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Clinical disease presentation and ECG characteristics of *LMNA* mutation carriers

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ABSTRACT

Objective: Mutations in the *LMNA* gene encoding lamins A and C of the nuclear lamina are a frequent cause of cardiomyopathy accounting for 5–8% of familial dilated cardiomyopathy (DCM). Our aim was to study disease onset, presentation and progression among *LMNA* mutation carriers.

Methods: Clinical follow-up data from 27 *LMNA* mutation carriers and 78 patients with idiopathic DCM without an *LMNA* mutation were collected. In addition, ECG data were collected and analysed systematically from 20 healthy controls.

Results: Kaplan-Meier analysis revealed no difference in event-free survival (death, heart transplant, resuscitation and appropriate implantable cardioverter-defibrillator therapy included as events) between *LMNA* mutation carriers and DCM controls (p=0.5). *LMNA* mutation carriers presented with atrial fibrillation at a younger age than the DCM controls (47 vs 57 years, p=0.003). Male *LMNA* mutation carriers presented with clinical manifestations roughly a decade earlier than females. In close follow-up non-sustained ventricular tachycardia was detected in 78% of *LMNA* mutation carriers. ECG signs of septal remodelling were present in 81% of the *LMNA* mutation carriers, 21% of the DCM controls and none of the healthy controls giving a high sensitivity and specificity for the standard ECG in distinguishing *LMNA* mutation carriers from patients with DCM and healthy controls.

Conclusions: Male *LMNA* mutation carriers present clinical manifestations at a younger age than females. ECG septal remodelling appears to distinguish *LMNA* mutation carriers from healthy controls and patients with DCM without *LMNA* mutations.

KEY QUESTIONS

What is already known about this subject?
► Although ventricular dilation and dysfunction may remain less severe than in other forms of dilated cardiomyopathy, the penetrance of cardiolaminopathy mutations is almost complete often resulting in serious arrhythmias or heart failure. Cardiomyopathy-causing *LMNA* mutations often present with typical ECG abnormalities, such as atrioventricular block and atrial or ventricular arrhythmias.

What does this study add?
► We report that most *LMNA* mutation carriers present with non-sustained ventricular tachycardia (NSVT) in close follow-up. In addition, we reaffirm that male *LMNA* mutation carriers have an earlier disease onset than females. We suggest that *LMNA* mutation carriers likely benefit from close follow-up. We also present a new ECG entity, septal remodelling, present in most *LMNA* mutation carriers and suggesting that the pathological process leading to cardiolaminopathy typically affects the myocardial septum.

How might this impact on clinical practice?
► The detection of septal remodelling in standard ECG should lead to an echocardiogram and thorough enquiry of cardiac family history.
► Even asymptomatic *LMNA* mutation carriers need follow-up to detect atrial fibrillation and NSVTs.

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INTRODUCTION

LMNA mutations are prevalent in familial dilated cardiomyopathy (DCM), accounting for about 5–8% of the cases.[1] The typical early manifestations of *LMNA* mutations are ECG abnormalities including flat P wave, atrioventricular block, supraventricular and ventricular arrhythmias.[2 3] *LMNA* mutations pose a risk for sudden cardiac death, and consequently implantable cardioverter-defibrillator (ICD) implantation has been suggested as primary prophylaxis for all *LMNA* mutation carriers, or after further risk assessment.[4 5] Cardiolaminopathy often follows an age-dependent disease progression in which the ECG and rhythm abnormalities tend to precede structural heart disease and systolic impairment, which in turn often does not fulfil the echocardiography criteria for DCM due to milder dilation of the left

ventricle or dilation with preserved ejection fraction.[3 6] Lately *LMNA* mutations have also been linked to familial forms of mainly right ventricular disease manifestations resembling arrhythmogenic right ventricular cardiomyopathy.[7 8]

Structural heart disease can result in general, non-localising ECG changes, such as left ventricular hypertrophy (LVH), ST depression, widening of the QRS complex, and P terminal force.[9 10] On the other hand, ECG changes in leads overlying affected regions can reflect regional disease processes. For instance, narrow and deep q waves are typical for localised wall thickening in hypertrophic cardiomyopathy.[11]

Late gadolinium enhancement (LGE) in cardiac MRI (CMR) is considered an effective tool in showing myocardial scarring.[12] In *LMNA* mutation carriers LGE has been mainly seen in the basal or mid-ventricular septum suggesting a possible localised disease process.[13 14]

The aim of this study was to assess disease presentation, progression and clinical outcome in symptomatic and asymptomatic *LMNA* mutation carriers.

METHODS
Patients and controls
This longitudinal retrospective study included all identified adult *LMNA* mutation carriers from Helsinki and Kuopio University Hospitals willing to participate in a follow-up study. Twenty-seven *LMNA* mutation carriers were recruited to the study between 1999 and 2010. The mutation carriers, each harbouring one of five *LMNA* mutations ((NM_170707.3 (LMNA), c427T>C, p.(Ser143Pro) in exon 2; c.394G>C, p.(Ala132Pro) in exon 2; c.568C>T, p.(Arg190Trp) in exon 3; c. 1493delG, p.(Ala499Leufs∗49) in exon 9; c. 1085delT, p.(Leu363Trpfs∗117) in exon 6) were either probands or their family members from nine families identified in two previous studies.[15 16] Clinical follow-up data from the *LMNA* mutation carriers and DCM controls were collected up to 31 December 2014. Control patients (n=78) with idiopathic DCM were collected from a patient database retrospectively. Probands with DCM, diagnosed and recruited before 2010 were included as DCM controls; patients recruited after possible heart transplantation, were excluded to minimise possible collection bias. Only probands who have been tested for cardiomyopathy-causing mutations using OsSeq, a next-generation-sequencing method, as described before were included to ensure that there were no *LMNA* mutation carriers among the DCM controls.[17]

Concerning the ECG abnormalities, the study patients were also compared with an available cohort of 20 (7 men, 13 women) healthy controls.

General
The criteria used for the diagnosis of DCM were Left ventricular end-diastolic diameter (LVEDD)>27 mm/m² and Left ventricular ejection fraction (LVEF)<45%.[15] Clinical end point data were collected from all available

hospital records. First incidences of atrial fibrillation, non-sustained ventricular tachycardia (NSVT), resuscitation or appropriate ICD therapy, cardiogenic embolism and pacemaker/ICD implantations were recorded. NSVT was defined as more than three consecutive ventricular beats in 24-hour Holter or clinical exercise test. To avoid bias, NSVTs were not recorded in the DCM controls due to the less vigorous follow-up of the DCM control group compared with the *LMNA* mutation carrier group. Owing to the small number of major clinical events in the *LMNA* mutation carrier group, a composite end point of resuscitation, appropriate ICD therapy, death and heart transplant was used. In *LMNA* mutation carriers with available CMR data, the presence of the ECG parameter septal remodelling was compared with CMR findings from a previous article;[13] the CMR methods were presented earlier.

The study patients gave written informed consent. The study was approved by the Ethics Committee of the Helsinki University Central Hospital (Decision number: Dnro 322/E5/03, Research permit number: T1010K0019).

ECG analyses
One standard 12-lead ECG recorded by 50 mm/s speed of each *LMNA* mutation carrier, DCM control and healthy control was analysed in a systematic manner manually by one investigator (KN) blinded to the clinical data. The ECG recording was from the time of study recruitment. The age at the time of ECG recording was 42 years for all *LMNA* mutation carriers; 49 years for those with DCM (*LMNA*-DCM subgroup), and 37 years for those without. The following definitions were used in the ECG analyses: first-degree atrioventricular block was defined as PR interval >200 ms,[18] P terminal force as negative portion of the P wave in lead V1≥0.4 mm/s,[19] flat P wave as P-wave amplitude <1 mm in lead II, and broad P wave as ≥120 ms in lead II[20] LVH was defined according to the Sokolow-Lyon criteria,[21] or Cornell voltage duration product (QRS-duration (ms)×(RaVL in mm+SV3 in mm with 6 mm added for women) ≥2440),[22 23] for ST segment depression we used ≥0.5 mm if the pattern was horizontal or descending, and ≥1 mm if ascending in ≥2 adjacent leads measured at the J point+60 ms,[24] for T-wave inversion ≥1 mm in ≥2 adjacent leads, except for leads aVR and V1 was used.[25] For fragmented QRS in ≥2 adjacent leads we used the definitions by Das *et al*.[26] Septal fragmentation was considered present if there was QRS fragmentation in ≥2 septal leads (V1–V3). Non-specific intraventricular conduction defect was defined as QRS duration ≥120 ms not fulfilling criteria for right or left bundle branch block. Owing to the high proportion of implanted pacemakers, we used anamnestic data of AV block in addition to the findings in the ECG used for analysis.

In addition to the established ECG changes, we introduced a novel ECG parameter, 'septal remodelling', which we define as one of the following present in V1–V3: (1) pathological Q waves in ≥2 parallel leads, or (2) septal fragmentation as defined above, (3) poor R-wave

progression (R wave <3 mm) in leads V1–V3 accompanied by QRS fragmentation, or disorderly distributed R-wave amplitudes, either RV2>RV3 or RV1>RV2. The possibility of lead switch was considered by assessing the morphology of the P and S waves in the precordial leads, and no suspicious cases were observed.[27] Any Q wave ≥40 ms in duration, or ≥3 mm deep, or qR-ratio ≥0.25, in ≥2 parallel leads except lead aVR was considered pathological.[28]

Statistical methods

Continuous variables were analysed using Student's t-test. The normality of continuous variables was assessed using the Shapiro-Wilk test for normality. In the few instances, where the variables were not normally distributed Mann-Whitney U test was used. For categorical variables, the χ^2 test was used when the expected count of 80% or more of the cells was ≥5. Otherwise the Fisher's exact test was used. All statistical tests were two-sided with a 5% level of significance, and no adjustments were made for multiplicity. However, concerning the ECG analyses the number of paired-wise comparisons (*LMNA* vs DCM and *LMNA* vs healthy control) was accounted for by multiplying the p values obtained by 2. The Kaplan-Meier analysis was used for survival analysis. SPSS V.22 was used for statistical analyses.

RESULTS
General

The frequencies and incidence ages of clinical manifestations are reported in table 1. The mean age at previous follow-up or major end point was 48 years for *LMNA* mutation carriers and 59 years for the DCM controls (p<0.001). Twelve *LMNA* mutation carriers fulfilled the criteria for DCM. Pacemakers were more common in the *LMNA*-DCM subgroup than in the DCM control group (83% vs 47%, p=0.047). NSVT was very common among the *LMNA* mutation carriers (78%). Heart transplants were more frequent in the *LMNA*-DCM subgroup than in the DCM control group (25% vs 11%), but the difference was not statistically significant. Atrial fibrillation was also more common among *LMNA* mutation carriers than in the DCM controls; p=0.007 when comparing the *LMNA*-DCM subgroup to the DCM control group. *LMNA* mutation carriers had their first episode of atrial fibrillation at a younger age than the DCM controls (47 vs 57 years, p=0.003). All the cases of likely cardiogenic thromboembolic events among the *LMNA* mutation carriers occurred among the *LMNA*-DCM subgroup. The frequency of thromboembolic events in the *LMNA*-DCM subgroup was roughly twice as high as in the DCM control group, but the difference was not statistically significant.

There were less major end points in the entire *LMNA* carrier group, and more in the *LMNA*-DCM subgroup than in the DCM control group. However, looking at major end points including deaths, heart transplantations and resuscitations, Kaplan-Meier analysis (figure 1A) revealed no difference in event-free survival between *LMNA* mutation carriers and DCM controls. When pacemakers were included in survival analysis, a statistically significant difference was seen;

Table 1 The frequencies and incidence ages of clinical *LMNA* mutation or cardiomyopathy manifestations

	All *LMNA* mutation carriers, n=27		*LMNA* mutation carriers with DCM, that is, *LMNA*-DCM subgroup, n=12		DCM controls, n=78
	N (%)	p Value*	N (%)	p Value*	N (%)
AF	15 (55.6)	NS	11 (91.7)	0.007	39 (50.0)
NSVT	21 (77.8)		11 (91.7)		
Pacemaker (any, including ICDs)	16 (59.3)	NS	10 (83.3)	0.020	37 (47.4)
ICD	9 (33.3)	NS	6 (50.0)	NS	26 (33.3)
Thrombosis	4 (14.8)	NS	4 (33.3)	NS	12 (15.4)
Major end point	7 (25.9)	0.039	7 (58.3)	NS	38 (48.7)
Males	13 (48.1)	0.026	6 (50.0)	NS	56 (71.8)
	Mean (SD)		Mean (SD)		Mean (SD)
Age at DCM diagnosis	48.7 (10.7)	NS	48.2 (10.4)	NS	47.4 (12.2)
Age at AF	46.9 (10.9)	0.003	47.9 (10.7)	0.014	56.9 (10.1)
Age at NSVT	45.6 (11.8)		49.1 (10.1)		
Age at PM	49.1 (10.6)	NS	49.6 (11.1)	NS	55.4 (13.0)
Age at ICD	48.5 (11.4)	NS	52.0 (12.7)	NS	53.0 (12.9)
Age at thrombosis	52.6 (10.0)	NS	52.6 (10.0)	NS	54.8 (12.5)
Age at major end point	51.0 (8.7)	NS	51.0 (8.7)	NS	59.0 (14.2)

Comparisons of all the *LMNA* mutation carriers and those *LMNA* mutation carriers fulfilling the criteria for DCM to the DCM controls.
*Comparisons to all DCM controls.
AF, atrial fibrillation; DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; NS, not significant; NSVT, non-sustained ventricular tachycardia; PM, pacemaker.
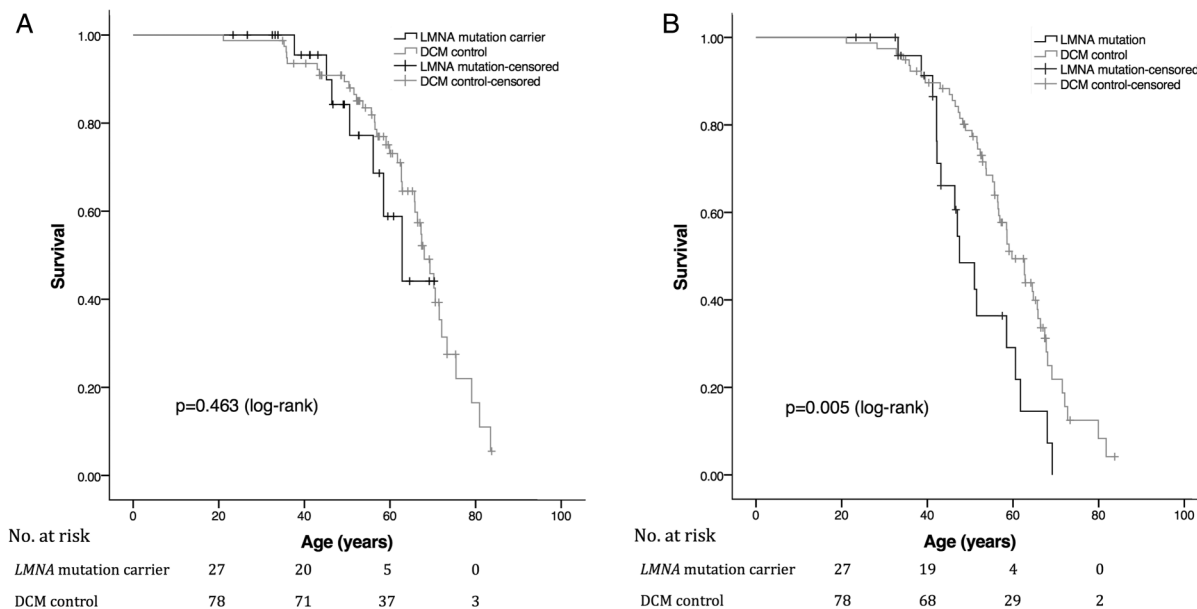
Figure 1 (A). Kaplan-Meier plot of event-free survival in 27 *LMNA* mutation carriers and 78 DCM control patients. Death, heart transplantation, resuscitation or appropriate ICD therapy included as events. Median age estimate for *LMNA* mutation carriers to first event was 63 years (CI 53 to 72) compared with 68 years (CI 64 to 72) for DCM controls. No statistically significant difference in event-free survival between the two groups was observed (p=0.463, log-rank test). (B). Kaplan-Meier plot of event-free survival in 27 *LMNA* mutation carriers and 78 DCM control patients. Deaths, heart transplants, resuscitations, appropriate ICD therapy or pacemaker implantations included as events. Median age estimate for *LMNA* mutation carriers was 48 years (CI 42 to 53) compared with 60 years (CI 55 to 64) for DCM controls (p=0.005, log-rank test). DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator.

Table 2 The frequencies and incidence ages of clinical *LMNA* mutation or cardiomyopathy manifestations

	LMNA-males, N=13 N (%)	p Value *LMNA* vs DCM	Male DCM controls, N=56 N (%)	*LMNA*-females, N=14 N (%)	p Value *LMNA* vs DCM	Female DCM controls, N=22 N (%)	p Value *LMNA*-males vs *LMNA*-females
AF	8 (61.5)	NS	29 (51.8)	7 (50.0)	NS	10 (45.5)	NS
NSVT	10 (76.9)			11 (78.6)			NS
Pacemaker (any, including ICDs)	9 (69.2)	NS	26 (46.4)	7 (50.0)	NS	11 (50.0)	NS
ICD	6 (46.2)	NS	16 (28.6)	3 (21.4)	NS	10 (45.5)	NS
Thrombosis	2 (15.4)	NS	8 (14.3)	2 (14.3)	NS	4 (18.2)	NS
Major end point	5 (38.5)	NS	27 (48.2)	2 (14.3)	0.03	11 (50.0)	NS
	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	
Age at DCM diagnosis	42.2 (7.0)	NS	47.8 (11.4)	54.1 (10.3)	NS	46.3 (14.2)	0.042
Age at AF	40.9 (9.3)	<0.001	55.4 (8.7)	53.7 (8.6)	NS	61.0 (13.1)	0.016
Age at NSVT	40.5 (9.7)			50.3 (11.9)			NS
Age at PM	41.8 (4.1)	<0.001	55.8 (12.7)	58.5 (8.6)	NS	54.6 (14.5)	0.001
Age at ICD	41.5 (3.6)	0.007	51.2 (11.6)	62.7 (6.1)	NS	55.8 (14.8)	<0.001
Age at thrombosis	48.5 (12.1)	NS	56.7 (10.2)	56.8 (9.3)	NS	51.1 (17.4)	NS
Age at major end point	47.7 (7.6)	NS	60.1 (13.9)	59.5 (4.8)	NS	56.3 (15.1)	NS

Comparisons of male *LMNA* mutation carriers to male DCM controls, female *LMNA* mutation carriers to female DCM controls and male *LMNA* mutation carriers to female *LMNA* mutation carriers.
AF, atrial fibrillation; DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; NS, not significant; NSVT, non-sustained ventricular tachycardia; PM, pacemaker.

Figure 2 The incidence ages of clinical *LMNA* mutation manifestations. Squares represent males, circles females. DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator.
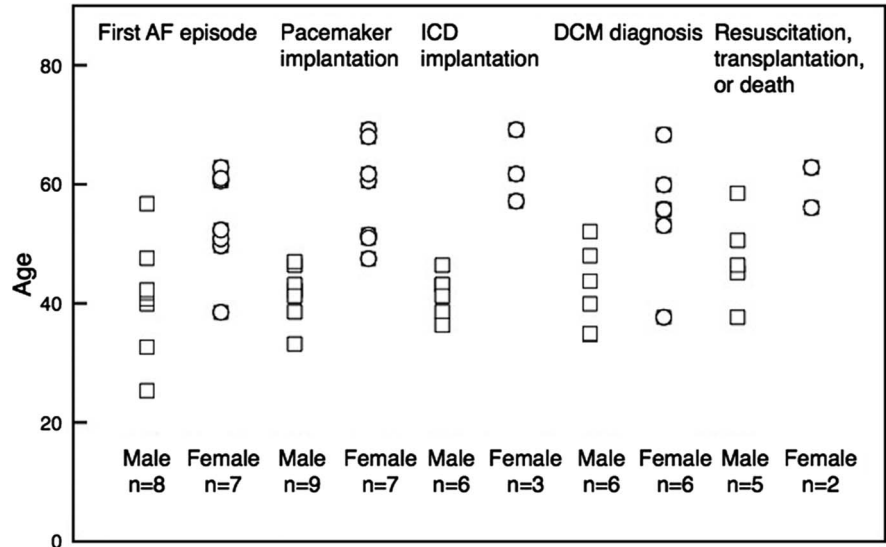

Table 3 The ECG characteristics of the *LMNA* mutation carriers, DCM controls and healthy controls

	LMNA mutation carriers, N=27%	DCM controls, N=78%	p Value *LMNA* vs DCM	Healthy controls, N=20%	p Value *LMNA* vs healthy control
Rhythm					
Sinus rhythm	70.4	75.6	NS	100	NS
AF	11.1	16.7		0	
Other*	18.5	7.7		0	
First AV block	37.0 (55.6)†	15.4 (20.7)	0.034	0	0.006
Current or previous AV block	59.3	24.4	0.002	0	<0.001
PTF	22.2 (30.0)	30.8 (40.0)	NS	10.0	NS
Flat P wave	33.3 (45.0)	6.4 (8.3)	0.002	0	0.012
Broad P wave	7.4 (10.0)	5.1 (6.7)	NS	0	NS
LVH	7.4 (11.8)	20.5 (34.0)	NS	0	NS
ST depression	18.5 (29.4)	32.1 (53.2)	NS	5.0	NS
T inversion	7.4 (11.8)	32.1 (53.2)	0.012	5.0	NS
QRS fragmentation	37.0	33.3	NS	5.0	0.028
Septal fragmentation	22.2	6.4	NS	0	0.062
Septal remodelling	81.5	20.5	<0.001	0	<0.001
Septal remodelling, flat P wave, or current or previous AV block	96.3	41.0	<0.001	0	<0.001
LBBB	7.4	20.5	NS	0	NS
RBBB	0	2.6	NS	0	NS
NSIVCD	3.7	7.7	NS	0	NS

*Physiological pacemaker or third AV block.
†The prevalence in brackets of only those applicable.
AF, atrial fibrillation; AV block, atrioventricular block; DCM, dilated cardiomyopathy; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; NS, not significant; NSIVCD, non-specific intraventricular conduction defect; PTF, P terminal force; RBBB, right bundle branch block.

median age estimate for *LMNA* mutation carriers to first event was 48 years (CI 42 to 53) compared with 60 years (CI 55 to 64, p=0.005) for DCM controls (figure 1B).

The Finnish founder mutation Ser143Pro was the most common mutation among the *LMNA* mutation carriers, with 15 of the 27 mutation carriers harbouring it.[15] There were no statistically significant differences between the Ser143Pro mutation carriers compared with the other *LMNA* mutation carriers (Ala132Pro, Arg190Trp, c. 1493delG, c. 1085delT) concerning the frequencies or incidence ages of the clinical manifestations. Of the DCM controls 28% had a genetic diagnosis. The most common cardiomyopathy-causing mutations

among the DCM controls were truncating titin gene mutations, which explained 18% of cases.

Differences between men and women

The frequencies and incidence ages of clinical manifestations in male and female *LMNA* mutation carrier and DCM control subgroups are presented in table 2. Male *LMNA* mutation carriers presented with clinical manifestations at an earlier age than female *LMNA* mutation carriers. This difference is illustrated in figure 2. There was a trend for a higher incidence of atrial fibrillation among the male *LMNA* mutation carriers compared with the women. Men presented with atrial fibrillation at an earlier age than female *LMNA* mutation carriers (41 vs 54 years, p=0.016). They also received pacemakers and ICDs at a younger age than females (42 vs 59 years for any pacemakers, p=0.001, 42 vs 63 for ICDs, p<0.001). In addition, they developed DCM at a younger age than women (42 vs 54 years, p=0.042). The vast majority of male and female *LMNA* mutation carriers had recorded NSVT episodes. Although there was no gender difference in the frequencies of NSVTs, men appeared to have the first recorded episode roughly 10 years earlier than women (41 vs 50 years, NS).

ECG

The ECG characteristics of the *LMNA* mutation carriers, DCM controls and healthy controls are presented in table 3. The novel ECG pattern, septal remodelling proved to be very frequent (81%) in *LMNA* mutation carriers, while this ECG pattern was present in only 21% of DCM controls and in none of the healthy controls. The differences were even more striking when combining the ECG parameters flat P wave and AV block to septal remodelling in the analyses. The sensitivities, specificities, and positive and negative predictive values for septal remodelling in classifying *LMNA* mutation carriers from the two control groups are given in table 4. Figure 3 shows ECGs with varying forms of septal remodelling together with CMR images of an *LMNA* mutation carrier presenting LGE in the septum. We had available CMR data from 17 of the 27 *LMNA* mutation carriers. In 76% of the cases (n=13), septal remodelling in the ECG and septal LGE in CMR were concordantly present. In the remaining four cases, either septal remodelling in ECG (n=2) or LGE in CMR (n=2) was present.

There were no mutation-specific ECG findings in this study when comparing all the five mutations, or the Finnish founder mutation Ser143Pro (n=15) to the other four mutations as one group (n=12).

DISCUSSION

Our data suggest a difference in the age of disease onset in cardiolaminopathy between men and women; men presented roughly a decade earlier than women regarding all studied clinical manifestations. Concerning the age of first incidence of atrial fibrillation, age of

Table 4 The sensitivities, specificities, and PPV and NPV for (ECG) septal remodelling in classifying *LMNA* mutation carriers from the DCM controls, healthy controls or the combined control group of DCM controls and healthy controls

	Septal remodelling, N (%)	Current or previous AV block, flat P wave or septal remodelling, N (%)
LMNA mutation carriers	22 (81.5)	26 (96.3)
Healthy controls	0	0
DCM controls	16 (20.5)	32 (41.0)
LMNA vs DCM controls	Per cent	Per cent
Sensitivity	81.5	96.3
Specificity	79.5	59.0
PPV	57.9	44.8
NPV	92.5	97.9
LMNA vs healthy controls		
Sensitivity	81.5	96.3
Specificity	100	100
PPV	100	100
NPV	80	95.2
LMNA vs DCM or healthy controls		
Sensitivity	81.5	96.3
Specificity	83.7	67.3
PPV	57.9	44.8
NPV	94.3	98.5

DCM, dilated cardiomyopathy; NPV, negative predictive value; PPV, positive predictive value.

pacemaker or ICD implantation, and age at DCM diagnosis, the difference was statistically significant. Also in a previous study of *LMNA* mutation carriers, the frequencies of malignant ventricular arrhythmias, end-stage heart failure and mortality were higher in men than in women, but the age of the first cardiac involvement was similar in both genders.[29] We suggest that the disease onset in *LMNA* mutation carriers in general takes place earlier in men than in women.

The incidence of ventricular arrhythmias is known to be high in *LMNA* mutation carriers with prevalence numbers over 50% cited in several studies.[14] [30] The prevalence of 78% (for NSVT) in this study is even higher, which may be explained by repeated documentations of Holter ECGs and clinical exercise testing of the same individuals over several years. This finding suggests that even if ventricular arrhythmias have not been detected in an individual *LMNA* mutation carrier, they likely will be in regular follow-up. Some years ago, it was even suggested that ICDs should be implanted prophylactically to all *LMNA* mutation carriers.[4] Recently, a risk assessment scheme was suggested to identify those *LMNA* mutation carriers at greater risk for malignant
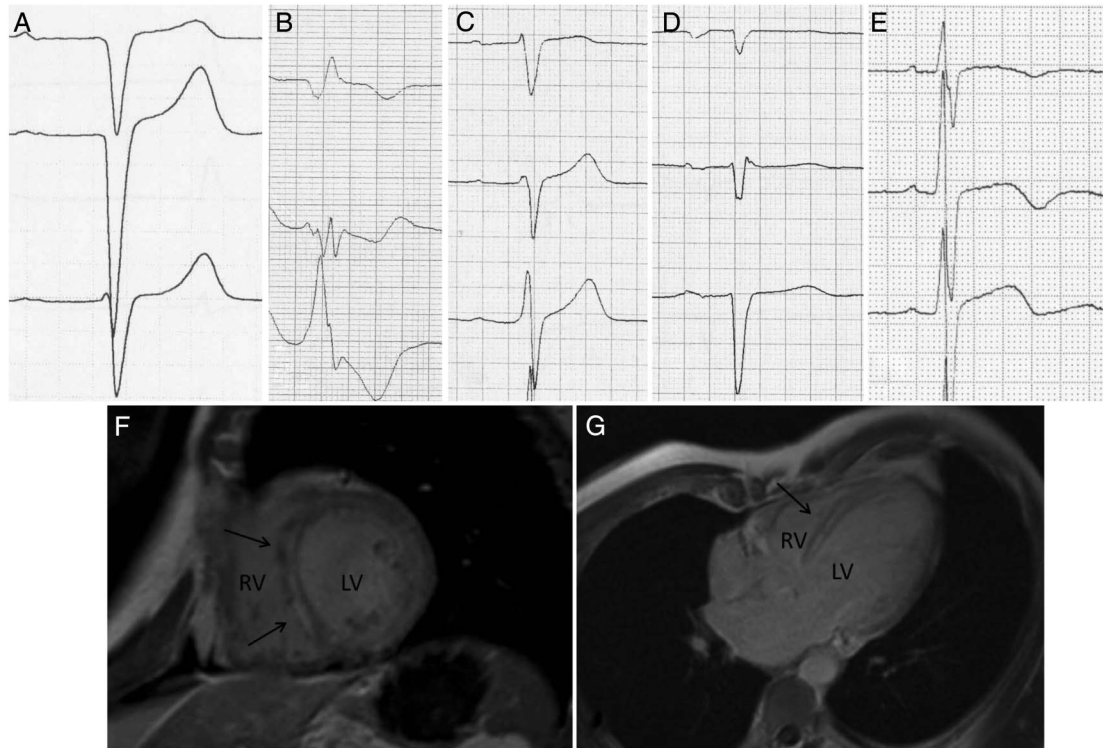
Figure 3 (A–E) Example ECGs presenting septal remodelling. (A) Q waves in V1–V2; (B) broad QRS with fragmentation in V2–V3, and a Q wave in V1; (C) RV1>RV2 with fragmented QRS in V2; (D) poor R-wave progression with QRS fragmentation in V2; (E) RV2>RV3 with fragmented QRS in V1. 3. (F and G) CMR image of an *LMNA* mutation carrier. Arrows point to the areas showing late gadolinium enhancement. CMR, cardiac MRI; LV, left ventricle; RV, right ventricle.

ventricular arrhythmias.[5] We agree with the proposed strategy for individual risk stratification among *LMNA* mutation carriers when considering the need for an ICD. However, the high prevalence of NSVT highlights the need for close follow-up of these patients, as the clinical presentation is likely to progress. It can also be speculated that close follow-up and timely interventions could reduce the risk of events, or slow down disease progression. Our results suggest a similar or lower incidence of major clinical end points, including heart transplantations, resuscitations or deaths, in *LMNA* mutation carriers than in DCM controls. The incidence of major end points was higher in the older DCM control group, but Kaplan-Meier analysis showed a similar event-free survival rate in the *LMNA* mutation carrier and the DCM control groups.

We introduce a novel ECG concept, septal remodelling, as a readily available clinical tool to assess cardiac involvement in *LMNA* mutation carriers. In our study of 27 *LMNA* mutation carriers of varying ages, 81% presented with this ECG finding compared with 21% of the DCM controls and none of the healthy controls. When combining this abnormality with the previously described ECG signs associated with laminopathy, flat P waves and AV block, all but one of the *LMNA* mutation carriers had at least one of these abnormalities.

ST segment depression, markers of increased left ventricular mass (LVH and broad QRS), and elevated filling pressure (P terminal force) are established ECG signs of structural heart disease.[9 10] ECG changes associated with regional disease processes, mainly fibrosis or necrosis, are less well established. We suggest that septal remodelling in the ECG leads V1–V3 represents a localised disease process typical to cardiolaminopathy. Our hypothesis is compatible with the fact that CMR studies using LGE as a marker for cardiac fibrosis suggest disease localisation in the basal and mid-ventricular septum and the basal left ventricular wall in *LMNA* mutations.[13 14] In this study in 76% (13/17) of the *LMNA* mutation carriers with available CMR data, septal remodelling in the ECG and LGE in the septum were concordant. ECG septal remodelling was very common in *LMNA* mutation carriers, quite rare in DCM controls and absent in healthy controls. However, it seems logical that any regional disease process, such as myocardial infarction or myocarditis, resulting in necrosis or fibrosis, would be reflected in a similar way on the 12-lead ECG. Therefore, we propose further clinical assessment, including family history and cardiac imaging to rule out structural heart disease, in individuals without a history of cardiac disease, who present with septal remodelling in their 12-lead ECG. Genetic testing may also be appropriate, taking into account the entire clinical presentation.

Owing to the explorative nature of this study, multiplicity correction was not performed.

In conclusion, our results suggest that male *LMNA* mutation carriers appear to present with cardiolaminopathy manifestations roughly a decade earlier than

women. The high incidence of atrial fibrillation and ventricular arrhythmias in *LMNA* mutation carriers supports close follow-up to enable timely initiation of medical and device-based antiarrhythmic therapy.

Finally, we introduce a novel ECG parameter, septal remodelling, which was frequently observed in *LMNA* mutation carriers and seemed to differentiate these individuals from patients with other forms of DCM.

Limitations

The number of *LMNA* mutation carriers in this study was rather small. It is possible that some non-significant statistical comparisons could have reached statistical significance in a larger patient material. Our definition of ECG septal remodelling is not based on exact experimental or CMR-based correlations between regional disease processes and electrophysiological changes. However, it represents a collection of previously published ECG parameters of localised heart disease.

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