Clinical Manifestations and Long-Term Mortality in Lamin A/C Mutation Carriers From a Japanese Multicenter Registry

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Background: Mutation in the lamin A/C gene (LMNA) is associated with several cardiac phenotypes, such as cardiac conduction disorders (CCD), atrial arrhythmia (AA), malignant ventricular arrhythmia (MVA) and left ventricular dysfunction (LVD), leading to sudden cardiac death (SCD) and/or end-stage heart failure. We investigated how these phenotypes are associated with each other and which of them are most important for total mortality.

Methods and Results: A multicenter registry included 110 LMNA mutation carriers (age, 43±15 years, male: 62%) from 60 families. After genetic diagnosis of LMNA mutation (missense: 27%, non-missense: 73%), patients or subjects were followed to evaluate the manifestations of their phenotypes and the risk of total mortality; 90 patients could be followed (median: 5 [0–35] years). Prevalence of the 4 clinical phenotypes was significantly increased during follow-up. Among these phenotypes, AA was significantly associated with MVA. CCD was significantly associated with LVD. LVD, meanwhile, was significantly associated with CCD and MVA. Male sex was significantly associated with MVA. Furthermore, during follow-up, 17 patients died: 12 end-stage heart failure, 4 SCD and 1 stroke. LVD was the only independent predictor for all-cause death (OR: 41.7, 95% CI: 4.1–422.3; P=0.0016).

Conclusions: Several cardiac phenotypes were age-dependently increased in LMNA mutation carriers, suggesting that ICD or CRT-D could suppress SCD after middle age; however, LVD leading to end-stage heart failure was the only independent predictor for total mortality.

Key Words: Arrhythmias; Heart failure; Lamin A/C; Phenotypes; Prognosis

Lamin A/C gene (LMNA) mutations are associated with a variety of clinical phenotypes, including not only major cardiac abnormalities but also premature aging, axonal neuropathy Charcot-Marie-Tooth type 2, and skeletal muscle diseases such as Emery-Dreifuss muscular dystrophy and limb-girdle muscular dystrophy. The most common cardiac manifestations associated with LMNA mutations are cardiac conduction disorders (CCD), atrial arrhythmias (AA), malignant ventricular arrhythmias (MVA) and left ventricular dysfunction (LVD) sometimes leading to end-stage heart failure (HF). The natural
history of each of these cardiac phenotypes typically consists of progressive decline towards end-stage HF and MVA.\(^8\) Although implantable cardioverter-defibrillator (ICD) therapy is effective for the prevention of sudden cardiac death (SCD) in LMNA mutation carriers,\(^5\) treatment for HF is the next biggest concern affecting patient prognosis.

Although LMNA-related cardiomyopathy seems to be rare, it has been suggested that 5–10% of patients with familial dilated cardiomyopathy may actually have an LMNA mutation.\(^6\) We recently reported that patients with LMNA truncation mutations presented worse clinical outcomes than those with missense mutations.\(^8\) However, how the 4 clinical phenotypes are associated with each other and which of them are the most important for total mortality in LMNA mutation carriers are still unclear. It is clinically important to clarify the detailed prevalence and outcomes of each type of cardiac event associated with LMNA mutation over long-term follow-up. In this multicenter registry study, we assessed the presentation and progression of each cardiac phenotype and the long-term follow-up prognostic outcomes of LMNA mutation carriers.

### Methods

#### Study Population and Design

This retrospective cohort consisted of 110 LMNA mutation carriers (60 probands and 50 relatives, 68 (62%) men, mean entry age: 43±15 years) (Table 1) who had been introduced to the registry from the following Japanese institutions: National Cerebral and Cardiovascular Center (Suita), Kyoto University Hospital (Kyoto), Shiga University of Medical Science (Otsu), Nara Medical University (Kashiwara), Nagasaki University Graduate School of Biomedical Sciences (Nagasaki), Niigata University Graduate School of Medical and Dental Sciences (Niigata); Ehime University (Toon) University of Tsukuba (Tsukuba), University of Occupational and Environmental Health (Kitakyushu) and Nihon University School of Medicine (Tokyo) between April 2008 and December 2017. All had pathogenic LMNA mutations or variants previously associated with cardiac laminopathy in published reports or newly identified LMNA variants with clinical or family evidence of possible cardiac laminopathy (Table S1).\(^8\)\(^10\) Unreported LMNA variants with insufficient clinical or genetic data were considered insignificant variants and were excluded.

All subjects gave informed consent prior to genetic analysis and clinical data acquisition. They then underwent clinical screening and peripheral blood sampling for genetic testing. After genetic diagnosis, LMNA mutation carriers were followed up by a cardiologist from one of the participating institutes or by a private doctor. The primary end point in this analysis was all-cause death during the follow-up period. Secondary end points were a composite of cardiac events and diagnosis including the first occurrence of CDD, AA, LVD or MVA. The protocol of this study was approved by the institutional ethics committees and performed in accordance with guidelines (Kyoto University, G194; National Cerebral and Cardiovascular Center, M24-031-4).

#### Genetic Analysis for LMNA Mutation

Details of the methods used for the genetic screening of LMNA have been described previously.\(^8\) In brief, genomic DNA was extracted from peripheral blood leukocytes to generate polymerase chain reaction primers to amplify the protein-coding exons of LMNA for mutational screening. Variants in LMNA were screened by genetic variant databases, a splicing site prediction tool, and in silico predictions.

#### Definition of Clinical Manifestations

The definition of each clinical manifestation was based on our previous report.\(^8\) LVD was defined as either left ventricular ejection fraction (LVEF) <50% and/or LV enlargement with a diameter of 5.5cm according to published normal values. MVA was defined as sustained ventricular tachycardia (VT), ventricular fibrillation (VF), SCD, cardiopulmonary resuscitation, and appropriate ICD treatment (ICD discharge for termination of VF/VT and antitachycardia pacing for sustained VT). Nonsustained VT was defined as ≥3 consecutive ventricular beats with a rate >120 beats/min and a duration <30s. The definition AA included paroxysmal, persistent, permanent atrial fibrillation (AF), atrial flutter (AFL) and atrial tachycardia (AT). Atrioventricular block (AVB) was classified as first, second or third degree. First-degree AV block was defined as a P-Q interval >200ms. Sinus node dysfunction was defined as a heart rate <45 beats/min and/or sinus pause >3s. CDD was defined as sinus node dysfunction and/or any degree of AVB. Family history of SCD was considered positive if at least 1 family member (up to the fourth degree) had died suddenly under the age of 60 years.

We assessed the manifestation and progression of each cardiac phenotype, the correlations among the phenotypes and their contribution to the prognostic outcomes of LMNA mutation carriers.

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Table 1. Baseline Characteristics of 110 Patients With LMNA Mutations

| No. of probands | 60 |
|-----------------|----|
| No. of relatives| 50 |
| Asymptomatic relatives | 7 |
| M/F             | 68 (62)/42 (38) |
| Type of mutation |     |
| Missense        | 30 (27) |
| Non-missense    | 80 (73) |
| Family history in 60 families |
| Cardiac disease | 54 (90) |
| SCD             | 26 (43) |
| CCD             | 52 (87) |
| LVD             | 22 (37) |
| MVA             | 31 (52) |

Values are n (%). CCD, conduction disorders; LVD, left ventricular dysfunction; MVA, malignant ventricular arrhythmia; SCD, sudden cardiac death.
Clinical Aspects of Japanese Cardiac Laminopathy

Results

Study Population and Clinical Characteristics

As shown in Table 1, 54 (90%) probands had a history of cardiovascular disease; of these, 26 (43%) had a family history of SCD. In contrast, 24 subjects (9 probands and 15 relatives) were phenotype-negative at the time of study entry, but all 9 probands and 8 relatives showed some phenotype at the last follow-up. During follow-up (median 5 years; 0–35 years), 17 patients died with a mean age at death of 53±14 years. Cause of death was HF death (HFD) in 12 subjects (mean age at death, 57±8 years), SCD in 4 subjects and stroke in 1 (66 years). The rate of each of the 4 clinical phenotypes (AA, CCD, MVA and...
LVD) was significantly increased during follow-up (AA: 35 [32%] to 58 [64%], CCD: 79 [72%] to 80 [89%], MVA: 20 [18%] to 38 [42%], LVD: 22 [20%] to 47 [52%], P<0.01 in all) (Table 2). In probands, the prevalence of each major phenotype also increased from study entry to the end of follow-up (AA: 28 [47%] to 44 [80%], CCD: 45 [75%] to 51 [93%], MVA: 16 [27%] to 28 [51%], LVD: 15 [25%] to 36 [66%], P<0.05 in all) (Table S2).

Figure 1. Box plot summarizing the age at first phenotypic manifestation in either CCD or AA (CCD/AA), LVD or MVA (LVD/MVA) and HFD. AA, atrial arrhythmias; CCD, cardiac conduction disorders; HFD, heart failure death; LVD, left ventricular dysfunction; MVA, malignant ventricular arrhythmia; SCD, sudden cardiac death.

Figure 2. (A) Serial change in the severity of AVB and (B) change in AA pattern during follow-up of LMNA mutation carriers (n=90). AA, atrial arrhythmias; AVB, atrioventricular block; AT, atrial tachycardia; AFL, atrial flutter; PAF, paroxysmal atrial fibrillation; Per AF, persistent atrial fibrillation.
Age at First Manifestation of Each Cardiac Phenotype

Although not all mutation carriers showed the 4 cardiac phenotypes during follow-up, we could compare the ages at first clinical manifestation among each cardiac phenotype. Age at manifestation of LVD and MVA was significantly older than that of CCD and AA, whereas CCD and AA (44±11 and 45±13 years old; P=0.058 by paired t-test) and LVD and MVA (48±12 and 49±12 years old; P=0.065 by paired t-test) occurred almost simultaneously (Figure S1). Thus, we combined these as CCD/AA, and LVD and MVA.

Age-Dependent Changes in AVB and AA

The degree of AVB and the pattern of AA changed naturally with increasing patient age. As shown in Figure 2A and Table 2, 44% of our subjects did not have AVB at study entry, yet half of these exhibited type III AVB at the last follow-up date. As shown in Figure 2A, among patients with AVB, no one improved the severity of AVB during follow-up.

Furthermore, though 68% of subjects did not have AF at study entry, more than half of them had persistent AF at the last contact (Table 2, Figure 2B). Interestingly, in LMNA mutation carriers, AF cannot be easily terminated, suggesting that, in most cases, AF (or AT/AFL) may develop into a persistent pattern. A total of 6 (6%) patients had a history of ischemic stroke at first clinical contact, but during follow-up, new incidence of ischemic stroke was 9 of 90 patients; thus, a total of 11 (12%) patients had stroke events at the last contact, and 9 of the 11 patients with stroke events had persistent AF, even though 8 of them (73%) had taken oral anticoagulation drugs. AF was a significant risk for ischemic stroke (odds ratio [OR]: 9.2, 95% confidence interval [CI]: 1.1–74.7, P=0.038).

Phenotype Correlations and Risk for Cardiac Prognosis

To investigate the associations among the 4 phenotypes linked to LMNA mutations, we looked for correlations among them. As shown in Table 3, AA was significantly associated with MVA and tended to be associated with LVD. CCD was significantly associated with LVD. LVD, meanwhile, was significantly associated with CCD and MVA, and tended to be associated with AA. Finally, MVA was significantly associated with AA but not significantly associated with LVD.

Sex has been reported to affect clinical outcome, especially with regard to MVA and end-stage HF. In this cohort, there were no significant sex differences in AA, CCD and LVD, but ventricular arrhythmia was more frequent in male subjects (male vs. female: 29 [42%] vs. 9 [27%], P=0.023) (Table S3). Our logistic regression model revealed that male sex was a risk factor for the occurrence of MVA (Table 3). Even though there was no statistical...
therapy during follow-up; 1 patient suddenly died despite having been implanted with a CRT-D.

**Discussion**

**Major Findings**
This is the largest LMNA cohort study in Japan or any other Asian countries showing age-dependent differences in the manifestation of cardiac phenotypes and prognosis. Our registry study showed that LMNA mutation carriers have a proclivity for clinically severe MVA and/or LVD leading to SCD or end-stage HF. Our findings are similar to those previously reported in Caucasian LMNA mutation carriers.2,9,10 On the other hand, this study is the first to report how the major clinical phenotypes seen in LMNA mutation patients are associated with each other. We found that LVD was the only independent predictor for all-cause death (Figure 4).

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**Table 4. Identification of Risk Factors for All-Cause Death**

| All-cause death | Univariate |          | Multivariate |          |
|-----------------|------------|----------|--------------|----------|
|                 | OR (95% CI)| P value  | OR (95% CI)  | P value  |
| AA              | 2.6 (0.84–9.6) | 0.10  | 0.89 (0.18–4.3) | 0.89    |
| III AVB         | 1.1 (0.41–3.2) | 0.79  | 0.60 (0.18–2.0) | 0.41    |
| MVA             | 2.7 (0.96–8.1) | 0.061 | 1.3 (0.35–5.0) | 0.67    |
| LVD             | 26.5 (5.1–488.8) | <0.0001 | 41.7 (4.1–422.3) | 0.0016* |
| Male            | 2.2 (0.73–8.4) | 0.16  | 1.4 (0.36–5.4) | 0.63    |
| Proband         | 1.2 (0.43–3.6) | 0.70  | 0.42 (0.11–1.6) | 0.20    |

*P<0.05. Abbreviations as in Tables 1–3.

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**Figure 3.** Distribution of patients implanted with a cardiac device during follow-up, namely, pacemaker, implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy with defibrillator (CRT-D) or left ventricular assist device (LVAD). Values are n (%)

**Figure 4.** Schematic illustrating the relationship between each phenotype and all-cause death in LMNA mutation carriers. Solid arrow shows statistically significant relationship (P<0.05), dotted arrow shows a weak but not statistically significant correlation. One-way arrow indicates the phenotype is associated with another in the direction of the arrow. Two-way arrow indicates an association between phenotypes.
Manifestation of Phenotypes

*LMNA* mutation can cause familial cardiomyopathy with LV remodeling, early-age onset of advanced AVB, and lethal ventricular arrhythmias. Screening for *LMNA* mutations might be beneficial for risk stratification and clinical management of this type of familial cardiomyopathy. To date, however, only a small number of cases had been reported in Japan. Recently, we reported a gene-based risk stratification for cardiac disorders in 77 *LMNA* mutation carriers from 45 Japanese families, in which the truncation mutation carriers presented worse prognosis than those with a missense mutation.8

The clinical significance of *LMNA* mutation with regard to the heart is well known: the 4 most common phenotypes are CCD, AA, MVA and LVD.2,10 The rate of cardiac penetrance is reportedly quite high,4 reaching almost 100% at age 60.15 Yet *LMNA* mutation carriers often exhibit no disease phenotype until adolescence.4 In this study, most of the *LMNA* carriers under 20 years old were phenotype-negative, whereas those over 40 years old typically manifested cardiac phenotypes (Figure 1). During follow-up (median 5 [0–35] years), the incidence of each of these phenotypes increased not only in probands but also in relatives (Table 2). Furthermore, 9 of 46 mutations were identified from several different probands or families. As shown in the Table S4, the phenotype was quite similar among probands with the same mutation. On the other hand, among family members, particularly in younger carriers, phenotype manifestation was inconsistent, probably because of age. Thus, although there is some variation in the time course of these diseases, with some patients showing relatively late onset and mild phenotype,16 cardiac disorders in *LMNA* mutation carriers are definitely progressive over time.

Our results are in keeping with previous comprehensive data from 122 *LMNA* mutation carriers published by Kumar et al, in which the prevalence of each clinical manifestation increased during follow-up (median 7 years).3 Age at first clinical contact and mean age at clinical appearance of AVB and AA in that study (approximately 43–44 years old) were quite similar to those in the present study. Age at first clinical manifestation of CCD and AA did not differ significantly in this study, yet the prevalence of CCD was much higher than that of AA at both first clinical contact and end of follow-up (CCD: 72% to 89% and AA: 32% to 64%, respectively). This might be because CCD (AVB ≥1) could be easily diagnosed during baseline ECG screening. Thus, as shown in Table 1, many of the *LMNA* mutation carriers were initially offered genetic screening because they had an ECG abnormality, especially CCD, and a family history of CCD and/or CCD and LVD.

AF and Prognosis

AA and especially AF are common in *LMNA* mutation carriers. Some *LMNA* carriers could be identified as familial AF patients with CCD.17 Yet *LMNA* mutations are not always the cause of AF even when conduction disease is present.18,19 *SCN5A* is another candidate gene that can be responsible for familial dilated cardiomyopathy with AF.20 In this study, at the first contact, almost 70% of *LMNA* carriers were free from AF. During follow-up, however, only 32% of carriers remained AF free and more than 50% developed persistent AF. Furthermore, our phenotype correlation analysis revealed that AA was significantly associated with the manifestation of MVA and had a weak tendency to LVD (Figure 4) leading to SCD or end-stage HF. Catheter ablation of VT associated with *LMNA* cardiomyopathy in patients with already reduced LVEF did not always have a good outcome.21 Therefore, treatment of AF in *LMNA* carriers might be useful to retard the progression of cardiac laminopathy.

Furthermore, *LMNA* mutation is reported as an independent risk factor for arterial and venous thromboembolic complications.22 In this cohort study, a total of 11 (10%) patients had experienced ischemic stroke episodes by the end of follow-up, representing a significantly elevated prevalence. Not all the *LMNA* patients had been treated with anticoagulants even if they had AF. Thus, their risk of stroke remains fairly low, *LMNA* mutation carriers with AF should be started on oral anticoagulants.23

MVA and LVD

Life-threatening VAs are common in patients with *LMNA* mutations and significant CCDs, even if LVEF is preserved. ICD is an effective treatment and should be considered in this patient population.5 Independent risk factors for MVA that should be considered are nonsustained VT, LVEF <45% at first clinical contact, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing).8 In this study, MVA was found in 18% of the *LMNA* mutation carriers at first clinical contact and in 42% by the end of follow-up. Our pathway analysis also suggested that MVA was significantly associated with the manifestation of AA and partially associated with LVD but not directly with CCD (Figure 4).

Although some undiagnosed family members died suddenly during this study, many genetically diagnosed *LMNA* patients have been recently implanted with ICD, which, when administered appropriately, can prevent SCD. In this study, 42% of *LMNA* mutation carriers exhibited MVA by the end of follow-up; similar proportions of patients in previous reports have exhibited MVA.24,25 The incidence of VT was 49%, consisting of 34% with sustained VT, 14% with VF and 5% with SCD. Nevertheless, we were unable to show a link between MVA and prognosis (P=0.68, hazard ratio: 1.3). This might be because prophylactic ICD implantation is more frequently recommended in expectation of progressive disease for *LMNA* mutation carriers with a previous pacemaker indication.

Our analysis of the relationships among the phenotypes revealed that LVD is linked to CCD and AA, but not to MVA. Furthermore, LVD is the only manifestation directly related to all-cause death. Our results suggested that, regardless of the presence or absence of MVA, LVD is the most crucial and inevitable manifestation associated with *LMNA* mutation that eventually leads to HF. In this study, only 2 patients had LVAD implantation during follow-up; in another study in Norway, however, heart transplantation was performed in 15 of 79 (19%) *LMNA* patients (age 42±16 years, LVEF: 45±13%) during 7.8±6.3 years of follow-up.6

Study Limitations

The cohort was obtained from 8 academic referral centers, and this situation could have introduced a referral bias towards more severely affected cases. There might also be selection bias, and there were missing data that could have led to overestimation of the influence of the risks. The accuracy of the information collected regarding family his-
Conclusions

This multicenter, retrospective cohort study demonstrated that Japanese LMNA mutation carriers have a high incidence of arrhythmic and cardiac dysfunctional penetration and age-dependent cardiac phenotypes. These results may enable us to identify specific cardiac phenotypes that warrant careful surveillance in advance of an expected malignant disease course.

Sources of Funding

This work was supported by JSPS KAKENHI (25461054 to T.M.), a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (C; 16K04999 to T.M., 15K09150 to T.A.), Health Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan (H24-033, H26-040, and H27-032 to T.A., M.H., and W.S.), and a research grant from Japan Agency for Medical Research and Development AMED (JP17km0405109 to N. Makita), (16ek0210073h0001 to T.A.), and Hoansha Foundation (T.M.).

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Supplementary Files

Supplementary File 1

Supplementary Methods

Appendix S1. List of Participating Institutes and Investigators

Figure S1. Correlation between age at first clinical manifestation of the cardiac phenotypes (CCD, AA, LVD, and MVA) in each mutation carrier.

Table S1. Genetic and clinical characteristics of 60 families (110 subjects) with LMNA mutations

Table S2. Manifestation of arrhythmia or heart failure during follow-up of 60 probands with LMNA mutations

Table S3. Manifestation of arrhythmia or heart failure at the end of follow-up in males and females

Table S4. Genetic and clinical characteristics of the same mutations among 45 LMNA mutations in 23 families

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-18-0339