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Location of *LMNA* Variants and Clinical Outcomes in Cardiomyopathy

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IMPORTANCE Prior studies have suggested that patients with nonmissense (ie, truncating) variants causing *LMNA* cardiomyopathy have worse arrhythmic outcomes compared to those with missense variants. However, the effect of the spatial distribution of missense and truncating variants on clinical outcomes remains poorly understood.

OBJECTIVE To determine the association of the spatial distribution of missense and truncating *LMNA* variants with cardiac outcomes.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, retrospective, observational cohort study used data from an international registry (from January 2013 on) and data derived from tertiary cardiomyopathy centers (January 2000 and June 2017). Patients with likely pathogenic/pathogenic *LMNA* variants and no prior malignant ventricular arrhythmia (VA) were eligible for inclusion. Data analysis was completed from March 2022 to March 2025.

MAIN OUTCOMES AND MEASURES The primary outcome of time to VA was defined as sudden cardiac death, appropriate implantable cardioverter-defibrillator therapy, or other manifestations of hemodynamically unstable VA. The secondary composite outcome of advanced heart failure was defined as nonsudden cardiac death, implantation of a left ventricular assist device, or cardiac transplant. Outcomes were stratified by type of variant (missense or truncating), affected transcript position (head, rod, or tail), and location on the *LMNA* gene.

RESULTS A total of 718 patients were included, among whom mean (SD) age was 41.1 (14.3) years, 381 patients (53.1%) were female, and mean (SD) baseline left ventricular ejection fraction was 55.8% (13.3%). Over a median follow-up of 4.2 years, 223 patients experienced the primary outcome of malignant VA and 109 experienced the secondary outcome of advanced heart failure. Patients with truncating variants had a higher risk of VA (hazard ratio [HR], 1.72; 95% CI, 1.19-2.48; $P = .004$) but no difference in advanced heart failure (HR, 0.94; 95% CI, 0.64-1.40; $P = .77$) compared with patients with missense variants. There were no significant differences in the primary and secondary outcomes when stratifying truncating variants by location on the *LMNA* gene or transcript position. In contrast, on multivariable analysis, missense variants affecting the tail domain of *LMNA* (HR, 0.35; 95% CI, 0.16-0.78; $P = .02$) and located in exons 7 through 12 (HR, 0.39; 95% CI, 0.17-0.89; $P = .035$) were associated with a significantly lower risk of the primary outcome of malignant VA.

CONCLUSIONS AND RELEVANCE In this retrospective cohort study, truncating LMNA variants were associated with worse arrhythmic outcomes independent of variant position, whereas missense variants affecting the tail domain and located in exons 7 through 12 had better arrhythmic and heart failure outcomes. Understanding the mechanisms underlying these differences may have future therapeutic implications.

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Supplemental content

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Pathogenic variants in the *LMNA* gene result in a wide spectrum of clinical disorders, including cardiomyopathy, driven by the ubiquitous nuclear, cytoskeletal, and signal transduction functions of lamin A/C as intermediate filament proteins. Of these, cardiac manifestations frequently drive adverse clinical outcomes due to their often-severe phenotype, including conduction system disease, malignant ventricular arrhythmias (VAs), and heart failure.[1-3]

Nonmissense (hereafter referred to as truncating) variants, including nonsense, intronic, insertion, and deletion variants, account for 28% to 45% of disease-causing variants in published *LMNA* cardiomyopathy registries.[4-6] Compared with missense variants, truncating variants have been associated with VA, prompting their incorporation into risk stratification guidelines for primary prevention of sudden cardiac death (SCD).[7,8] In contrast, pathogenic missense variants have been shown to cluster in exons encoding the head or rod regions of the transcribed protein.[9] These variants have been associated with more severe cardiac and skeletal expression compared with those encoding for the tail region, suggesting a different pathologic mechanism to truncating variants.[10,11] However, cardiac outcomes relative to the spatial distribution of missense and truncating variants on the *LMNA* gene have not been well described.

The aim of this study is to characterize the clinical features and outcomes of patients with *LMNA* cardiomyopathy using a large, multinational clinical registry, stratified by type of missense or truncating variants, location on the *LMNA* gene, and encoding amino acid position on the *LMNA* transcript. We hypothesize that all truncating variants subject to nonsense-mediated messenger RNA (mRNA) decay, regardless of their location in the *LMNA* gene, have similar clinical outcomes with respect to malignant VA given their inferred loss-of-function consequence. Conversely, we hypothesize that the location of missense variants significantly influences clinical outcomes.

Key Points

Question What is the association of the spatial distribution of missense and truncating *LMNA* variants with cardiac outcomes?

Findings In this multicenter cohort study that included 718 patients with *LMNA* cardiomyopathy, variants affecting the *LMNA* tail domain had a lower risk of malignant ventricular arrhythmias and incident end-stage heart failure. Truncating variants had worse arrhythmic outcomes; however, their location was not associated with outcomes.

Meaning While the location of missense *LMNA* variants is relevant, the location of truncating variants does not appear to be associated with cardiac outcomes; overall, the effect and location of *LMNA* variants can provide hypothesis-generating findings for future precision therapeutics.

Methods

Study Population

The study population included all patients enrolled in the French nationwide registry on laminopathies (NCT03058185) since January 2013, as well as consecutive patients referred between January 2000 and June 2017 to the tertiary cardiology centers of Saint Bartholomew's Hospital in London, United Kingdom; Brigham and Women's Hospital in Boston, Massachusetts; University Hospital in Bern, Switzerland; the University Medical Centre in Leiden, the Netherlands; and the Royal Melbourne Hospital and University of Melbourne, in Melbourne, Australia. Data from this sample have been partially analyzed in the past.[4]

This study complies with the ethical principles formulated in the Declaration of Helsinki and was approved by the ethics committees in France (Les Comités de Protection des Personnes Ile de France VI, Paris, France) and at Brigham and

Table 1. Baseline Characteristics of Patient Population

Parameter at baseline	No./total No. (%)			*P* value
	Missense variants (n = 475)	Truncating variants (n = 243)	Total (N = 718)	
Sex, No. (%)				
Female	261 (54.9)	120 (49.4)	381 (53.1)	.16
Male	214 (45.1)	123 (50.6)	337 (46.9)	
Age, mean (SD), y	41.7 (14.8)	39.9 (13.0)	41.1 (14.3)	.19
Probands/families	206/475 (56.6)	87/241 (36.1)	292/718 (40.7)	.05
Asymptomatic	62/344 (18.0)	34/159 (21.4)	96/505 (19.0)	.41
Neuromuscular involvement				
None	332/475 (69.9)	169/241 (70.1)	503/718 (70.1)	<.001
EDMD	66/475 (13.9)	14/241 (5.8)	80/716 (11.2)	
LGMD	48/475 (10.1)	45/241 (18.7)	93/716 (13.0)	
Others	29/475 (6.1)	13/241 (5.4)	42/716 (5.9)	
1st-Degree AV block	165/368 (44.8)	130/197 (66.0)	295/565 (52.2)	<.001
LVEF at baseline, mean (SD), %	56.0 (13.8)	55.3 (12.4)	55.8 (13.3)	.24
Atrial arrhythmias	119/470 (25.3)	93/242 (38.4)	212/712 (29.8)	<.001
2nd-/3rd-Degree AV block	40/473 (8.5)	42/241 (17.9)	82/714 (11.5)	<.001
Nonsustained VT	52/405 (12.8)	43/221 (19.5)	95/626 (15.2)	.03

Abbreviations: AV, atrioventricular; EDMD, Emery-Dreifuss muscular dystrophy; LGMD, limb-girdle muscular dystrophy; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia.

Table 2. Baseline Characteristics of Missense Variants Stratified by Position of Encoded Amino Acid

Parameter at baseline	No./total No. (%)		*P* value
	Missense and domain 2 (rod) (n = 310)[a]	Missense and domain 3 (tail) (n = 165)[a]	
Sex, No. (%)			
Female	149 (48.1)	112 (67.9)	<.001
Male	161 (51.9)	53 (32.1)	
Age, mean (SD), y	41.9 (14.4)	41.2 (15.7)	.499
Probands/families	117/310 (37.7)	89/165 (53.9)	<.001
Asymptomatic	45/198 (22.7)	17/146 (11.6)	.008
Neuromuscular involvement			
None	216/310 (69.7)	116/165 (70.3)	.006
EDMD	37/310 (11.9)	29/165 (17.6)	
LGMD	41/310 (13.2)	7/165 (4.2)	
Others	16/310 (5.2)	13/165 (7.9)	
1st-Degree AV block at baseline	135/237 (57.0)	30/131 (22.9)	<.001
LVEF at baseline, mean (SD), %	54.2 (14.4)	59.8 (11.6)	<.001
Atrial arrhythmias	98/305 (32.1)	21/165 (12.7)	<.001
2nd-/3rd-Degree AV block	33/308 (10.7)	7/165 (4.2)	.02
Nonsustained VT	42/268 (15.7)	10/137 (7.3)	.02

Abbreviations: AV, atrioventricular; EDMD, Emery-Dreifuss muscular dystrophy; LGMD, limb-girdle muscular dystrophy; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia.

[a] Rod domain: p.28-381; tail domain: p.382-664.

Women's Hospital (US), which granted waivers of participant consent. The ethics committee at Barts Hospital (UK) was informed, although it did not request formal approval under the local research governance arrangements.

Patients 16 years of age and older at time of first cardiac evaluation were included, with the first documented visit to a cardiologist taken as the starting point of the time-to-event analysis. Those with a likely pathogenic/pathogenic variant in *LMNA*, as per current American College of Medical Genetics and Genomics criteria, were included. A full list of variants is included in eTable 1 in Supplement 1. Patients with a personal history of malignant VA at or before the initial evaluation, a congenital or childhood-onset laminopathy (eg, progeria, Werner syndrome, or congenital muscular dystrophy), a pathogenic variant in a cardiomyopathy-related gene besides the *LMNA* variant, or missing clinical data were excluded from this analysis.

In this analysis, all variants that involved a change in a single nucleotide that led to a change in amino acid to another without resulting in a premature termination codon (PTC) were classified as missense variants. All other nonmissense variants, including single-nucleotide variants that resulted in a PTC, in-frame and frameshifting insertions and deletions, and all intronic variants with proven RNA consequences, were classified as truncating variants.

Study Outcome

The primary end point of this study was time to malignant VA, defined as (1) SCD; (2) appropriate implantable cardioverter-defibrillator (ICD) therapy, defined as a shock or antitachycardia pacing to terminate VA; or (3) other manifestations of hemodynamically unstable VA. Death was classified as sudden if it occurred unexpectedly (1) within 1 hour of onset of cardiac manifestations, in the absence of previous hemodynamic deterioration; (2) during sleep; or (3) within 24 hours after the patient was last seen alive and apparently stable clinically.

The predefined secondary outcome was advanced heart failure, as determined by a composite of nonsudden cardiac death, implantation of a left ventricular assist device, or cardiac transplant. Patients were first stratified by the type of variant (missense vs truncating) and then stratified by the affected amino acid position encoded by the variant on the *LMNA* transcript, divided into 3 domains: head (p.1-27), rod (p.28-381) and tail (p.382-664).[12] Of note, no missense variants affecting the head region were present in this registry. As an additional sensitivity analysis, patients were also stratified by the location of variants on the *LMNA* gene by dividing the gene into 4 comparably spaced quartiles based on the distribution of the total number of variants throughout the gene in the study population: quartile 1 was exons 1-2 c.-212-513; quartile 2 was exons 3-5 c.514-936; quartile 3 was exon 6 c.937-1157; and quartile 4 was exons 7-12 c.1158-1969. A full list of variants is provided in eTable 1 in Supplement 1.

Statistical Analysis

Normally distributed data are displayed as mean and standard deviation or median and interquartile range. Continuous variables were compared using independent-sample *t* tests where normally distributed and Mann-Whitney *U* tests where non-normally distributed. Where multiple groups were present, analysis of variance and Kruskal-Wallis tests were used to compare normally and non-normally distributed continuous data, respectively. Categorical variables were compared using χ^2 or Fisher exact test.

Time-to-event analysis for the primary and secondary outcomes was performed using the Kaplan-Meier method. Patients who had experienced the primary or secondary outcome at baseline were excluded from survival analyses. Univariable and multivariable predictors of the primary and

Figure 1. Schematic Diagram of *LMNA* Gene, Encoding Transcript and Final Lamin A/C Proteins

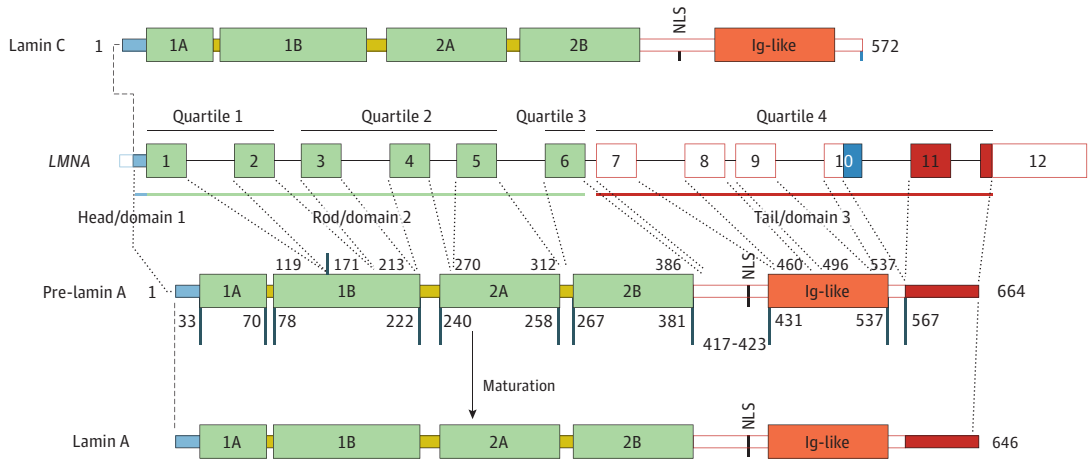


Diagram of the *LMNA* gene with exons numbered within boxes and corresponding transcript regions in blue (head), green (rod), and orange (tail). Numbers along the pre–lamin A transcript indicate amino acid positions, with the total number of amino acids indicated on the right-hand side. Ig indicates immunoglobulin; NLS, nuclear localization signal.

secondary outcomes were analyzed using the Fine-Gray model, where all variables with $P > .20$ in the univariable analysis were included for the multivariable analysis. All tests were 2-sided, with significance at $P < .05$. All statistical analysis was performed using SAS version 9.4 (SAS Institute).

Results

A total of 721 patients were identified from registry databases, with 718 patients with available variant data included in this study. Mean (SD) patient age was 41.1 (14.3) years, 381 patients (53.1%) were female, and mean (SD) baseline left ventricular ejection fraction (LVEF) was 55.8% (13.3%). Of these 718 patients, 475 (66.2%) had a missense variant. A total of 293 patients (40.8%) were probands, with the remaining 425 patients (59.2%) being relatives identified through cascade testing. Of the included patients, 2 families with more than 5 patients per family were included. These included 15 relatives with a c.16C>T; p.(Gln6*) truncating variant and 27 relatives with a c.28dup; p.(Thr10Asnfs*31) truncating variant. Patients were followed up over a median period of 4.2 years.

Missense vs Truncating Variants

Differences in baseline characteristics between patients with missense and truncating variants are shown in **Table 1**. Of the 505 patients with complete baseline characteristic data available at the time of study inclusion, 96 (19.0%) were asymptomatic, with no evidence of cardiac phenotype, including LVEF greater than 55%. Neuromuscular involvement was present in 215 patients (29.9%). Sex, age at first clinical contact, and LVEF were not significantly different. However, the prevalence of second- or third-degree atrioventricular (AV) block (17.9% vs 8.5%; $P < .001$), atrial arrhythmias (38.4% vs 25.3%; $P < .001$) and nonsustained ventricular tachycardia (VT) at baseline (19.5% vs 12.8%; $P = .03$) were all significantly higher in patients with truncating variants.

Association of the Spatial Distribution of Variants With Baseline Phenotype

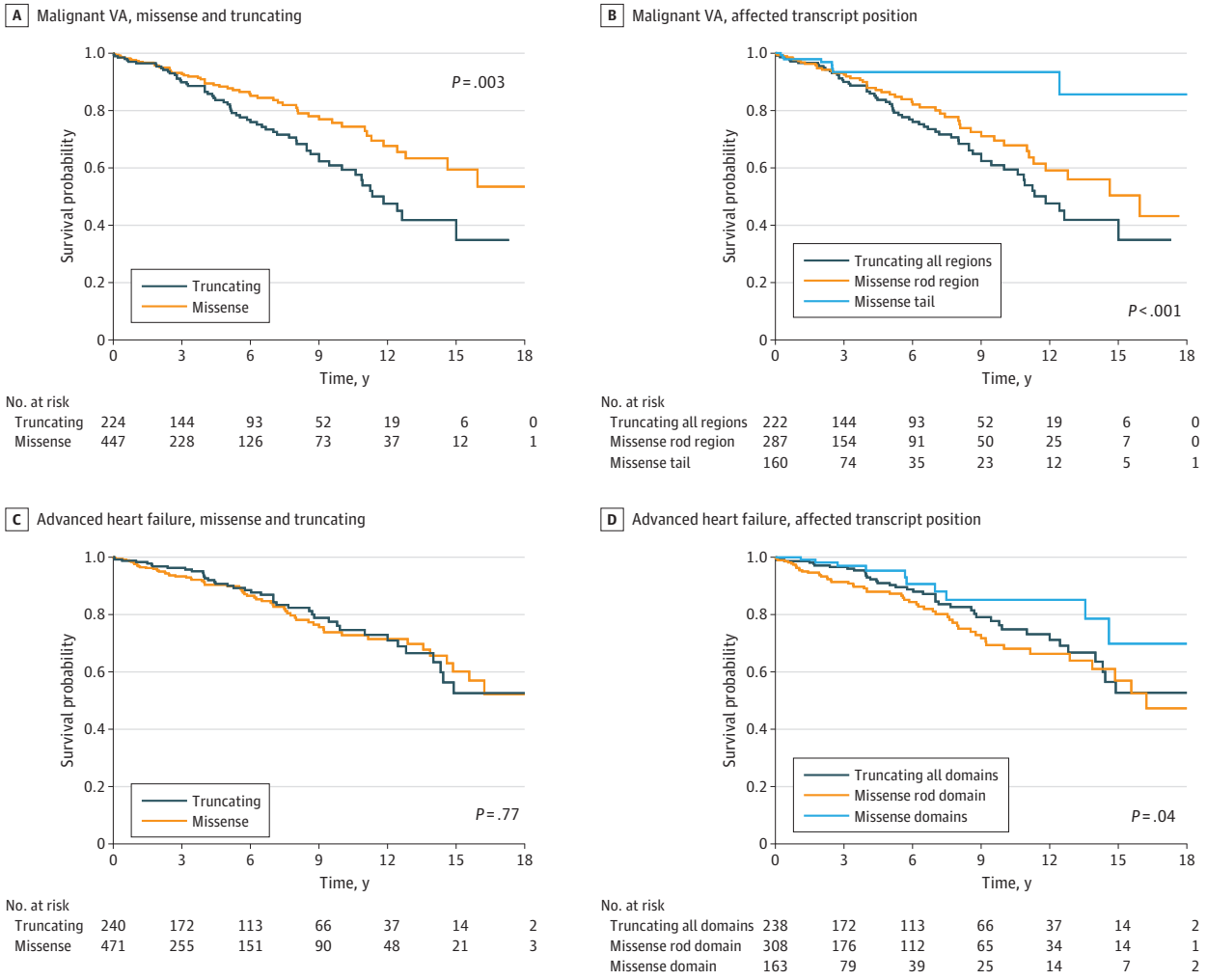
In patients with truncating variants, the only significant difference in baseline characteristics was the prevalence of second- or third-degree AV block when stratified by the affected amino acid transcript position (19.6% in head domain vs 25.0% in rod domain vs 7.8% in tail domain; $P = .006$; eTable 2 in Supplement 1). All other baseline characteristics were not significantly different. This was confirmed when stratifying variants by their position on the *LMNA* gene (eTable 3 in Supplement 1).

When comparing the spatial distribution of missense variants on the *LMNA* transcript, there was a lower prevalence of second- or third-degree AV block (4.2% vs 10.7%; $P = .02$), atrial arrhythmias (12.7% vs 32.1%; $P < .001$), and nonsustained VT (7.3% vs 15.7%; $P = .02$), as well as higher mean (SD) LVEF (59.8% [11.6%] vs 54.2% [14.1%]; $P < .001$), with variants affecting the tail domain compared with the rod domain (**Table 2**). This was also seen in more distally located missense variants in the *LMNA* gene (**Figure 1**; eTable 4 in Supplement 1). Of note, 68 patients (44.4%) with tail domain missense variants involved the R482 hot spot associated with familial partial lipodystrophy 2.[13]

Incident Clinical Outcomes

A breakdown of the primary and secondary outcomes is listed in eTable 5 in Supplement 1, and a breakdown of the number of cases excluded from outcomes analysis by variant position is listed in eTable 6 in Supplement 1. The primary outcome of malignant VA was significantly worse in patients with truncating variants (hazard ratio [HR], 1.72; 95% CI, 1.19-2.48; $P = .004$; **Figure 2**A). There were no significant differences in VA outcomes when stratifying truncating variants by the affected transcript position ($P = .18$, eFigure 1A in

Figure 2. Survival Curves of the Primary and Secondary Outcomes



Survival curves for the primary and secondary outcomes (malignant VA and advanced heart failure, respectively) stratified by missense vs truncating (A and C) and affected transcript position on *LMNA* (B and D). Head domain: p.1-27; rod domain: p.28-381; and tail domain: p.382-664. VA indicates ventricular arrhythmia.

Supplement 1) or their location on the *LMNA* gene (P = .18; eFigure 1B in Supplement 1). In contrast, missense variants affecting the tail domain (HR, 0.36; 95% CI, 0.17-0.76; P = .007; Figure 2B) and located in the distal aspect of the *LMNA* gene (HR, 0.37; 95% CI, 0.18-0.79; P = .01; eFigure 1C in Supplement 1) had significantly better VA outcomes. The annual event rate was lowest in patients with missense variants affecting the tail domain (1.27 per 100 person-years), followed by missense variants affecting the rod domain (3.59 per 100 person-years) and truncating variants affecting any domain (4.95 per 100 person-years; eTable 7 in Supplement 1).

The secondary outcome of advanced heart failure was not significantly different between patients with missense and truncating variants (HR, 0.94; 95% CI, 0.64-1.40; P = .77; Figure 2C). There were no significant differences in incident advanced heart failure when stratifying truncating variants by their position on the transcript (eFigure 2A in Supplement 1) or location on the *LMNA* gene (eFigure 2B in Supplement 1). However, missense variants affecting the tail domain (HR, 0.44; 95% CI, 0.22-0.85; P = .006; Figure 2D) and located in the distal aspect of the *LMNA* gene (HR, 0.35; 95% CI, 0.17-0.74; P = .006; eFigure 2C in Supplement 1) had significantly less advanced heart failure.

Predictors of Clinical Outcomes

Univariable analysis for predictors of the primary and secondary outcomes for patients with truncating variants are displayed in eTable 8 in Supplement 1. Neither the affected transcript position nor the location of truncating variants on the *LMNA* gene were associated with either outcome.

Univariable analysis for predictors of the primary and secondary outcomes for patients with missense variants are displayed in eTable 8 in Supplement 1. Patients with missense variants affecting the tail domain of *LMNA* were associated with a lower risk of VA (HR, 0.36; 95% CI, 0.17-0.76; P = .007) and advanced heart failure (HR, 0.44; 95% CI, 0.22-0.85; P = .02)

Table 3. Multivariable Analysis of Predictors of Primary Outcome[a]

Variable	Rod or tail domain		Missense by quartiles	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.002 (0.990-1.020)	.84	1.002 (0.990-1.020)	.84
Sex, male	1.676 (1.150-2.440)	.007	1.678 (1.160-2.450)	.02
LVEF, %	0.973 (0.960-0.990)	.002	0.973 (0.960-0.990)	.001
1st-/3rd-Degree AV block	1.606 (1.050-2.450)	.03	1.564 (1.050-2.440)	.03
NSVT	1.656 (1.040-2.640)	.03	1.649 (1.040-2.620)	.03
Variant by transcript position				
Missense rod domain vs truncating (all domains)[b]	0.717 (0.480-1.070)	.03	NA	NA
Missense tail domain vs truncating (all domains)[b]	0.349 (0.160-0.780)		NA	
Variant by location on gene				
Missense quartiles 1-3 vs truncating quartiles 1-4[b]	NA	NA	0.692 (0.460-1.030)	.03
Missense quartile 4 vs truncating quartiles 1-4[b]	NA	NA	0.392 (0.170-0.890)	

Abbreviations: AV, atrioventricular; HR, hazard ratio; LVEF, left ventricular ejection fraction; NA, not applicable; NSVT, nonsustained ventricular tachycardia.

[a] Primary outcome defined as time to malignant ventricular arrhythmia, composed of sudden cardiac death, appropriate implantable cardioverter-defibrillator therapy (shock and antitachycardia pacing), and hemodynamically unstable sustained ventricular arrhythmia.

[b] Quartile 1: exons 1-2 c.-212-513; quartile 2: exons 3-5 c.514-936; quartile 3: exon 6 c.937-1157; and quartile 4: exons 7-12 c.1158-1969. Head domain: p.1-27; rod domain: p.28-381; and tail domain: p.382-664.

compared to the rod domain. This was also seen in missense variants that were located more distally in the *LMNA* gene (eTable 9 in Supplement 1).

On multivariable analysis, the affected transcript position and variant location on the *LMNA* gene were both significant predictors of the primary outcome of malignant VA (**Table 3**). Missense variants affecting the tail domain (HR, 0.35; 95% CI, 0.16-0.78; *P* = .02) and located distally in the *LMNA* gene (HR, 0.39; 95% CI, 0.17-0.89; *P* = .04) had a significantly lower risk of VA.

Discussion

In this cohort study, we report the association between the effect and location of variants and clinical outcomes using a large multinational cohort of *LMNA* cardiomyopathies. We found that patients with truncating *LMNA* variants had worse VA outcomes irrespective of their spatial distribution. However, the location of missense variants was highly relevant, as variants affecting the tail domain and located in exons 7 to 12 had a lower baseline prevalence of systolic dysfunction, arrhythmias, and conduction disease, as well as a lower risk of incident VA and advanced heart failure.

Previous studies have demonstrated consistently poorer outcomes in patients with nonmissense (truncating) variants, with a malignant VA risk almost 4-fold higher than with missense variants.[4-6] Given the frequent initiation of nonsense-mediated mRNA decay, it has been hypothesized that many truncating variants, especially those leading to frameshift, are pathogenic due to haploinsufficiency and give rise to a uniformly severe phenotype. Our clinical study favors this hypothesis by showing that neither the affected transcript position of a truncating variant nor its location on the *LMNA* gene were associated with arrhythmic or heart failure outcomes in the studied registries. These clinical findings further strengthen the hypothesis of allelic loss-of-function haploinsufficiency in truncating variants seen in preclinical murine and human induced pluripotent stem cell-based models.[14-17]

We demonstrate better VA outcomes in patients with missense variants affecting the tail domain of *LMNA*. In fact, more than one-third of patients with missense variants in our study involved the tail domain, with no sudden deaths on follow-up and a primary outcome event rate of 1.27 per 100 person-years. This VA incidence is lower than those of prior primary prevention ICD studies, including the DANISH substudy control group (1.8 per 100 person-years; aged ≤70 years; mean LVEF, 25%) and the Ontario ICD database (3.6 per 100 person-years; LVEF ≤35%; 22% nonischemic cardiomyopathy).[18,19] This raises the possibility of engaging these patients in a shared decision-making process rather than a more prescriptive recommendation for primary preventive ICD implantation.

Similarly, we demonstrate better heart failure outcomes in patients with missense variants affecting the tail domain of *LMNA*. By pooling cohorts from multiple international referral centers, we have overcome the limited statistical power of prior studies that failed to show these differences in the past.[6] In fact, it was only by incorporating the spatial distribution of missense variants that these differences in incident advanced heart failure could be identified. Indeed, missense variants affecting the rod domain had similarly poor heart failure outcomes to truncating variants, highlighting a subgroup that may benefit from closer monitoring, aggressive medical therapy, and earlier consideration for transplant.

By using more clinically translatable time-to-event outcome data, this study's findings augment the results of prior studies, which have stratified variant position relative to the nuclear localization signal (*LMNA* residues 415-423) and demonstrated less cardiac involvement and phenotype severity with variants affecting the tail domain.[10,11,20] Two hypotheses for this observation are (1) the critical pathomechanistic role of the highly conserved rod domain, which is vital for coiled-coil and heptad interactions that give rise to structurally robust dimers and protein function[21,22]; and (2) the potential compensatory role of intact lamin C expression in the absence of functional lamin A, as demonstrated in a murine model.[23] Notably, the *LMNA* gene encodes both the lamin A and lamin C proteins due to alternative splicing that affects only the tail domain. Variants in the *LMNA* gene 3′ of the alterna-

tive untranslated region following exon 10 affect the regions (exons 11-12) encoding for lamin A only, leaving lamin C fully intact and functional. Our findings may also be partially explained by the high prevalence (44%) of missense tail domain variants affecting the R482 hot spot, which has been associated with a less severe cardiac phenotype compared with other tail domain variants.[24] Regardless, we still observed advanced heart failure events in 6% of patients with missense variants affecting the tail domain, including 4 advanced heart failure events in R482 variants, highlighting the variability in clinical disease expression likely due to a combination of factors, such as variant-specific effects, multigenic contributors, and environmental influences.

Limitations

Our data are retrospective and derived from large, international clinical registries. While completeness of baseline characteristic data may not parallel that of prospective studies, there was minimal loss of clinical outcomes data (<1%) in our study. Our findings are limited to patients 16 years of age and older. Extrapolation of these results to patients younger than 16 years should be performed with caution. Additionally, although we were able to assemble a large cohort, specific regions of *LMNA* were underrepresented for variants, which limits the resolution of our analyses. We chose to analyze gene regions both by quartile and protein domain as a tractable approach, since smaller domain analyses or variant-specific analyses would be infeasible without a substantially larger cohort. Finally, we included ICD therapies in our primary outcome, similar to prior studies investigating SCD risk in inherited cardiomyopathies, despite our awareness that ICD therapies many not consistently equate to SCD.

Conclusions

In conclusion, truncating variants in *LMNA* are associated with worse arrhythmic outcomes independent of variant position. In contrast, missense variants affecting the tail domain and located in exons 7 to 12 had better arrhythmic and heart failure outcomes.

ARTICLE INFORMATION

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