Genetic Disorders

Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

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Objectives

The purpose of this study was to determine risk factors that predict malignant ventricular arrhythmias (MVA) in Lamin A/C (LMNA) mutation carriers.

Background

LMNA mutations cause a variety of clinical phenotypes, including dilated cardiomyopathy and conduction disease. Many LMNA mutation carriers have a poor prognosis, because of a high frequency of MVA and progression to end-stage heart failure. However, it is unclear how to identify mutation carriers that are at risk for MVA.

Methods

In this multicenter cohort of 269 LMNA mutation carriers, we evaluated risk factors for MVA, defined as sudden cardiac death, resuscitation, and appropriate implantable cardioverter-defibrillator (ICD) treatment.

Results

In a median follow-up period of 43 months (interquartile range: 17 to 101 months), 48 (18%) persons experienced a first episode of MVA: 11 persons received successful cardiopulmonary resuscitation, 25 received appropriate ICD treatment, and 12 persons died suddenly. Independent risk factors for MVA were nonsustained ventricular tachycardia, left ventricular ejection fraction \( \leq 45\% \) at the first clinical contact, male sex, and non-missense mutations (insertion/truncating or mutations affecting splicing). MVA occurred only in persons with at least 2 of these risk factors. There was a cumulative risk for MVA per additional risk factor.

Conclusions

Carriers of LMNA mutations with a high risk of MVA can be identified using these risk factors. This facilitates selection of LMNA mutation carriers who are most likely to benefit from an ICD.

Lamin A/C gene (LMNA) mutations can cause a variety of clinical phenotypes including premature aging, metabolic disorders, skeletal muscle disease and cardiac abnormalities (1). The cardiac phenotype associated with LMNA mutations is characterized by atrial fibrillation, conduction disturbances, ventricular arrhythmias, and dilated cardiomyopathy (2–6). Cardiac

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abnormalities are not an integral part of all LMNA related disorders, but may occur in isolation or in association with skeletal muscle disease (Emery-Dreifuss or limb girdle muscular dystrophy type 1b) (7–10).

Previous studies have shown that LMNA mutation carriers have a poor prognosis caused by progression to end-stage heart failure and malignant ventricular arrhythmias (MVA) (5,10,11). One small study suggested that implantable cardioverter-defibrillator (ICD) therapy may be effective in preventing sudden cardiac death in LMNA mutation carriers (11). However, it is unclear whether all LMNA mutation carriers are at similar risk and, by inference, might benefit from primary ICD implantation.

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The primary aim of this study was to determine clinical and genetic risk factors that predict MVA in persons carrying a LMNA mutation. Therefore, the data of a cohort 269 persons carrying a LMNA mutation from 6 countries in Europe were collected and analyzed.

Methods

Study settings and design. Data from all persons (proband and relatives) diagnosed with a LMNA mutation considered to be pathogenic and followed up at 8 centers from 6 European countries were retrospective collected. All genetic diagnoses were made between 2000 and 2010. Only mutation carriers older than 15 years of age who had been investigated by a cardiologist at least once were enrolled in this cohort. Persons with a previously published pathogenic LMNA mutation with cardiac involvement and persons with a newly identified LMNA mutation with clinical or family evidence of a laminopathy with possible cardiac involvement were included. A mutation was considered pathogenic when the variation satisfied 2 or more of the following criteria: 1) cosegregation of the variant with the cardiac phenotype within the family or family history highly suspicious for a LMNA mutation; 2) affects an amino acid, which is highly conserved among species; 3) is localized in a highly conserved region among species; 4) is localized within a functionally important domain; 5) the amino acid change leads to different physicochemical properties; and 6) additional functional data are available. In all cases, the reported mutations were absent in at least 150 ethnically matched control persons (12–14).

Baseline clinical information from the first documented visit to the cardiologist and follow-up data were recorded. Data were obtained for all major events, including details on cardiovascular-events. The decision to implant an ICD was made on clinical grounds by the managing cardiovascular specialists at each center.

Clinical definitions. Nonsustained ventricular tachycardia (VT) on 24-h Holter monitoring was defined as 3 or more consecutive ventricular beats with a rate of ≥120 beats/min and a duration of <30 s.

Dilated cardiomyopathy was defined as a either left ventricular ejection fraction (LVEF) <45% (15) and/or left ventricular enlargement with a left ventricular diameter of ≥6.4 cm for males and ≥5.8 cm for females (16). End-stage heart failure was defined as cardiac transplantation or death caused by heart failure.

Atrial tachyarrhythmias were classified as paroxysmal (episode of atrial fibrillation for >30 s), persistent, permanent atrial fibrillation, and atrial flutter.

Atrioventricular (AV) block was classified as first, second, or third degree. First-degree AV block was defined by a PR interval ≥0.20 s.

A history of sudden cardiac death within a family was considered positive if at least 1 family member (up to third degree) died suddenly below the age of 60 years.

Type of mutations was divided into non-missense (ins-del/ truncating or mutations affecting splicing) and missense mutations.

Endpoints and follow-up. The endpoint for the survival analysis was a composite endpoint, defined by the first occurring MVA. MVA were defined as appropriate ICD treatment, cardiopulmonary resuscitation, or sudden cardiac death. Appropriate ICD treatment was classified as an ICD discharge for termination of ventricular fibrillation or VT or antitachycardia pacing for termination of sustained VT. Sudden cardiac death was defined as witnessed sudden cardiac death with or without documented ventricular fibrillation or death within 1 h of acute symptoms or nocturnal deaths with no antecedent history of worsening symptoms. Cardiopulmonary resuscitation was defined as a successful basic life support for a cardiac arrest.

Statistical analysis. Clinical and demographic characteristics were compared using the Mann-Whitney U test for continuous variables, and the chi-square test for categorized variables expressed as proportions (or the Fisher exact test for subgroups containing ≤5 observations).

We used 2 different start points for the time-to-event analyses. The data available during the first visit to the cardiologist were used for the analysis of the diagnostic variable parameters. Because this time point is dependent on when a person was first consulting the cardiologist, the parameters could be biased by selection. For this reason, the constant factors during lifetime were also analyzed from date of birth. In persons without an event, the follow-up period extended to the most recent evaluation or censoring event up to March 2010. The log-rank test was used to compare failure-time curves between subgroups of patients. Cox regression analysis was used to identify independent predictors of events. Hazard ratios and 95% confidence
interval (CI) were calculated; robust standard errors were calculated to account for the family-clustering in the data (17,18). Variables reaching p < 0.05 on univariable analysis were included in the multivariable model. The SPSS software (version 17.0, SPSS Inc., Chicago, Illinois) and the R statistical package (version 2.10.1) were used for analyses (19). A p value of ≤0.05 was considered statistically significant.

Results

Study population and characteristics. The study cohort comprised 269 persons with pathogenic LMNA mutations from 109 different families (range 1 to 24 persons per family) (Table 1). Median follow-up from first contact with the cardiologist until end of follow-up was 43 months (interquartile range [IQR]: 17 to 101 months), with a total follow-up of 1,227 patient-years.

At the end of the follow-up, 45 (17%) persons had died at a mean age of 50 ± 11 years. Heart failure was the most prevalent cause of death (n = 21; 47%), followed by sudden cardiac death (n = 14; 31%), death during or after cardiac transplantation (n = 6; 13%), and other causes of death (n = 4; 9%).

Table 1: Baseline Characteristics of 269 Persons Carrying a LMNA Mutation (N = 269)

<table>
<thead>
<tr>
<th>Age, yrs</th>
<th>36 (27–45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>148 (55)</td>
</tr>
</tbody>
</table>

Symptoms

- Unexplained syncope (n = 260)*
- NYHA classification ≥3 (n = 260)*
- Dysrhythmias
  - Atrial tachyarrhythmias (n = 239)*
  - Sinus node dysfunction (n = 259)*
  - AV block (n = 244)*
  - Nonsustained VT on Holter monitoring (n = 227)*

Cardiomyopathies

- LVEF <45% (n = 243)*
- LVEF, % (n = 242)*
- LV enlargement (n = 236)*

Comorbidities

- Coronary artery disease (n = 267)*
- Hypertension (n = 269)*
- Diabetes mellitus (n = 267)*

Medication

- Beta-blocker (n = 260)*
- ACE inhibitor or ARB (n = 260)*

Type of mutation

- Missense (n = 269)*
- Muscular dystrophy (n = 198)*
- Family history of sudden cardiac death (n = 262)*
- Unaffected (n = 248)*

Values are median (interquartile range) or n (%). *Number of persons for whom there were available data. †Number of carriers with LVEF <45%, no dysrhythmias, and no muscular dystrophy.

Thirty-six (13%) patients underwent orthotopic cardiac transplantation. Together with those persons who died from heart failure, one-fifth (n = 57; 21%) of the whole population had end-stage heart failure (Fig. 1).

Malignant ventricular arrhythmias. A total of 48 (18%) persons experienced a first episode of MVA: 11 persons received successful cardiopulmonary resuscitation, 25 received appropriate ICD treatment, and 12 persons died suddenly (Fig. 1).

Eleven of 269 (4%) patients received successful cardiopulmonary resuscitation (Table 2), of whom 1 did not receive an ICD afterward and died a year later because of sudden cardiac death. The other 10 (4%) patients, however, received an ICD; 3 of these received appropriate ICD therapy, with a rate of appropriate ICD treatment of 13 per 100 person-years (median follow-up period, 21 months; IQR: 12 to 40 months).

An ICD was implanted for primary prophylaxis in 107 (40%) persons; of these, 25 received appropriate ICD therapy. Rate of appropriate ICD treatment was 8 per 100 person-years (median follow-up period 29 months; IQR: 14 to 49 months).

In total, 14 persons died suddenly. One person died suddenly despite a working ICD in situ. This person, with a LVEF of 30%, had severe ventricular arrhythmias with a large number of ICD discharges. He finally died of incessant ventricular tachycardia that could not be converted.

A total of 11 (9%) persons received inappropriate ICD shocks, in all cases due to atrial tachyarrhythmias with a high ventricular response.

After having survived a first event of MVA (n = 36), 6 (17%) patients died of heart failure, and 9 (25%) underwent cardiac transplantation. The median duration from MVA until end-stage heart failure was 16 months (IQR: 9 to 32 months).

Prognostic stratification of malignant ventricular arrhythmias. Nonsustained VT, LVEF <45%, being male, left ventricular enlargement, being a proband, and atrial tachyarrhythmias were all univariates associated with MVA (p < 0.001, p < 0.001, p < 0.001, p < 0.001, p = 0.041, and p = 0.049, respectively) (Table 3). Nonsustained VT, LVEF <45%, being male, and left ventricular enlargement were highly significant also after Bonferroni adjustment for multiple testing. Atrial tachyarrhythmias and being a proband were not significant after adjustment. Conduction disturbances and type of mutation were not significantly related to the risk of MVA. Also the diagnosis of muscular dystrophy or a positive family history for sudden cardiac death did not convey a statistically significant risk for MVA.

In a multivariable analysis (corrected for age at first visit to the cardiologist), LVEF <45%, nonsustained VT, and being male were independent predictors for MVA with

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hazard ratios of 4.4 (95% CI: 1.7 to 11.0), 4.4 (95% CI: 1.9 to 10.4), and 2.9 (95% CI: 1.2 to 7.0), respectively (p = 0.021, p = 0.003, and p = 0.030, respectively).

These analyses were similar when appropriate ICD treatment for VT was excluded.

The cumulative event-free survival for patients with and without MVA is illustrated in Figure 2. None of the persons without these risk factors had a malignant ventricular arrhythmia during follow-up. One (1.7%) mutation carrier with 1 risk factor had a malignant ventricular arrhythmia. In LMNA mutation carriers with 2 or 3 risk factors, 16 (27%) persons and 19 (54%), respectively, had MVA (p = 0.001, log-rank test on 3 degrees of freedom).

We also analyzed survival according to sex and type of mutation, from date of birth until first MVA. Both in the univariate and the multivariate analysis, male sex and non-missense mutations (ins-del/ truncating or mutations affecting splicing) were life-time risk factors for MVA, with hazard ratios of 3.9 (95% CI: 1.9 to 7.9) and 2.5 (95% CI: 1.4 to 4.5), respectively.

When we compared persons with 1, 2, 3, or 4 of the risk factors (nonsustained VT, LVEF < 45% at the first visit to the cardiologist, being male, and non-missense mutations) for MVA (Fig. 3), there was a significant event-free survival difference (p < 0.001, log-rank test on 3 degrees of freedom). In persons without any risk factor or with only 1 risk factor, no MVA occurred in a median follow-up period of 43 months (IQR: 16 to 92 months). Additionally, in persons free from nonsustained VT and a LVEF < 35% at the first visit to the cardiologist, no MVA occurred. When we used a cut-off value for LVEF of ≥ 35% (instead of < 45%), sensitivity dropped from 80% to 59%.

We also compared the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines with our clinical risk stratification. Both ways of stratifying risk predict MVA. The sensitivity of the combination of a LVEF < 45% and nonsustained VT was 100%, with a specificity of 55%. The sensitivity of the risk factors from the guideline (LVEF ≥ 35% in combination...
with NYHA functional classification II or III) is 36%, with a specificity of 91% (20).

Nine of 13 (71%) LMNA mutation carriers with 4 risk factors had MVA with an age of onset of 20 years. In LMNA mutation carriers with 2 and 3 risk factors, 11 of 65 (17%) and 16 of 40 (40%), respectively, developed MVA. The age of onset was 34 years in persons with 2 risk factors and 26 years in persons with 3 risk factors. No MVA occurred in persons with only the combination of the risk factors male sex and non-missense mutations.

Discussion

This study confirms the high rate of sudden cardiac death, ventricular arrhythmias, and progression to heart failure in persons with LMNA mutations. In addition, it identifies 4 independent clinical and genetic factors that predict MVA. The 4 independent risk factors were nonsustained VT, LVEF <45% at the first clinical contact, male sex, and non-missense mutations (ins-del/ truncating or mutations affecting splicing). These findings could have important implications for counseling and treatment of affected families carrying LMNA mutations.

Lamin A and C are nuclear matrix proteins located on the nuclear surface of the inner nuclear membrane encoded by the same gene (LMNA). Some mutations in LMNA result in dilated cardiomyopathy and conduction disease alone, whereas others cause juvenile-onset muscular dystrophies or familial partial lipodystrophy with insulin-resistant diabetes. In patients with a predominant cardiac phenotype, the natural history is characterized by atrial arrhythmia and

### Table 3: Identification of Risk Factors for Composite Malignant Ventricular Arrhythmias in 269 Persons Carrying a LMNA Mutation

<table>
<thead>
<tr>
<th>Characteristics at Time of First Cardiologist Visit</th>
<th>All (N = 269)</th>
<th>Rhythm Events* (% of Subgroup)</th>
<th>p Value (Log-Rank)</th>
<th>HR (95% CI)</th>
<th>p Value (Multivariable Cox Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsustained VT on Holter monitoring (n = 227)†</td>
<td>No</td>
<td>142</td>
<td>8 (6)</td>
<td>-0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>85</td>
<td>30 (35)</td>
<td>4.4 (1.9–10.4)</td>
<td>0.021‡</td>
<td></td>
</tr>
<tr>
<td>LVEF (n = 243)†</td>
<td>≥45</td>
<td>154</td>
<td>8 (5)</td>
<td>-0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;45</td>
<td>89</td>
<td>33 (37)</td>
<td>4.4 (1.7–11.0)</td>
<td>0.041§</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>121</td>
<td>10 (8)</td>
<td>-0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>148</td>
<td>38 (26)</td>
<td>2.9 (1.2–7.0)</td>
<td>0.014§</td>
<td></td>
</tr>
<tr>
<td>LV enlargement (n = 236)†</td>
<td>No</td>
<td>195</td>
<td>25 (13)</td>
<td>-0.001§</td>
<td>0.144</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>14 (34)</td>
<td>0.041§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probands</td>
<td>No</td>
<td>160</td>
<td>21 (13)</td>
<td>-0.001§</td>
<td>0.119</td>
</tr>
<tr>
<td>Yes</td>
<td>109</td>
<td>27 (25)</td>
<td>0.049§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial tachyarrhythmias (n = 239)†</td>
<td>No</td>
<td>153</td>
<td>18 (12)</td>
<td>-0.001§</td>
<td>0.104</td>
</tr>
<tr>
<td>Yes</td>
<td>86</td>
<td>27 (31)</td>
<td>0.049§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV block (n = 244)†</td>
<td>No</td>
<td>130</td>
<td>13 (10)</td>
<td>-0.001§</td>
<td>0.119</td>
</tr>
<tr>
<td>Yes</td>
<td>114</td>
<td>29 (25)</td>
<td>0.119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of SCD (n = 262)†</td>
<td>No</td>
<td>49</td>
<td>12 (24)</td>
<td>-0.001§</td>
<td>0.474</td>
</tr>
<tr>
<td>Yes</td>
<td>213</td>
<td>35 (16)</td>
<td>0.474</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of MD or family history of MD (n = 268)†</td>
<td>No</td>
<td>214</td>
<td>37 (17)</td>
<td>-0.001§</td>
<td>0.510</td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>10 (19)</td>
<td>0.510</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained syncope (n = 255)†</td>
<td>No</td>
<td>227</td>
<td>37 (16)</td>
<td>-0.001§</td>
<td>0.623</td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>7 (25)</td>
<td>0.623</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of mutation</td>
<td>Missense</td>
<td>149</td>
<td>21 (14)</td>
<td>-0.001§</td>
<td>0.836</td>
</tr>
<tr>
<td>Non-missense</td>
<td>120</td>
<td>27 (23)</td>
<td>0.836</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional classification ≥3 (n = 260)†</td>
<td>No</td>
<td>221</td>
<td>38 (17)</td>
<td>-0.001§</td>
<td>0.836</td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>6 (15)</td>
<td>0.836</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise indicated. *Rhythm events were defined as appropriate ICD treatment, cardiopulmonary resuscitation, or sudden cardiac death. †Number of persons for whom there were available data. §After backward stepwise regression. §Not significant in the multivariable Cox model. Multivariate analysis was corrected for age at first visit to cardiologist and family clustering. CI = confidence interval; HR = hazard ratio; MD = muscular dystrophy; SCD = sudden cardiac death; other abbreviations as in Table 1.
progressive AV conduction disease that often precedes the development of MVA, LV dilation, and systolic dysfunction by several years (3,6,21).

Laminopathies with predominant cardiac involvement are associated with mutations along the entire LMNA gene, although the majority are missense mutations in the central rod domain (6,21,22). The pathophysiological mechanisms are poorly understood. LMNA mutations have effects on nuclear fragility, alterations in cellular signaling, and gene expression resulting in abnormal interaction between lamins and other nuclear proteins such as desmin, and abnormal processing of pre-lamin A (23).

To date, there have been few studies that have examined the relation between specific genotypes and the pattern of clinical expression. Pasotti et al. (5) were the first who described a relation between the type of mutation and the risk for sudden cardiac death. They described that LMNA splice-site mutations were an independent risk factor for MVA. The results of this study indicate that a significant risk is conveyed by non-missense mutations (ins-del/ truncating or mutations affecting splicing) in comparison to missense mutations. It has been proposed that ins-del/ truncating or mutations affecting splicing could induce nonsense-mediated mRNA decay, thereby inducing haploinsufficiency. Mice models heterozygous for a lamin-null allele confirmed that the loss of half the lamin AC alleles suffices to cause a similar cardiac phenotype with conduction system disease, arrhythmias and heart failure (24).

At present, management guidelines for patients with dilated cardiomyopathy give little consideration to the possible influence of the underlying molecular etiology. In the past, the high incidence of conduction disorders in patients with LMNA mutations led to frequent implantation of pacemakers. Furthermore, the occurrence of sudden cardiac deaths even in pacemaker recipients has led to the recommendation that patients requiring a pacemaker should receive an ICD (10). The timing of ICD implantation has, however, been a major challenge as there have been no previous studies examining risk factors for sudden cardiac death in people with LMNA mutations. The major finding in this study is that a relatively simple clinical algorithm identifies patients at the highest risk of MVA.

Although this study was not designed to determine the effect of ICD therapy on survival, it is notable that the 31% prevalence of sudden cardiac death was lower than the 46% reported previously. The high rate of appropriate ICD therapies in patients who had received a device for primary

Figure 2 Kaplan-Meier Event-Free Survival From Date of First Visit to Cardiologist
Kaplan-Meier event-free survival stratified by 3 independent risk factors (RF): nonsustained ventricular tachycardia, left ventricular ejection fraction <45% at the first visit to the cardiologist, and being male. Event: occurrence of malignant ventricular arrhythmias, defined as appropriate implantable cardioverter-defibrillator treatment, cardiopulmonary resuscitation, or sudden cardiac death.

Figure 3 Kaplan-Meier Event-Free Survival All 4 Risk Factors
Kaplan-Meier event-free survival stratified by 4 independent risk factors (RF): nonsustained ventricular tachycardia, left ventricular ejection fraction <45% at the first visit to the cardiologist, being male, and non-missense mutations (ins-del/truncating or mutations affecting splicing). Event: occurrence of malignant ventricular arrhythmias, defined as appropriate implantable cardioverter-defibrillator treatment, cardiopulmonary resuscitation, or sudden cardiac death.
prophylaxis also suggests that ICDs are potentially life-saving in LMNA mutation carriers. Thus, it seems prudent to consider an ICD in persons with 2 or more of the 4 risk factors identified. Although, further research needs to be conducted to clarify this assumption. Conversely, the low incidence of MVA in the absence of the clinical risk factors nonsustained VT and LVEF <45% suggests that persons carrying a LMNA mutation with a normal ventricular function and no evidence for ventricular arrhythmias can be reassured, but due to the possibility of progression of the disease, it means these persons with such mutations require regular and detailed reassessment for markers of arrhythmic risk (5,10).

Our study was designed to identify risk factors to predict MVA. Because of the high incidence of MVA in this specific population, it seems justified to implant an ICD in high-risk persons (5,10,25). Nevertheless, this study cannot provide direct evidence regarding the efficacy of ICD implantation and the additional effect on survival.

In addition, the need for early use of best medical therapy to prevent or retard progressive ventricular function is suggested by the very high rate of heart failure and transplantation, even in those with an ICD. However, further research needs to be done to define the best medical therapy.

**Study limitations.** There are important limitations to this study that need to be taken into account. Most important, the cohort was obtained from 8 academic referral centers and that may have resulted in a referral bias toward more severely affected persons. Because of the study design, it is possible that there is a selection bias and there are missing data that can introduce an overestimation from the influence of the risk factors. After imputation of missing values, the influences of the risk factors were comparable. Another important limitation as result of the study design is the uncertainty regarding the endpoint MVA. Not all the cardiopulmonary resuscitations and sudden cardiac deaths are well documented, which could potentially lead to an overestimation regarding the diagnosis MVA.

**Conclusions**

This large cohort study of LMNA mutation carriers confirms the suspected high risk of malignant arrhythmias and identifies 4 risk factors that facilitate identification of the patients at the highest risk of having MVA.

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**REFERENCES**


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