Case reports of a c.475G>T, p.E159* lamin A/C mutation with a family history of conduction disorder, dilated cardiomyopathy and sudden cardiac death

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Abstract

Background: Patients with some mutations in the lamin A/C (LMNA) gene are characterized by the presence of dilated cardiomyopathy (DCM), conduction abnormalities, ventricular tachyarrhythmias (VT), and sudden cardiac death (SCD). Various clinical features have been observed among patients who have the same LMNA mutation. Here, we show a family with cardiac laminopathy with a c.475G > T, p.E159* LMNA mutation, and a family history of conduction disorder, DCM, VT, and SCD.

Case presentation: A proband (female) with atrial fibrillation and bradycardia was implanted with a pacemaker in her fifties. Twenty years later, she experienced a loss of consciousness due to polymorphic VT. She had a serious family history; her mother and elder sister died suddenly in their fifties and sixties, respectively, and her nephew and son were diagnosed as having DCM. Genetic screening of the proband, her son, and nephew identified a nonsense mutation (c.475G > T, p.E159*) in the LMNA gene. Although the proband’s left ventricular ejection fraction remained relatively preserved, her son and nephew’s left ventricular ejection fraction were reduced, resulting in cardiac resynchronization therapy by implantation of a defibrillator.

Conclusions: In this family with cardiac laminopathy with a c.475G > T, p.E159* LMNA mutation, DCM, SCD, and malignant VT occurred. Clinical manifestation of various atrial and ventricular arrhythmias and heart failure with reduced ejection fraction occurred in an age-dependent manner in all family members who had the nonsense mutation. It appears highly likely that the E159* LMNA mutation is related to various cardiac problems in the family of the current report.

Keywords: Lamin A/C, Dilated cardiomyopathy, Sudden cardiac death, c.475G > T, p.E159*, Case report

Background

Some mutations in the lamin A/C (LMNA) gene cause familial dilated cardiomyopathy (DCM), and the phenotype is also characterized by progressive conduction abnormalities, atrial arrhythmias, ventricular tachyarrhythmia (VT), and sudden cardiac death (SCD) [1–7]. The LMNA gene encodes lamins A and C, which are major components of the nuclear lamina, a dynamic protein meshwork in the nuclear membrane. The nuclear lamina has a vital role in a multitude of functions, ranging from providing structural support for the nucleus, to facilitating chromatin organization, gene regulation and DNA repair [8]. The LMNA mutation causes a variety of clinical illnesses, such as skeletal muscle disease, premature aging, lipodystrophies, and cardiomyopathies [9].

Approximately 6.2% of all DCM cases are caused by LMNA mutations [10]. DCM patients with LMNA
mutations have poor long-term outcomes with various clinical courses, and the SCD rate is reported to be as high as 46% [11, 12]. Several reports have shown sex-specific differences in the prognostic effects of DCM patients with LMNA mutations [13, 14]. Three multicenter studies of patients with LMNA mutations in several countries suggested that male sex was an independent predictor for malignant VT [11, 13, 15]. Additionally, a study of a large cohort of LMNA mutation carriers demonstrated that male patients have a higher incidence of worse VT and end-stage heart failure than female patients [14]. A study by Arimura et al. found that nuclear accumulation of the androgen receptor and testosterone is associated with cardiac remodeling in DCM with LMNA mutations [16]. Thus, as well as the genetic identification, sex difference should also be considered for the management of therapies in individual patients with LMNA mutations [17].

To determine the details of the phenotype of a c.475G>T, p.E159* LMNA mutation (the ClinVar accession number, SCV000996024), we report patients from the same family who have histories of conduction disorder, sick sinus syndrome, DCM, VT, and SCD.

Case presentations
Case 1
A female proband (II-4) in her fifties suffered from atrial fibrillation with bradycardia, and was implanted with a pacemaker. About 20 years later, she was admitted to our hospital with loss of consciousness due to polymorphic VT. Consciousness was recovered via transient chest oppression. Electrocardiogram after recovery showed a pacing rhythm with a heart rate of 70 ppm and a QTc interval of 441 msec (Fig. 1a). After admission, polymorphic VT intermittently occurred (Fig. 1b), and therefore intravenous lidocaine and magnesium sulfate were administered. Furthermore, the patient was diagnosed as having influenza, and was administered lannamivir. Her laboratory findings revealed a low potassium level of 3.3 mEq/L, an increased white cell count of 11,900/μL, an increased C-reactive protein level of 2.38 mg/dL, and a B-type natriuretic peptide level of 59.0 pg/mL, as shown in Table 1. She had not been administered any medication that prolonged the QT interval. Intravenous and oral potassium was administered. Her polymorphic VT did not recur after treatment. Her chest X-ray revealed slight congestion, with a cardiothoracic ratio of 71.0% with a pacemaker (Fig. 1c). Echocardiogram showed a normal left ventricular ejection fraction of 62%, a slightly large left ventricular diastolic diameter of 53.8 mm, and a large left atrial diameter of 54 mm.

Fig. 1 Images of Case 1 (II-4). a On admission, electrocardiogram showed pacing rhythm, a heart rate of 70 ppm, and a QTc interval of 441 msec. b Polymorphic ventricular tachycardia intermittently occurred. c Chest X-ray revealed slight congestion, with a cardiothoracic ratio of 71.0% with a pacemaker. d Echocardiogram showed a normal left ventricular ejection fraction of 62%, a slightly large left ventricular diastolic diameter of 53.8 mm, and a large left atrial diameter of 54 mm.
ventricular (LV) ejection fraction of 62%, a slightly large LV diastolic diameter of 53.8 mm, and a large left atrial diameter of 54 mm (Fig. 1d).

The patient's family history suggested familial cardiac disease, including complete atrioventricular block, atrial fibrillation, VT, pacemaker implantation, SCD, DCM, and cardiac resynchronization therapy defibrillator (CRTD) implantation (Fig. 2a). Genetic testing was performed as described previously [15, 18], on the patient, her sons (III-4, details were described as Case 3, and III-6), and her nephew (III-1, details were described as Case 2). The details of the genetic testing are described in the Supplementary Materials. In brief, genomic DNA was extracted from blood leukocytes. Next-generation sequencing was performed for 56 genes associated with inherited primary arrhythmia syndromes, cardiomyopathy, and LMNA. Then, LMNA was detected in the patient's family members. We developed polymerase chain reaction primers to amplify the protein-coding exons of LMNA for mutational screening. Genetic variant databases (NCBI NC_000001; NCBI NM_170707; NCBI NP_733821; NCBI NM_005572; NCBI NP_005563) were used for searches for the presence of the LMNA variants identified in the patients. An RNA splice site prediction tool (Berkeley Drosophila Genome Project: http://www.fruitfly.org) and in silico prediction tools of Polyphen2 (http://genetics.bwh.harvard.edu/pph2), SIFT (http://sift.jcvi.org/) and Condel (http://bg.upf.edu/fannsdb/) were also used. We then discovered an LMNA nonsense mutation, c.475G > T, p.E159*, (the ClinVar accession number, SCV00996024) in the patient, her eldest son, and her nephew (Fig. 2b, c). Her second son did not have any LMNA mutations. The patient’s mother (I-2) had SCD in her fifties, and her older sister (II-2, clinical course was described in Fig. 3) was implanted with a pacemaker due to sick sinus syndrome in her sixties, 3 years after which she suffered ventricular fibrillation and died suddenly.

In Case 1 (II-4), implantation of a cardiovascular defibrillator (ICD) was recommended because of polymorphic VT, LMNA mutation, and family history of SCD. However, she refused the implantation and was discharged.

Case 2
A man (nephew of the patient in Case 1, III-1) in his forties developed complete atrioventricular block (Fig. 4a). Echocardiogram revealed normal LV function, and he was implanted with a pacemaker. Five years later he was admitted to hospital with VT (Fig. 4b). Echocardiogram revealed a reduced LV ejection fraction of 42.7%, and coronary angiography showed no significant stenosis of his coronary arteries. He was diagnosed as having DCM, and medical treatment with amiodarone, carvedilol, and imidapril was initiated. In the same year, he underwent genetic testing, and the same LMNA nonsense mutation seen in Case 1 was detected. He had an

| Parameters | Case 1 | Case 2 | Case 3 |
|------------|--------|--------|--------|
| White cell count, /μL | 11,900 | 6300 | 10,200 |
| Red blood cell, /μL | 372 × 10⁴ | 436 × 10⁴ | 414 × 10⁴ |
| Hemoglobin, g/dL | 10.9 | 13.9 | 13.7 |
| Platelet count, /μL | 21.4 × 10⁴ | 25.7 × 10⁴ | 30.1 × 10⁴ |

| Blood count | Case 1 | Case 2 | Case 3 |
|-------------|--------|--------|--------|
| AST, IU/L | 23 | 37 | 35 |
| ALT, IU/L | 14 | 30 | 38 |
| LDH, IU/L | 173 | 218 | 275 |
| ALP, IU/L | 249 | 180 | 761 |
| Total bilirubin, mg/dL | 0.8 | 0.7 | 1.2 |
| CRP, mg/dL | 2.38 | 0.05 | 1.15 |
| BUN, mg/dL | 7 | 14 | 10 |
| Creatinine, mg/dL | 0.52 | 0.77 | 0.72 |
| eGFR, mL/min/1.73 m² | 84.3 | 82.0 | 90.0 |
| Sodium, mEq/L | 133 | 139 | 141 |
| Potassium, mEq/L | 3.3 | 4.3 | 4.3 |
| Chlorine, mEq/L | 95 | 106 | 96 |
| Calcium, mg/dL | 8.1 | – | – |
| IP, mg/dL | 2.5 | – | – |
| Magnesium, mg/dL | 2.0 | – | – |
| Total protein, g/dL | 7.2 | 7.2 | 8.2 |
| Albumin, g/dL | 4.1 | 4.1 | 3.9 |
| Uric acid | – | 5.4 | 6.1 |
| Creatine kinase, IU/L | 152 | 152 | 24 |
| CK-MB, IU/L | 2.7 | 0.7 | |
| Troponin I, ng/mL | 0.176 | 0.215 | |
| BNP, pg/mL | 59.0 | 59.5 | 317.4 |
| Triglyceride, mg/dL | – | 74 | 214 |
| HDL-C, mg/dL | – | 79 | 40 |
| LDL-C, mg/dL | – | 75 | 110 |
| FT3, pg/mL | – | 2.61 | 2.69 |
| FT4, ng/mL | – | 2.21 | 1.06 |
| TSH, uIU/mL | – | 2.720 | 6.450 |
| Glucose, mg/dL | – | 98 | 118 |
| HbA1c (NGSP), % | – | 5.8 | 6.3 |

AST Aspartate transaminase, ALP Alkaline phosphatase, ALT Alanine aminotransferase, BNP B-type natriuretic peptide, BUN Blood urea nitrogen, CK-MB Creatine kinase MB, CRP C-reactive protein, eGFR Estimated glomerular filtration rate, FT3 Free triiodothyronine, FT4 Free thyroxine, HbA1c Hemoglobin A1c, HDL-C High-density lipoprotein, IP Inorganic phosphorus, LDH Lactate dehydrogenase, LDL-C Low-density lipoprotein, NGSP National Glycohemoglobin Standardization Program, TSH Thyroid stimulating hormone

Table 1 Laboratory findings on admission in Cases 1, 2, and 3

## Supplemental figure captions

- **Fig. 1a**: Diagram revealing a reduced LV ejection fraction of 42.7%.
- **Fig. 1b**: Diagram reveals normal LV function.
- **Fig. 2a**: Diagram showing genetic testing results.
- **Fig. 2b**: Diagram illustrates genetic testing results.
- **Fig. 3**: Diagram depicting genetic testing results.
- **Fig. 4a**: Diagram illustrating genetic testing results.
- **Fig. 4b**: Diagram showing genetic testing results.
indication for CRTD implantation, and was referred to our hospital.

On admission, his blood pressure and heart rate were 118/72 mmHg and 60 ppm, respectively, and physical examination showed no sign of skeletal muscle disease. Laboratory findings revealed a B-type natriuretic peptide level of 59.5 pg/mL and a high troponin I level of 0.176 ng/mL (normal range: 0.000 to 0.056 ng/mL), as shown in Table 1. Electrocardiogram showed pacing rhythm, and chest X-ray showed no sign of congestion (Fig. 4c, d). Echocardiogram detected a reduced LV ejection fraction of 33.2% (Fig. 4e). Implantation of a CRTD, which was an upgrade from the patient’s pacemaker, was successfully performed. In the cardiopulmonary exercise test performed before discharge, his peak oxygen uptake was extremely low, at 10.3 mL/kg/min. After discharge, VT did not recur over a six-month follow-up period.

**Case 3**

A man (eldest son of the patient in Case 1, III-4) in his fifties complaining of shortness of breath was admitted to a hospital due to heart failure with reduced LV ejection fraction. He was referred to our hospital for heart failure treatment. On admission, his blood pressure and heart rate were 122/68 mmHg and 40 bpm, respectively, and physical examination showed no sign of skeletal muscle disease. Laboratory findings revealed a high B-type natriuretic peptide level of 317.4 pg/mL and a high troponin I level of 0.215 ng/mL, as shown in Table 1. Electrocardiogram showed atrial fibrillation with complete atrioventricular block, and a heart rate of 40 bpm (Fig. 5a). Chest X-ray showed slight congestion with a cardiothoracic ratio of 60.4% (Fig. 5d). Echocardiogram showed atrial fibrillation with complete atrioventricular block, and a heart rate of 40 bpm (Fig. 5a). Chest X-ray showed slight congestion with a cardiothoracic ratio of 60.4% (Fig. 5d). 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index of 2.03 L/min/m². Cardiovascular magnetic resonance showed late gadolinium enhancement in the left ventricle (Fig. 5f). Endomyocardial biopsy revealed interstitial fibrosis, but no significant findings of myocarditis, amyloidosis, or sarcoidosis (Fig. 5g, h). The patient was diagnosed as having DCM. Monitor electrocardiogram revealed repetitive non-sustained VT (Fig. 5b), and implantation of a CRTD was successfully performed. Electrocardiogram after CRTD implantation is described in Fig. 5c. He also underwent genetic testing, and the same LMNA nonsense mutation seen in Case 1 was detected.

The clinical courses of Case 1 (II-4, female), 2 (III-1, male), 3 (III-4, male), and the older sister of the patient in Case 1 (II-2) are shown in Fig. 3.

All parameters of the laboratory findings, electrocardiogram, chest X-ray, echocardiography, magnetic resonance imaging, cardiac pathology, and cardiac catheterization, were obtained from the hospital archive.

Discussion and conclusions

The current study described five individuals, among one family, with conduction disorder, sick sinus syndrome, DCM, VT, and SCD, three of whom were available for testing, studied in detail, and shown to have the E159* LMNA mutation. Although the same mutation was briefly reported in a previous paper, the present report is the first to reveal detailed clinical presentations of family members, including those with the E159* LMNA mutation [15].

Truncation mutations like the E159* LMNA mutation are a risk factor for early onset of cardiac conduction disease, VT, and reduced LV ejection fraction, compared with missense mutations [13, 18]. However, clinical variability regarding severity, penetrance, age at onset, and sex difference has been observed among patients with the same LMNA mutations, even in identical twins [5, 19]. Several studies have demonstrated that patients with LMNA mutations have a higher incidence of lethal ventricular arrhythmias related to SCD in males than in females [11, 13–15]. However, unlike patients with other LMNA mutations, in the current study, SCD and malignant VT occurred in both males (III-1 and III-4) and females (I-2, II-2, and II-4) among family members with the E159* LMNA mutation. Having a history of SCD and VT in females is unusual, compared to other families with LMNA mutations. A previous multicenter study showed that male patients with LMNA mutations had a higher prevalence of end-stage heart failure than female patients with the
same mutations [14]. Regarding LV function among family members with the E159* LMNA mutation, our male patients (III-1 and III-4) had worse LV function. The female proband (II-4) did not exhibit manifestations of reduced LV ejection fraction. Polymorphic VT developed in our female patient (II-4). To our knowledge, there has yet to be a report on polymorphic VT in patients with the LMNA mutation, although VT is a common finding among such patients. Inflammation caused by influenza as well as low potassium levels are considered to affect the manifestation of polymorphic VT. The arrhythmic substrate of a patient with the LMNA mutation could also be associated with the occurrence of polymorphic VT.

Only one patient (III-4) underwent endomyocardial biopsy and cardiovascular magnetic resonance among the family members. Interstitial myocardial fibrosis detected by endomyocardial biopsy, and late gadolinium enhancement observed in this patient are consistent with other reported cases of LMNA mutations [20, 21]. Cardiac magnetic resonance imaging was considered to be useful for evaluating myocardial fibrosis in patients with the E159* LMNA mutation.

The LMNA has three domains; a short globular N-terminal head, a central rod and a long globular C-terminal tail [22]. LMNA interacts with a lot of large chromatin domains and is involved in genomic organization, recruitment of epigenetic regulators, and gene expression [23]. The E159* LMNA nonsense mutation removes more than half of the alpha-helical coiled-coil forming rod domain, as well as all of the C-terminal domain (Fig. 2c). Patients with these effects have both one normal LMNA gene and one mutated gene, and therefore any disease association would be due to haploinsufficiency [17]. LMNA mutations result in altered structure and altered interactions with chromatin and nuclear proteins. The LMNA mutation position predicts the involvement of several organ systems [24]. LMNA mutations localized upstream of the nuclear localization signal (exons 1 to 6) and tail have been reported to have more cardiac organ involvement compared with other systems [22, 24]. Such mutations were reported to have a more malignant cardiac phenotype compared with downstream mutations [22]. The E159* LMNA mutation is localized in exon 2 and upstream of the nuclear localization signal as shown in Fig. 2c. These findings suggest that patients with E159* nonsense mutation have cardiac problems.

LMNA mutation carriers can be asymptomatic [10, 25], and genetic screening for LMNA mutations in family members is clinically important to evaluate the risk of heart failure, arrhythmia, and SCD. Such screenings are recommended by the European Heart Rhythm...
Association [17, 26]. In family members similar to those in the current report, genetic screening should be considered even if the subject is asymptomatic.

ICD implantation is recommended at an early stage for DCM patients with LMNA mutations, compared to those with other causes [27]. CRTD implantation is considered to be a treatment for heart failure and prevention of SCD in DCM patients with LMNA mutations and reduced LV systolic function [18, 28]. Among the current cases, we performed CRTD implantation for our male patients (III-1 and III-4), because these patients had LV systolic dysfunction and VT.

A limitation of this study was that the genetic testing was performed in only four members of the family. Additional genetic testing on unaffected family members would strengthen the finding that the E159* LMNA mutation is associated with cardiac problems. Further study is required to demonstrate the causality between the E159* LMNA mutation and the cardiac problems.

In conclusion, clinical manifestations of various atrial and ventricular arrhythmias and heart failure with reduced left ventricular ejection fraction age-dependently occurred in family members carried with the E159* LMNA mutation. It appears highly likely that the E159* LMNA mutation is related to various cardiac problems, as characterized by the family of the current report.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12872-019-01282-6.

Additional file 1: Supplementary Methods. Table S1. Genes for target screening.

Abbreviations
CRTD: Cardiac resynchronization therapy defibrillator; DCM: Dilated cardiomyopathy; ICD: Implantable cardiovascular defibrillator; LMNA: Lamin A/C; LV: Left ventricular; SCD: Sudden cardiac death; VT: Ventricular tachyarrhythmia

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Authors’ contributions
Study design: TY and YT. Collection and interpretation of data: SI, NH, TK, AY, HK, KN, TI, SO, and HO. Manuscript writing: TY, TA, and YT. All authors have read and approved the final manuscript.

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Availability of data and materials
The data that support the findings in this study are available from Tetsuro Yokokawa upon reasonable request and permission of Fukushima Medical University.

Ethics approval and consent to participate
This study was approved by Fukushima Medical University Hospital and the National Cerebral and Cardiovascular Center. Written informed consent was provided by the patients.

Consent for publication
Written informed consent for publication was obtained from the patients.

Competing interests
Tetsuro Yokokawa belongs to a department supported by Actelion Pharmaceuticals Japan. Takashi Kaneshiro belongs to a department supported by Biontronic Japan and Abbott Japan. Akiko Yoshishita belongs to a department supported by Fukuda Denso Co. Ltd. These companies were not associated with the contents of this study.

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References
1. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. Nat Rev Cardiol. 2013;10:531–47.
2. Watkins H, Ashrafin H, Redwood C. Inherited cardiomyopathies. N Engl J Med. 2011;364:1643–56.
3. Andelman F, Moubarak G, Savoure A, Godin B, Borz B, Drouin-Garraud V, Gay F. Implantable cardioverter-defibrillators in Lamin a/C mutation carriers with cardiac conduction disorders. Heart Rhythm. 2013;10:1492–8.
4. Arbustini E, Pilotto A, Repetto A, Grasso M, Negri A, Diegoli M, Campana C, Scelli L, Baldini E, Gavaa A, Tavazza L. Autosomal dominant dilated cardiomyopathy with atrioventricular block: a Lamin a/C defect-related disease. J Am Coll Cardiol. 2002;39:981–90.
5. Taylor MR, Fair PR, Sinagra G, Robinson AD, Carmel E, Di Lenarda A, Bohmleymer TJ, Ferguson DA, Brodsky GL, Boucek MM, Lascor J, Moss AC, Li WL, Stetler GL, et al. Natural history of dilated cardiomyopathy due to Lamin A/C gene mutations. J Am Coll Cardiol. 2003;41:771–80.
6. Mestroni L, Taylor MR. Lamin a/C gene and the heart: how genetics may impact clinical care. J Am Coll Cardiol. 2008;52:1261–2.
7. Tobita T, Nomura S, Fujita T, Morita H, Asano Y, Onoue K, Ito T, Imay M, Suzuki A, Ko T, Satoh M, Fujita K, Naito AT, Furutani Y, Toko H, et al. Genetic basis of dilated cardiomyopathy and the genotypes involved in prognosis and left ventricular reverse remodeling. Sci Rep. 2018;8:1998.
8. Ho CY, Lammerding J. Lamin A at a glance. J Cell Sci. 2012;125:2087–93.
9. Capell BC, Collins FS. Human laminopathies: nuclei gone genetically awry. Nat Rev Genet. 2005;6:940–52.
10. Hasselberg NC, Haland TF, Sabenick J, Brekke PH, Berge KE, Leren TP, Edvardsen T, Haugaas KH. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. Eur Heart J. 2018;39:3865–8.
11. Kumar S, Baldiringer SH, Gandjikchak E, Maury P, Sellal JM, Androulakis AF, Waintraub X, Charon P, Rollin A, Richard P, Stevenson WG, MacIntyre CJ, Ho CY, Thompson T, Vohra JK, et al. Long-term arrhythmic and nonarrhythmic outcomes of Lamin A/C mutation carriers. J Am Coll Cardiol. 2016;68:2299–307.
12. van Berlo JH, de Voogt WG, van der Kooi AJ, van Tintelen JP, Bonne G, Yao RB, Dubou D, Rossenbacker T, Heidbuchel H, de Visser M, Crinj HJ, Pinto YM. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do Lamin A/C mutations portend a high risk of sudden death? J Mol Med (Berl). 2005;83:79–83.
13. van Rijspingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, van den Berg MP, Pilotto A, Pasotti M, Jenkins S, Rowland C, Aslam U, Wilde AA, Perrot A, et al. Risk factors for malignant ventricular arrhythmias in Lamin a/c mutation carriers: an European cohort study. J Am Coll Cardiol. 2012;59:493–500.
14. van Rijspingen IA, Nannenberg EA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, van den Berg MP, Grasso M, Serio A, Jenkins S, Rowland C, Richard P, Wilde AA, et al. Gender-specific differences in major cardiac events and mortality in Lamin A/C mutation carriers. Eur J Heart Fail. 2013;15:736–84.
15. Nakajima K, Aiba T, Makiyama T, Nishiiuchi S, Ohno S, Kato Y, Yamamoto Y, Doi T, Shizuta S, Onoue K, Yagihara N, Ishikawa T, Watanabe I, Kawakami H, Oginoasa Y, et al. Clinical manifestations and long-term mortality in Lamin A/C mutation carriers from a Japanese multicenter registry. Circ J. 2018;82(11):2707–14.
16. Arima T, Onoue K, Takahashi-Tanaka Y, Ishikawa T, Kuhawara M, Setou M, Shigenobu S, Yamaguchi K, Bertrand AT, Machida N, Takayama K, Fukusato M, Tanaka R, Somekawa S, Nakano T, et al. Nuclear accumulation of androgen receptor in gender difference of dilated cardiomyopathy due to Lamin A/C mutations. Cardiovasc Res. 2013;99:304–11.
17. Captur G, Arbustini E, Bonne G, Syrris P, Mills K, Wahlb K, Mohiddin SA, McKenna WN, Pettit S, Ho CY, Muchir A, Gissen P, Elliott PM, Moon JC. Lamin and the heart. 2010;184:4688–79.
18. Nishiiuchi S, Makiyama T, Aiba T, Nakajima K, Hirose S, Kohitanii H, Yamamoto Y, Hattori T, Hayano M, Wuriyyanghi Y, Chen J, Sasaki K, Yagihara N, Ishikawa T, Onoue K, et al. Gene-based risk stratification for cardiac disorders in LMNA mutation carriers. Circ Cardiovasc Genet. 2017;10. https://doi.org/10.1161/CIRCGENETICS.116.001693.
19. Lee E, Park KT, Kang J, Park HJ, Park JJ, Oh IY, Yoon YE. A novel c.563 T>G p. L189R Lamin A/C mutation in identical twins with dilated cardiomyopathy. Korean J Intern Med. 2017;32:178–81.
20. van Tintelen JP, Tio RA, Kerstjens-Frederikse WS, van Berlo JH, Boven LG, Suurmeijer AJ, White SJ, den Dunnen JT, te Meerman GJ, Vos YI, van der Hout AH, Osinga J, van den Berg MP, van Veldhuisen DJ, Buys CH, et al. Severe myocardial fibrosis caused by a deletion of the 5' end of the Lamin A/C gene. J Am Coll Cardiol. 2007;49:2430–9.
21. Fontana M, Barison A, Botto N, Panchetti L, Rizzi G, Milanesi M, Poretti R, Positano S, Scialino G, Passino C, Lombardi M, Emdin M, Masci PG. CMR-verified intestinal myocardial fibrosis as a marker of subclinical cardiac involvement in LMNA mutation carriers. JACC. Cardiovasc Imaging. 2016;9:124–6.
22. Captur G, Arbustini E, Syrris P, Radenkovic D, O'Brien B, McKenna WN, Moon JC. Lamin mutation location predicts cardiac phenotype severity: combined analysis of the published literature. Open Heart. 2018;5:e000915.
23. Mareddy Cheedipudi S, Matkovskij SI, Coarfa C, Hu X, Robertson MJ, Sweet ME, Taylor M, Mestoni L, Cleveland JC, Willerson JT, Gurha P, Marian AJ. Genomic reorganization of Lamin-associated domains in cardiac Myocytes is associated with differential gene expression and DNA methylation in human dilated cardiomyopathy. Circ Res. 2019;124:1198–213.
24. Hegele R. LMNA mutation position predicts organ system involvement in laminopathies. Clin Genet. 2005;68:31–4.
25. Möller DV, Pham TT, Gustafsson F, Hedley P, Erbsdoll MK, Bundgaard A, Andersen CB, Torp-Pedersen C, Kober L, Christiansen M. The role of Lamin A/C mutations: do Lamin a/C mutations portend a high risk of sudden death? J Heart Fail. 2009;11:1031–5.
26. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Collob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (EHRA) and the European heart rhythm association (EHRA). Europace. 2011;13:1077–108.
27. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggreve M, Camm J, Elliott PM, Fitzsimons D, Hatata R, Hindricks G, Kirschhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with
Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36:2793–867.

28. Kawakami H, Ogimoto A, Tokunaga N, Nishimura K, Kawakami H, Higashi H, Iio C, Kono T, Aono J, Ietani T, Nagai T, Inoue K, Suzuki J, Ikeda S, Okura T, et al. A novel truncating LMNA mutation in patients with cardiac conduction disorders and dilated cardiomyopathy. Int Heart J. 2018;59:531–41.

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