarrhea	+	-	-	-	-
Skin					
Angiokeratoma	+	-	-	-	+

ECG: Electrocardiogram; AF: Atrial fibrillation; SR: Sinus rhythm; LVPWD: Left ventricular posterior wall dimensions; IVST: Interventricular septal diastolic thickness; EF: Ejection fraction; hsTNI: High-sensitivity cardiac troponin I; NT-proBNP: N terminal pro B type natriuretic peptide.

Imaging examinations

CMR showed patchy enhancement of interventricular septum and left ventricular anterior wall hypertrophy. Delayed enhancement suggested the formation of a large number of fibrous scars in left ventricular hypertrophy (Figure 3).

FINAL DIAGNOSIS

The final diagnosis of the presented case was FD.

TREATMENT

The proband underwent atrial fibrillation radiofrequency ablation 7 years ago. Three



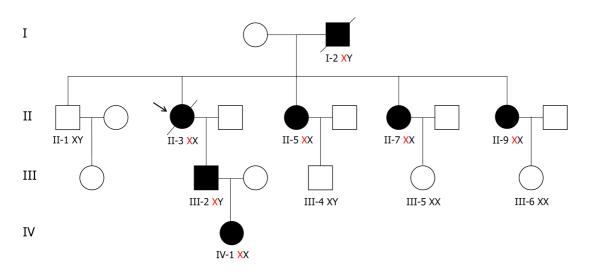


Figure 1 Family tree. The four-generation pedigree with the mutation p.G116fs in the GLA gene is shown. Roman numerals indicate generations; individuals within a generation are numbered from left to right. The proband (II-3) is denoted with an arrow. Oblique lines indicate patients who are already dead. Filled squares and circles indicate male and female patients, respectively. Black color represents patients with Fabry disease (FD), which were confirmed by genetic analysis. The proband's father (I-2) suffered from cardiovascular disease and stroke. The proband (II-3) died of end-stage heart failure. The proband's son (III-2) started enzyme replacement therapy in July 2020. The proband's granddaughter (IV-1) was born before her father (III-2) was diagnosed with FD.

1 18	4 7 480	3 488	3 488 4 816 5 476 6 460 7 624 8 500 9 784 10		6 460 7 624 8 500 9 784 10 476 11 780 12 472 1464 500 15 25mm/s 10mmmm 1 31 97 120 77 127 177 128 130 120 117 79					1040			1044	1044 3 1048		1040	Į 924	1092	Ţ 10	40 25	25mm/s 10mm/mV								
12	4 125	3 123	74	127	131	97	120	17	127	1 "	12	8 130	120	117	17	9		l.		58	58	58		58	65	55	5	8	58
י י ר																		1~		1~	1	1	1	~	1	1	1	Ĩ	~
-10/	~	v~v	~~~~	V-V	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~	\sim	~~~~	-v	٧~~~	~	γ	γ^{-}	γ	γ~	~~~~		n ~~		~~	-h~	~h~		,	-h~	-h	- der		~~~~~
- m	T	m	~~~~	YY	N	^	m	m	-y	v~	Y	V	r	r	r			-m		r	~~~				4	4	~~~		
ave		j-j	~~~~	-h1	i		j	,		V~~	-1-	-j	·	-1	·~	-i-	. [[WR		<u> </u>	~~~			~	j-	p	-j-		~~~~
L.	h	L.	~~~	L	~^		~~	4		h		1	1_	h	1_		. [[- Jvi		L				······	-h	-l			l
-ayr	V	v	~~~	vv	\sim_{γ}	~~~	m	<u>~</u>	~~~	v~~	~~~	γ	γ^{\sim}	γ^{\sim}	\sim	~~~~		avi]		~h~~	-h	-h		h	h	~}~		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
w.	m	m)	~~~	ηγ	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~~~	~	r	-p	γ~~	~~~	m	Y	1-	m			4-		ŀ	rþ	- P	-rf-	r	f^	1	rf-	-1	1
va	m	1	~~~	1-1	~	~1	M	\sim	1	h	4	Yn	h	h	r	-	. [[1/2~		h~~	~~~	~ ~~	-p	~~^	1-		1pm	-1	~~~
va^	h	h	~	m	~1	\sim	h	r	1	¶~-	-1-	h	1	m	r	-		- /a ~		~~	~h~	~~~		~^	-	- ~~-	$\sim \sim$	-1	~~~h
v	\uparrow		~	+	\sim	~	2	r-		p	-	r	1~	\uparrow	r	-h		to		m-	~~			<i></i>	h-	h	$\sim h \sim$		v~~
vs	\uparrow	\uparrow	~	1-1	-	~	h	\vdash		+	-	t	\uparrow	\uparrow	\uparrow	\neg		VEV		w-	-h-	-w	-m	,	m	w	-h-		~~~~
Logh	h	In		1-1		~~~~	m	1	-p-	f	1	1-	1-	1 20	19/9/8	20:20:23	- I L	Ver		hr	-			~~~~	to	to	abr	2019	11/27-16:56:51

Figure 2 Electrocardiogram of the patient indicating atrial fibrillation rhythm. Pathological Q waves in inferior and lateral leads, and T wave inversion are shown.

> years ago, she was given prednisone and tacrolimus because of edema and proteinuria. The son of the proband was given enzyme replacement therapy with agalsidase- β 65 mg (biweekly, intramuscularly) starting from July, 2020.

OUTCOME AND FOLLOW-UP

After 6 mo of ERT, serum creatinine in the son of the proband had no significant decrease. The pain in his skin was markedly relieved.

DISCUSSION

FD (MIM301500) was first described in 1898 by William Anderson and Johannes Fabry. After 65 years, Sweeley and Klionsky found an accumulation of a glycosphingolipid, globotriaosylceramide (Gb3), in patients with FD[9]. The incidence of FD in male newborns is 1/110000 to 1/4 million[10]. The main international databases for FD is the Fabry Outcome Survey in Europe, which currently lists 967 different GLA mutations in the human gene mutation database, including 671 missense/nonsense mutations^[5].





Figure 3 Cardiac magnetic resonance imaging showed patchy enhancement of interventricular septum and left ventricular anterior wall hypertrophy. Delayed enhancement suggested the formation of a large number of fibrous scars in left ventricular hypertrophy.

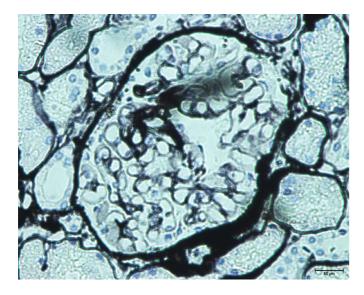


Figure 4 Light microscopy of renal biopsy (periodic acid-Schiff staining, 400 ×) showing membranous nephropathy. Heterogeneous thickening of the glomerular capillary basement membrane is visible.

The GLA gene encoding α-Gal A is located on Xq22.1, with 7 exons and 12 kb in length[11]. Herein, we report a novel frameshift mutation in the GLA gene in four members of a family with classical FD phenotype, with early-onset signs in affected men. Genotype-phenotype correlation in FD is challenging. Many GLA mutations are family-specific; in some families, there are quite marked phenotype variations. In contrast, the disease manifestation may vary within patients carrying the same mutation[12]. Garman *et al*[13] discovered two types of α -GLA mutations that are responsible for the disease progression: Mutations near the active sites and mutations of buried residues far from the active sites. Mutations near the active sites have a higher pathogenic frequency and severe clinical phenotype, while mutations far from the enzyme active sites are relatively mild[13]. The structure of α-GLA is a homodimeric glycoprotein with each monomer composed of two domains. The first domain contains the active site and extends from residues 32 to 330, and the second domain is comprised of residues 331-429, burying much surface area within one monomer. Rickert *et al*[6] found that patients with active site or buried mutations showed a severe phenotype with multi-organ involvement and early disease manifestation. Patients with other mutations had a milder phenotype with less organ impairment and later disease onset. In addition, the α -GalA activity was lower in patients with active site or buried mutations than in those with other mutations while lyso-Gb3 levels were higher.





Figure 5 Angiokeratoma on both hands of the proband's son (III-2).

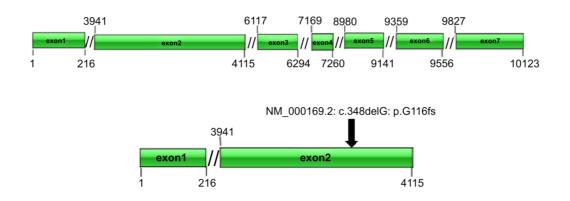


Figure 6 Schematic diagram of NM_000169.2: c.348delG:p.G116fs.

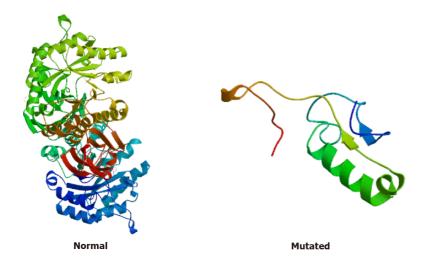


Figure 7 Protein structure prediction of the normal and mutated galactosidase gene.

In the proband of our study, a frameshift mutation (348delG:p.G116fs) occurred due to the guanine deletion at position 348 of the GLA gene, resulting in a series of changes in the code of the 116th amino acid and its downstream, so that the GLA peptide chain was transformed into a completely different peptide sequence. Enzyme activity tests confirmed that the enzyme activity of the female members of the family was

Baisbideng® WJCC https://www.wjgnet.com

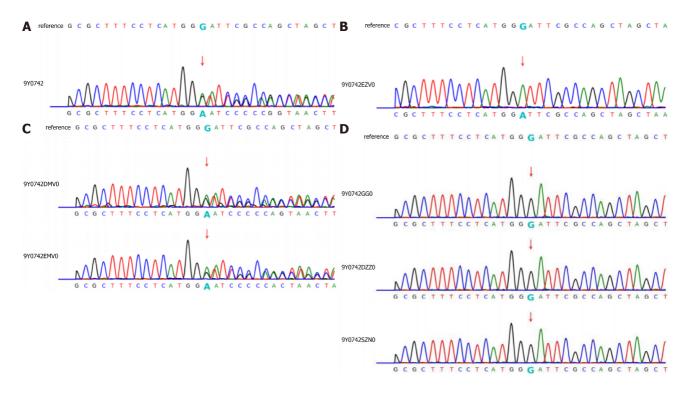


Figure 8 Conventional sequencing results for four of the family members. (A) The proband (II-3), (B) Proband' son (III-2), and (C) Proband' two sisters (II-5, II-7) showing the same mutation; (D) Proband's elder brother (II-1), eldest nephew (III-4), and the third niece (III-6) showing no mutant gene.

moderately decreased and that of the male members was extremely decreased.

The α -Gal activity in female subjects who carry a heterozygous pathogenic variant in the *GLA* gene, is subject to X chromosome inactivation, typically random, celldependent, often nonuniform across the silenced chromosome[14]. Likewise, it complicates correlations among the genetic variants, functional data, and organ involvement. Nevertheless, as a group, α -Gal activity is higher in female subjects with pathogenic GLA variants than in male subjects' corresponding values. Consequently, up to one-third of X-chromosomal genes are expressed from both the active and inactive X chromosomes (Xa and Xi, respectively) in female cells, with the degree of "escape" from inactivation varying between genes and individuals[15], posing significant diagnostic challenges. In this study, the proband was a heterozygote but had classical characteristics such as heart failure and renal failure. Her sisters present nonclassical characteristics, whose manifestations are limited to cardiac involvement.

Clinically, FD diagnosis is primarily based on the clinical manifestation of multiple systems involving the brain, kidney, heart, and peripheral nerves, and also based on the comprehensive interrogation of family history. Patients may seek help from multiple medical specialists before a correct diagnosis is made, resulting in delayed treatment initiation[16]. Cardiac involvement is characterized by progressive cardiac hypertrophy, fibrosis, arrhythmias, heart failure, and sudden cardiac death. As myocardial fibrosis develops, the posterior and inferior LV wall can thin and become hypokinetic or akinetic[17]. Thinning of the LV posterior wall is a feature of FD related cardiomyopathy in the late stage. Further laboratory tests may include GLA activity test, pathological biopsy, and gene test, which are also considered the gold standard for diagnosis. Also, microscopic formation of typical onion-like osmiophilic inclusion bodies (such as myeloid corpuscle and zebra-corpuscle) in glomerular and tubular epithelial cell lysosomes is a typical pathological feature of lysosomal glycolipid aggregation, which is of great value in disease diagnosis. Early detection and treatment are crucial for achieving the best outcome.

Genetic testing, performed by whole-exome sequencing, and targeted analysis of the *GLA* gene could confirm clinical diagnosis. Nevertheless, the findings of a missense variant should not be considered an unequivocal validation of the diagnosis. Recently, a study examined 115 Japanese families with FD. No pathogenic mutations were identified in six families (5.2%). In total, 73 different disease-causing mutations were identified: 41 missense (56.2%), 11 nonsense (15.1%), four in-frame deletion (5.5%), 10 frameshift (13.7%), six splice site (8.2%), and one intronic (1.4%)[18]. As a result, many GLA variants of unknown significance (VOS) were identified. Therefore, the diagnosis

Baishideng®

of FD should not over-rely on genetic testing, and both clinical manifestations and family history should be considered comprehensively [19].

The treatment of FD relies on specific and non-specific treatments. Non-specific treatment is used to deal with the involvement of various organs. In this family, all the women (II3, II5, and II7) developed atrial fibrillation and underwent radical ablation, and in one case (II5) left atrial appendage occlusion was performed. Specific treatments include ERT, which is currently approved to be marketed as a galactosidase- α and a galactosidase- β . In this study, the son of the proband had started ERT treatment, and the effect will be followed closely. The European Union also approved the molecular chaperone migalastat in 2016 for the long-term treatment of specific mutated FD in patients over the age of 16 years, which could increase endogenous α-Gal A activity in a prospective observational multicenter study^[20]. Pretreatment clinical assessment, continuous clinical monitoring, and establishment and improvement of disease database should be made during treatment.

Since FD is an X-linked genetic disorder, genetic counseling and prenatal diagnosis should also be performed for all patients. Here we report a female patient who had a son who was also diagnosed with FD. The son had a daughter and he definitely passed the abnormal X chromosome to her (with 1 abnormal X chromosome and 1 normal X chromosome). However, the daughter has a heterozygous GLA allele, which may have relatively mild clinical manifestations and still need to be followed closely.

CONCLUSION

In summary, our findings suggest that the novel mutation 348delG:p.G116fs may be associated with classical manifestations of FD. These new data can be helpful in the diagnosis of FD and increase clinical and molecular knowledge about the correlations between mutations in the GLA gene, enzyme activity, and clinical phenotype of FD.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the technical staff from the Berry Genomics for providing the genetic tests. We would also like to thank the Shanghai Jiaotong University School of Medicine, Shanghai Institute for Pediatric Research, and the Key Laboratory of Cardiovascular Intervention and Regenerative Medicine of Zhejiang Province for their help with enzyme activity testing

REFERENCES

- 1 Germain DP. Fabry disease. Orphanet J Rare Dis 2010; 5: 30 [PMID: 21092187 DOI: 10.1186/1750-1172-5-30
- GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993- [PMID: 2 203012951
- Vedder AC, Linthorst GE, van Breemen MJ, Groener JE, Bemelman FJ, Strijland A, Mannens MM, 3 Aerts JM, Hollak CE. The Dutch Fabry cohort: diversity of clinical manifestations and Gb3 levels. J Inherit Metab Dis 2007; 30: 68-78 [PMID: 17206462 DOI: 10.1007/s10545-006-0484-8]
- Basta M, Pandya AM. Genetics, X-Linked Inheritance. 2021 May 8. In: StatPearls [Internet]. 4 Treasure Island (FL): StatPearls Publishing; 2021 Jan- [PMID: 32491315]
- Cooper DN BE, Stenson PD, Phillips AD, Evans K, Heywood S, Hayden MJ, Azevedo L, Mort ME, Hussain M. The Human Gene Mutation Database (2017) [cited 2019 Sep 8]. Available from: http://www.hgmd.cf.ac.uk/ac/index.php
- Rickert V, Wagenhäuser L, Nordbeck P, Wanner C, Sommer C, Rost S, Üceyler N. Stratification of Fabry mutations in clinical practice: a closer look at α-galactosidase A-3D structure. J Intern Med 2020; 288: 593-604 [PMID: 32583479 DOI: 10.1111/joim.13125]
- 7 Studer G, Rempfer C, Waterhouse AM, Gumienny R, Haas J, Schwede T. QMEANDisCo-distance constraints applied on model quality estimation. Bioinformatics 2020; 36: 1765-1771 [PMID: 31697312 DOI: 10.1093/bioinformatics/btz828]
- Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R, Heer FT, de Beer TAP, 8 Rempfer C, Bordoli L, Lepore R, Schwede T. SWISS-MODEL: homology modelling of protein structures and complexes. Nucleic Acids Res 2018; 46: W296-W303 [PMID: 29788355 DOI: 10.1093/nar/gky427]
- 9 Miller JJ, Kanack AJ, Dahms NM. Progress in the understanding and treatment of Fabry disease. Biochim Biophys Acta Gen Subj 2020; 1864: 129437 [PMID: 31526868 DOI:



10.1016/i.bbagen.2019.129437]

- 10 Shi Q, Chen J, Pongmoragot J, Lanthier S, Saposnik G. Prevalence of Fabry disease in stroke patients--a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2014; 23: 985-992 [PMID: 24126289 DOI: 10.1016/j.jstrokecerebrovasdis.2013.08.010]
- 11 Kornreich R, Desnick RJ, Bishop DF. Nucleotide sequence of the human alpha-galactosidase A gene. Nucleic Acids Res 1989; 17: 3301-3302 [PMID: 2542896 DOI: 10.1093/nar/17.8.3301]
- Verovnik F, Benko D, Vujkovac B, Linthorst GE. Remarkable variability in renal disease in a large 12 Slovenian family with Fabry disease. Eur J Hum Genet 2004; 12: 678-681 [PMID: 15162124 DOI: 10.1038/sj.ejhg.5201184]
- 13 Garman SC, Garboczi DN. The molecular defect leading to Fabry disease: structure of human alphagalactosidase. J Mol Biol 2004; 337: 319-335 [PMID: 15003450 DOI: 10.1016/j.jmb.2004.01.035]
- Berletch JB, Yang F, Disteche CM. Escape from X inactivation in mice and humans. Genome Biol 14 2010; 11: 213 [PMID: 20573260 DOI: 10.1186/gb-2010-11-6-213]
- Tukiainen T, Villani AC, Yen A, Rivas MA, Marshall JL, Satija R, Aguirre M, Gauthier L, Fleharty 15 M, Kirby A, Cummings BB, Castel SE, Karczewski KJ, Aguet F, Byrnes A; GTEx Consortium; Laboratory, Data Analysis & Coordinating Center (LDACC)-Analysis Working Group; Statistical Methods groups—Analysis Working Group; Enhancing GTEx (eGTEx) groups; NIH Common Fund; NIH/NCI; NIH/NHGRI; NIH/NIMH; NIH/NIDA; Biospecimen Collection Source Site—NDRI; Biospecimen Collection Source Site—RPCI; Biospecimen Core Resource—VARI; Brain Bank Repository-University of Miami Brain Endowment Bank; Leidos Biomedical-Project Management; ELSI Study; Genome Browser Data Integration & Visualization-EBI; Genome Browser Data Integration & Visualization-UCSC Genomics Institute, University of California Santa Cruz, Lappalainen T, Regev A, Ardlie KG, Hacohen N, MacArthur DG. Landscape of X chromosome inactivation across human tissues. Nature 2017; 550: 244-248 [PMID: 29022598 DOI: 10.1038/nature24265
- Reisin R, Perrin A, García-Pavía P. Time delays in the diagnosis and treatment of Fabry disease. Int J 16 Clin Pract 2017; 71 [PMID: 28097762 DOI: 10.1111/ijcp.12914]
- Linhart A, Germain DP, Olivotto I, Akhtar MM, Anastasakis A, Hughes D, Namdar M, Pieroni M, 17 Hagège A, Cecchi F, Gimeno JR, Limongelli G, Elliott P. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. Eur J Heart Fail 2020; 22: 1076-1096 [PMID: 32640076 DOI: 10.1002/ejhf.1960]
- Marian AJ. Challenges in the Diagnosis of Anderson-Fabry Disease: A Deceptively Simple and Yet 18 Complicated Genetic Disease. J Am Coll Cardiol 2016; 68: 1051-1053 [PMID: 27585510 DOI: 10.1016/j.jacc.2016.06.026]
- 19 Kobayashi M, Ohashi T, Kaneshiro E, Higuchi T, Ida H. Mutation spectrum of α-Galactosidase gene in Japanese patients with Fabry disease. J Hum Genet 2019; 64: 695-699 [PMID: 30988410 DOI: 10.1038/s10038-019-0599-z
- Lenders M, Nordbeck P, Kurschat C, Karabul N, Kaufeld J, Hennermann JB, Patten M, Cybulla M, 20 Müntze J, Üçeyler N, Liu D, Das AM, Sommer C, Pogoda C, Reiermann S, Duning T, Gaedeke J, Stumpfe K, Blaschke D, Brand SM, Mann WA, Kampmann C, Muschol N, Canaan-Kühl S, Brand E. Treatment of Fabry's Disease With Migalastat: Outcome From a Prospective Observational Multicenter Study (FAMOUS). Clin Pharmacol Ther 2020; 108: 326-337 [PMID: 32198894 DOI: 10.1002/cpt.1832]





Published by Baishideng Publishing Group Inc 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA Telephone: +1-925-3991568 E-mail: bpgoffice@wjgnet.com Help Desk: https://www.f6publishing.com/helpdesk https://www.wjgnet.com

