Journal of Cardiology 62 (2013) 63–69

Contents lists available at SciVerse ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Japanese patients with Fabry disease predominantly showing cardiac and neurological manifestation with novel missense mutation: R220P

Motoki Fukutomi (MD)[a,b,*], Nobuaki Tanaka (MD, FJCC)[b], Hitoshi Uchinoumi (MD)[b], Masashi Kanemoto (MD)[b], Fumiaki Nakao (MD)[b], Jutaro Yamada (MD)[c], Toshiaki Kamei (MD)[d], Toshihiro Takenaka (MD, FJCC)[e], Takashi Fujii (MD, FJCC)[b]

[a] *Yanai Municipal Heigun Clinic, Yamaguchi, Japan*
[b] *Department of Cardiology, Yamaguchi Grand Medical Center, Yamaguchi, Japan*
[c] *Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-kogushi, Ube, Yamaguchi 755-8505, Japan*
[d] *Department of Pathology, Yamaguchi Grand Medical Center, Yamaguchi, Japan*
[e] *Division of Cardiac Repair and Regeneration, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan*

ARTICLE INFO

Article history:
Received 12 October 2012
Received in revised form 19 January 2013
Accepted 20 February 2013
Available online 19 April 2013

Keywords:
Fabry disease
Novel missense mutation
Left ventricular hypertrophy
Neurological manifestation

ABSTRACT

Background: Fabry disease, an X-linked lysosomal sphingolipid storage disorder caused by mutation of the α-galactosidase A (GLA) gene, results in systemic organ damage. However, the age of onset of clinical manifestations and course of the disease are variable even within the same family.
Objective: In this study, we evaluated the clinical phenotype and the molecular lesions associated with the GLA gene in a Japanese family with Fabry disease that predominantly showed cardiac and neurological manifestations.
Methods: A genetic analysis of the GLA gene using conventional genomic sequencing was performed in all seven members of this family, including four hemizygous males and three heterozygous females. Endomyocardial biopsy was performed in two patients with severe left ventricular (LV) hypertrophy.
Results: A novel missense mutation was identified at codon 220 in exon 5, thus resulting in an arginine to proline substitution (R220P) in all seven family members. The three adult hemizygous males had LV hypertrophy and developed neurological manifestations in their 50 s. One of the adult hemizygotes developed complete atrioventricular block. On the other hand, we could not find any organ damage in a young hemizygous male or the three heterozygous females.
Conclusion: We identified a novel missense mutation in a Japanese family with Fabry disease showing cardiac and neurological manifestations. In patients with Fabry disease, advanced organ damage in the heart and brain can be life-threatening, even if renal failure is lacking.

Introduction

Fabry disease is an X-linked sphingolipid storage disorder, caused by mutations in the α-galactosidase A (GLA) gene, which results in the systemic intralysosomal accumulation of glycosphingolipids throughout the body, particularly in the skin, nervous system, eyes, kidneys, and heart [1]. This disease typically presents during childhood or adolescence. Clinical manifestations usually become apparent around the age of 10 years in affected males and several years later in females. In general, the first signs and symptoms reflect the damage to small nerve fibers, resulting in peripheral neuropathic pain in the feet and hands [2–4]. With age, various complications involving the kidneys, heart, and brain cause considerable morbidity and premature death [5,6]. Renal failure has been found to be a frequent cause of death, while the importance of cardiac disease is now increasingly being recognized [6]. In terms of the clinical aspects, these manifestations can present in patients at different times throughout their life, contributing to the complicated phenotype of this disease.

To date, a variety of disease-related mutations including missense, nonsense, and splice-site mutations have been documented in cases of Fabry disease [7]. However, the analysis of genotype–phenotype correlations in Fabry disease is complicated by a number of factors. First, there is a high proportion of private mutations, that is, most of the families carry different mutations [8]. Second, there is a high degree of clinical variability both among patients from the same family and among those from unrelated families with the same mutation. Therefore, it is difficult to predict the exact clinical phenotype of each patient based only on their genotype.

* Corresponding author at: Yanai Municipal Heigun Clinic, Yamaguchi, Japan. Tel.: +81 820 47 2032; fax: +81 820 47 2032.
E-mail address: 98080mf@jichi.ac.jp (M. Fukutomi).

0914-5087/$ – see front matter
http://dx.doi.org/10.1016/j.jjcc.2013.02.012

We herein present a Japanese family with Fabry disease due to a novel missense mutation, R220P. Clinically, all adult male members of this family predominantly showed cardiac and neurological manifestations in their 50 s. Thus, we will additionally discuss the clinical phenotype of Fabry disease in relation to the findings from this family.

Methods

We studied seven members of a three-generation family. All seven of these family members provided their written, informed consent in accordance with the principles of the Declaration of Helsinki. The medical records of each participant, which included interviews, physical examinations, blood and urine tests, and radiography were reviewed. The estimated glomerular filtration rate (eGFR) was calculated using a validated equation described in the Modification of Diet in Renal Disease study in Japan [9].

Enzyme activity

The plasma GLA activity was measured in all seven members of this family. The assay was performed using the method described by Nakao et al. [10] using 5 ml of a heparinized blood sample. The normal values averaged 8.4 ± 2.4 nmol/ml/h (range 4.8–17.6) in samples obtained from 89 normal males who were aged 52 ± 19 (range 14–80) years.

Gene analysis

Genomic DNA was isolated from whole blood using a standard procedure [11]. A mutation analysis was performed by polymerase chain reaction (PCR) amplifying each of the seven GLA exons and their flanking intronic sequences from genomic DNA using the primers shown in Table 2. Sequencing reactions were performed using the BigDye Terminatory v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Sequencing was performed on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems).

Cardiac examinations

Echocardiography and electrocardiography (ECG) were performed in all adult hemizygotes. M-mode echocardiographic measurements of the left ventricular (LV) diameters and interventricular septal and LV posterior wall thicknesses were performed according to the recommendations of the American Society of Echocardiography [12]. Coronary angiography and endomyocardial biopsy of the LV were performed in subjects II/1 and II/2.

Nerve conduction study

A nerve conduction study was performed in subject II/2. In this study, the compound muscle action potential and nerve conduction velocity were recorded on the right side of the median nerve, ulnar nerve, tibial nerve, peroneal nerve, and sural nerve.

Histological studies

Heart tissue biopsy specimens from subjects II/1 and II/2 were fixed in 10% buffered formalin, and the sections were stained with hematoxylin and eosin (H&E) and Azan–Mallory staining for histological examination. The tissue block used for electron microscopy was dehydrated with ethanol and embedded in propylene oxide and epoxy resin to prepare ultra-thin sections, which were stained with uranyl acetate and lead.

Results

Subject II/2 (proband)

The proband, subject II/2 was a 57-year-old male, who was admitted to our hospital to be investigated for repeated episodes of fainting with unconsciousness under resting conditions. A brain computed tomography did not uncover any significant abnormal findings. However, his chest X-ray showed an enlargement of the heart shadow, and ECG displayed high voltages, intraventricular conduction disturbance, and negative T waves in leads, I, II, III, aVL, aVF, and V3–6 (Fig. 1). Furthermore, echocardiography detected severe LV hypertrophy with a preserved ejection fraction (Fig. 2). His other laboratory data showed proteinuria with a slightly reduced eGFR, increased B-type natriuretic peptide, and an absence of plasma GLA activity (Table 1). We therefore diagnosed the patient to have Fabry disease. We could not find any other specific evidence of this disease in his eyes, skin, or ears, but he did have a past history of painful peripheral neuropathy (acroparesthesias) during his childhood.

During this admission, we detected a 15 beats run of asymptomatic non-sustained ventricular tachycardia in his monitoring ECG. Two days after this arrhythmia occurred, he presented with a loss of consciousness and complete atrioventricular block. We performed emergency temporary cardiac pacing and subsequently implanted an implantable cardioverter-defibrillator (ICD). Cardiac catheterization showed no significant coronary artery stenosis. The results from an endomyocardial biopsy showed interstitial fibrosis and cardiomyocyte hypertrophy with cytoplasmic vacuolization, which are the typical histological findings of the heart in patients with Fabry disease. In a nerve conduction study, the peroneal nerve showed a low level of compound muscle action potential (ankle, 0.93 mV; head of fibula, 0.79 mV), whereas this site of nerve conduction velocity was below the normal limit (42.3 m/s). This finding indicates the presence of chronic axon degeneration in the lower extremities. Soon after discharge from our hospital, he presented with double vision. Because of the presence of the implanted ICD, we could not evaluate his brain by magnetic resonance imaging.

Subject II/1

Subject II/1, an elder brother of the proband, was a 59-year-old male. He had developed a cerebral infarction at 57 years of age. During this admission, he was pointed out to have LV hypertrophy and was followed up for hypertrophic cardiomyopathy. His ECG and echocardiographic findings were similar to those of subject II/2 (Figs. 1 and 2). We also found an absence of GLA activity in his plasma (Table 1), thus leading to the diagnosis of Fabry disease. Coronary angiography showed normal coronary artery, and the results from endomyocardial biopsy showed the same findings as were observed in subject II/2 (Fig. 3). He had also experienced episodes of acroparesthesias, but lacked any manifestations in other organs.

Subject II/3

Subject II/3 was a first cousin of subjects II/1 and II/2 (Fig. 4). He also had experienced an episode of acroparesthesias, and had a history of transient ischemic attack (TIA) at the age of 52 years. His laboratory data showed proteinuria with a slightly reduced eGFR and an absence of plasma GLA activity (Table 1). His ECG showed high voltage of the QRS complex, and echocardiography showed mild LV hypertrophy (Figs. 1 and 2).

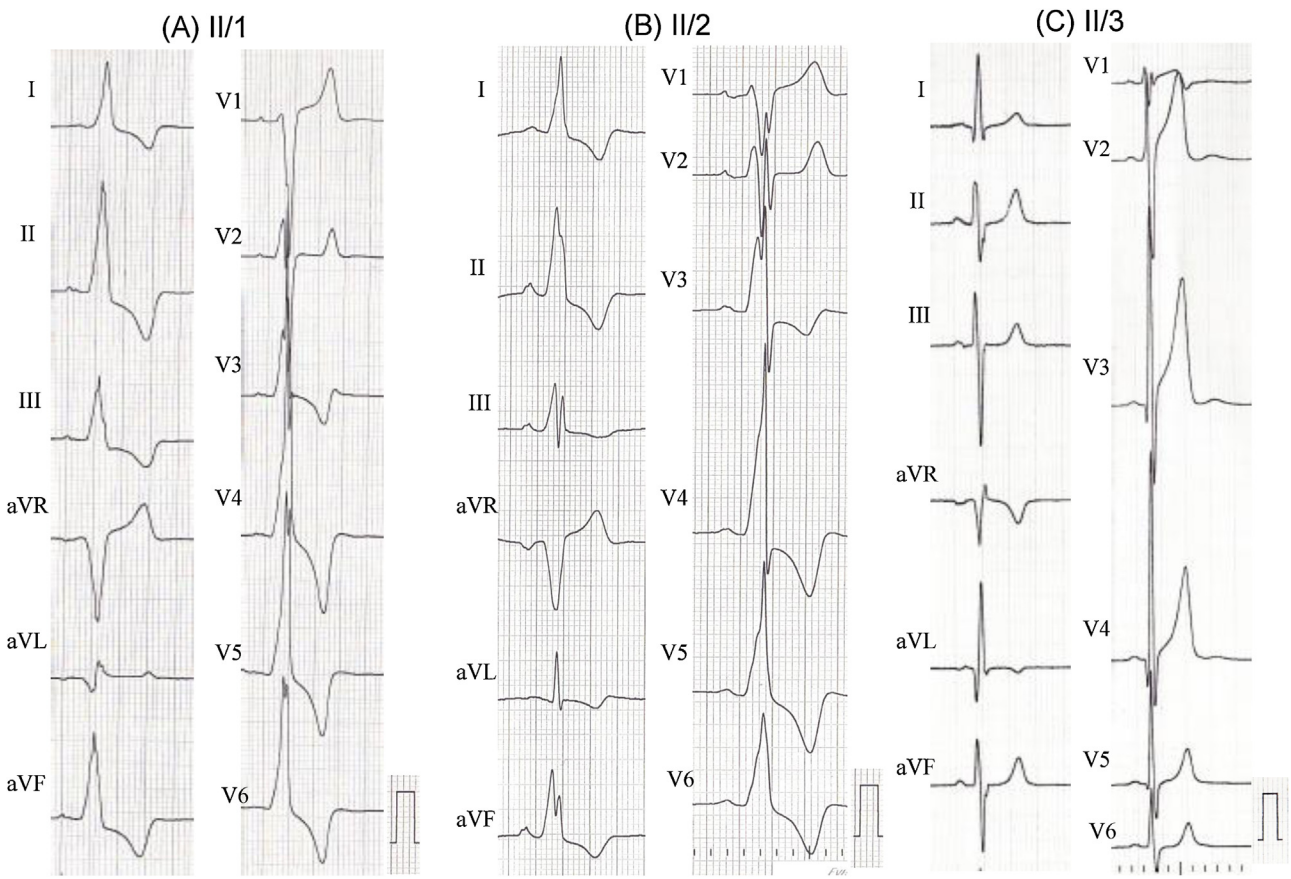

Fig. 1. Twelve-lead electrocardiogram (ECG) of hemizygous adult males. (A) II/1 displayed high voltages and wide QRS wave complex with negative T waves. (B) ECG of II/2 is similar to that of II/1. (C) II/3 displayed left axis deviation, high voltage of the QRS wave complex and ST elevation of V1–V4.

Subjects III/1 and IV/1–3

Subject III/1 was an asymptomatic daughter of subject II/2. Subjects IV/1 and IV/2 were daughters, and IV/3 was a son, of subject III/1 (Fig. 4). None of them showed any cardiac, neurological, or renal symptoms. The activity of plasma GLA was decreased in subjects III/1, IV/1, IV/2, and completely lacking in subject IV/3 (Table 1).

Molecular genetic findings of the family

In the male subjects in this study including II/1, 2, 3, and IV/3, a novel missense mutation was identified at codon 220 in exon 5, thus resulting in an arginine (CGA) to proline (CCA) substitution (Fig. 5). These findings confirmed that they were hemizygous males with Fabry disease. On the other hand, subjects III, IV/1, and IV/2 were diagnosed as heterozygous carriers of Fabry disease, as shown in Fig. 5.

Discussion

In this report, we presented a Japanese family with Fabry disease showing a novel missense mutation. We considered these individuals to have the classic type of Fabry disease based on their clinical phenotype and lack of plasma GLA activity. All of the hemizygous males predominantly presented with cardiac and cerebrovascular manifestations in their 50 s. To the best of our knowledge, this is the first study showing the presence of the R220P mutation in exon 5 and its relationship with the clinical features of Fabry disease. To date, more than 400 disease-related mutations of GLA have been reported [7], and a recent report from Japan also identified three novel mutations of GLA [13].

Of the seven GLA exons, exons 5 and 6 are known to be common areas in which the disease-related mutations are present [7]. Therefore, the R220P mutation occurred in a relatively frequently affected area of GLA. Clinically, all three hemizygous male showed not only cardiac manifestations but also neurological manifestations. Therefore, this family seems to be characterized into the classic type of Fabry disease. According to previous data, a R220X nonsense mutation was documented as the cause of classic type of Fabry disease in Japanese [14] and in Australian families [15]. These reports described members of these families with cardiac, neurological, and renal manifestations. In our case, we took the histories of other members of the family who died of chronic renal failure (CRF). Therefore, no major differences were observed in the phenotypes between our family with the R220P mutation and those with the R220X mutation.

In this study, three adult hemizygous males showed LV hypertrophy with typical histological findings. In addition, subject II/2 developed complete atrioventricular block resulting in permanent pacemaker implantation. This type of arrhythmia is a relatively rare, but potentially fatal complication in Fabry patients [16,17]. The LV myocardium in Fabry patients is known to include a progressive accumulation of glycosphingolipids, predominantly globotriasylceramide (GL3) [16,18]. Ikari et al. revealed a considerable deposition of glycosphingolipids to exist in the bundle of His and the bundle branches in Fabry patients showing complete atrioventricular block [16]. It is therefore strongly recommended that Fabry patients should be evaluated by ambulatory ECG, especially those with LV hypertrophy and episodes of syncope.

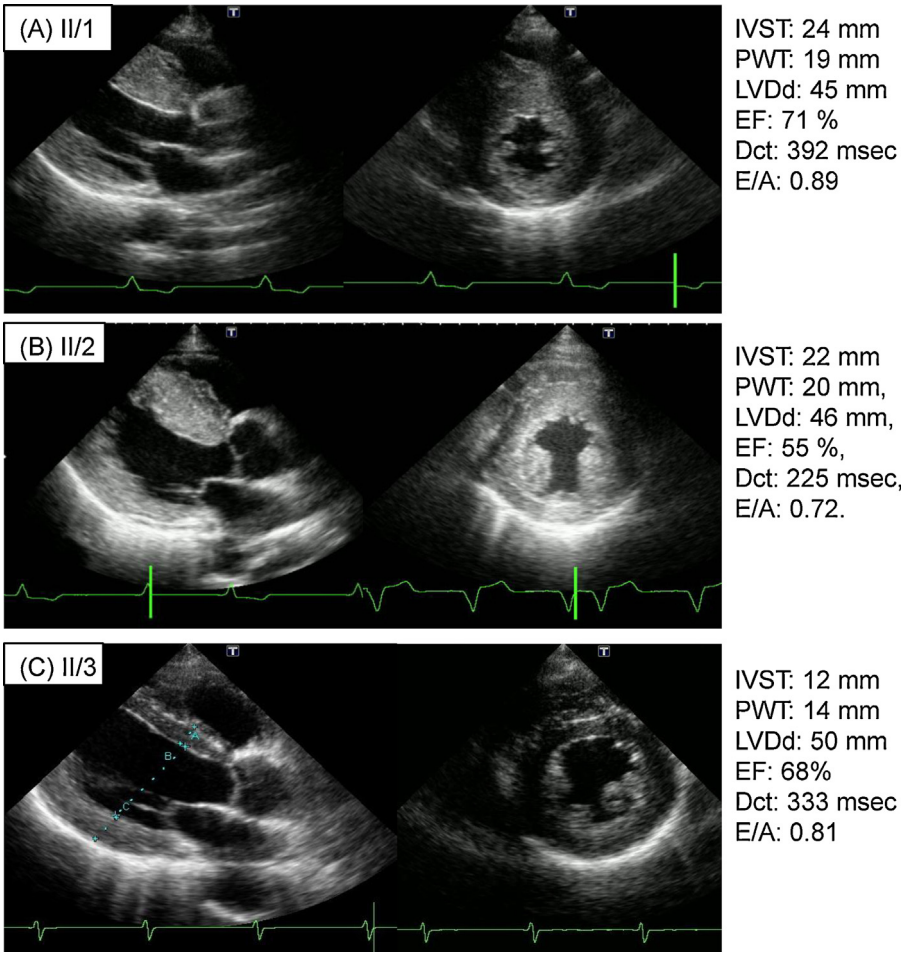

Fig. 2. Transthoracic echocardiogram shows (A) severe diffuse left ventricular hypertrophy (LVH) with preserved EF in subject II/1 and (B) subject II/2. (C) Subject II/3 shows mild LVH with normal EF.

Table 1
Clinical characteristics of family members.

Subjects	Age/sex (y)	P-GLA activity (nmol/h/ml)	Genetic diagnosis	Creatinine (mg/dl)	eGFR (ml/min/1.73 m^2)	Qualitative proteinuria	BNP (pg/ml)	Cardiac complications	Neurological complications
II/1	59M	0	Hemizygote	0.56	119.0	(−)	713.1	LVH	Ischemic stroke (57 y) Acroparesthesias
II/2 (proband)	57M	0	Hemizygote	0.80	77.6	(2+)	152.4	LVH Complete AVB (57 y)	Double vision (57 y) Axon degeneration in peroneal nerve Acroparensthesias
II/3	56M	0	Hemizygote	0.79	79.0	(1+)	30.1	LVH	TIA (52 y) Acroparesthesias
III	37F	1.3	Heterozygous	0.46	118.0	(−)	20.5	Normal	
IV/1	17F	3.4	Heterozygous	0.53	–	(−)	5.8	Normal	
IV/2	11F	8.2	Heterozygous	0.55	–	(−)	9.0	Normal	
IV/3	8M	0	Hemizygote	0.32	–	(−)	–	Normal	Acroparesthesias

eGFR was calculated using a validated equation based on the Modification of Diet in Renal Disease study in Japan

Table 2
Primer sequences for amplification of the GLA gene.

Fragment	Nucleotide position	Sequence	Size (bp)
Genomic DNA amplification			
Exons 5–7	10,078–10,094	Forward: 5′-CTCACAAGGATGTTAGT-3′	1224
	11,301–11,285	Reverse: 5′-CAGGAAGTAGTAGTTGG-3′	
Sequencing primer			
Exon 5 reverse	10,349–10,365	5′-TATTTACCTTGAATGTC-3′	

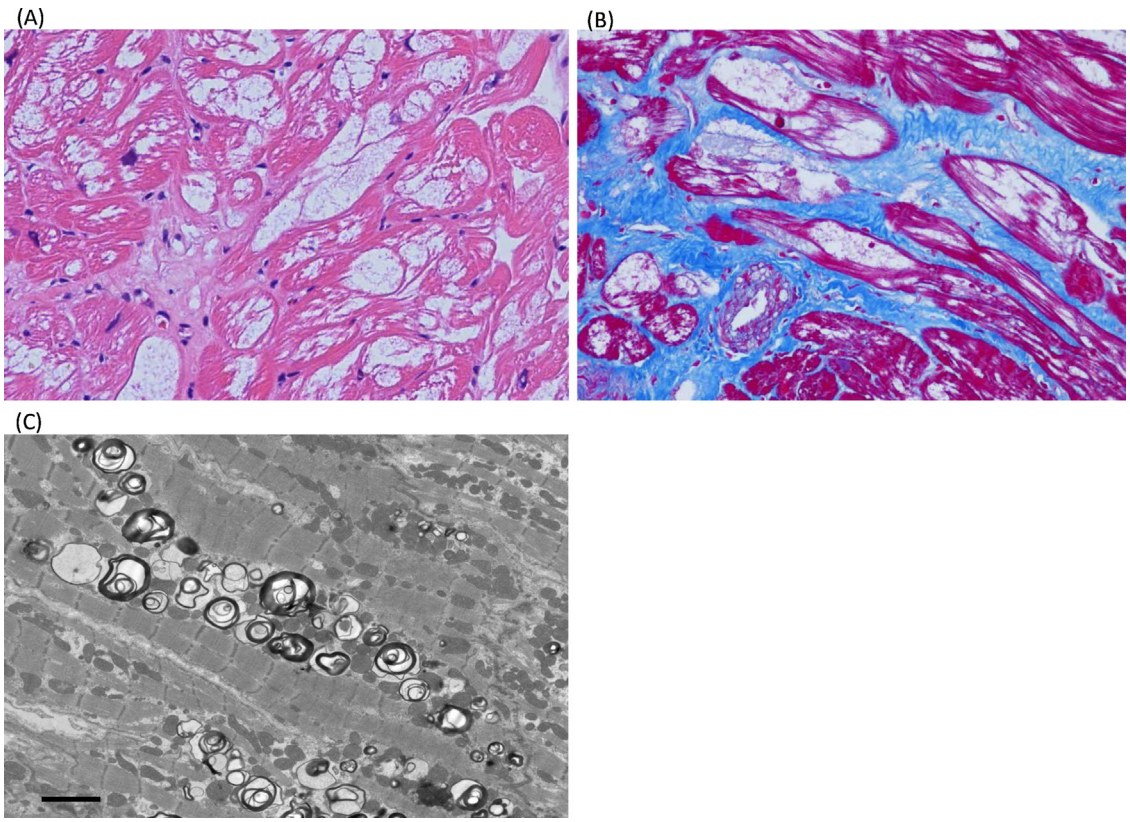

Fig. 3. The histological finding of subject II/1. Light microscopic findings show (A) sarcoplasmic vacuolization of the myocardial cells (hematoxylin and eosin stain, 200×), and (B) interstitial myocardial fibrosis (Azan–Mallory stain, 200×). (C) Electron microscopy shows the central vacuolar degeneration of myocytes with concentric lamellar structure (original magnification: 4800×, the scale bar represents 1 μm).

The current therapeutic approaches for Fabry disease aim to increase the GLA activity, and thereby decrease the GL3 levels. To date, the methods to achieve this have included enzyme replacement therapy (ERT) [19,20], molecular chaperone therapy [21], and gene therapy [22]. Because only ERT is clinically available at the present time, we are planning to start this therapy for subjects II/1, II/2, and II/3. Subject IV/3 has been regularly checked by a pediatrician to determine an adequate start time for ERT. We will start ERT when he presents with proteinuria or an elevation of the urinary GL3 level, because the use of ERT before significant organ damage is important for achieving optimal therapeutic outcomes for patients with Fabry disease [23].

Subjects II/1 and II/3 both had past histories of ischemic stroke in their early 50 s. On the other hand, subject II/2 presented with double vision and abnormality of nerve conduction test in the lower extremities. Therefore, all these adult hemizygous males showed neurological manifestations in later adulthood. Ischemic stroke is one of the potentially life-threatening complications of Fabry

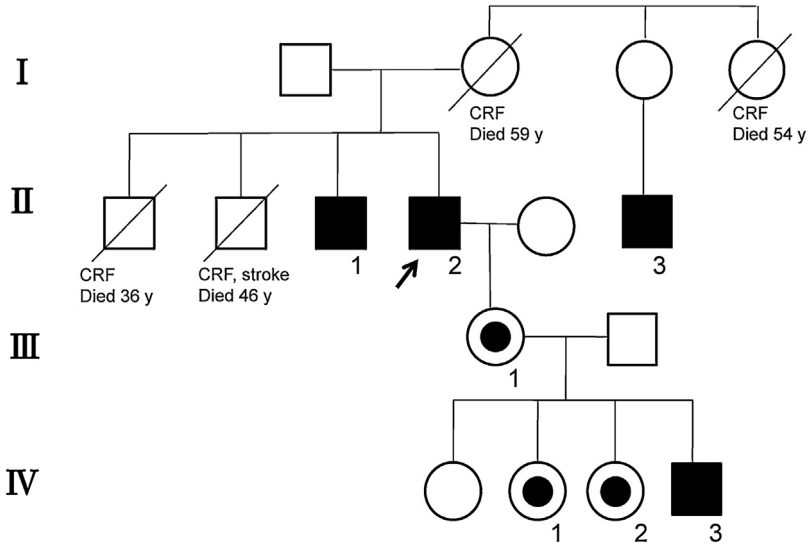

Fig. 4. The pedigree of the family. The shaded square indicates hemizygous male, and the circles with a dot indicate heterozygous female carrier. The arrow indicates proband.

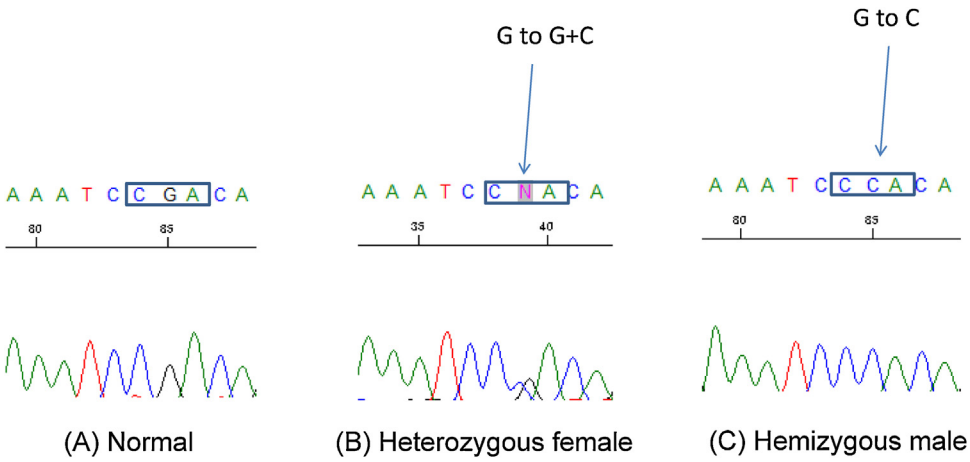

Fig. 5. (A) Chromatography of normal control and (B) genomic DNA from subject III/1 and (C) subject II/2 for GLA exon5.

disease, along with end-stage renal disease (ESRD) and cardiac disease. The pathogenesis of ischemic stroke in Fabry disease is likely to involve specific mechanisms related directly or indirectly to glycolipid deposition in vessel walls. According to the Fabry Outcome Survey (FOS) database, in patients with TIA, the proportion of LV hypertrophy was higher (67%) than that in patients without TIA (29%) [7]. It is therefore suggested that the co-existence of LV hypertrophy and TIA is relatively common in patients with Fabry disease who survive to later adulthood without renal failure.

As mentioned above, classic Fabry disease is usually associated with not only interfamilial, but also intrafamilial variation in phenotype. However, it is currently difficult to estimate the phenotype of manifestations based on only the information provided by a genotype analysis, because there are few data supporting the genotype–phenotype correlation in Fabry disease, and also because such a large number of mutations have so far been identified. In a previous report, MacDermot et al. investigated the natural history of hemizygous males of Fabry disease in a large cohort study, and revealed the age-specific frequency of disease manifestation [24]. They concluded that "age stratification" for this disease manifestation may contribute to phenotype classification and might be helpful for clinical management of these patients. According to their data, about 30% of classic Fabry disease patients developed ESRD, and the mean age of onset of renal dialysis was 36.7 years. It is known that about one-third of all Fabry disease patients will develop severe renal disease, thus contributing to a high rate of death in early adulthood. On the other hand, in cases with no symptoms of advanced renal failure, cardiac or neurological manifestations become obvious in later adulthood. Of note, in the family described in the present report, several other members were found to have died of CRF. Therefore, the findings of this report suggested that age stratification was partly useful for the phenotype classification of classic Fabry disease.

Conclusions

The present study showed a family with classic Fabry disease who had a novel missense mutation, R220P. In this family, the hemizygous adult males showed cardiac and neurological manifestations, suggesting that the development of these complications should be carefully checked in families known to have a history of Fabry disease, even when they have no history of renal failure.

Acknowledgments

This research was supported in part by a Grant-in-Aid for Idiopathic Cardiomyopathy Research Committee from the Ministry of Health, Labor and Welfare of Japan.

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