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LMNA Variants and Risk of Adult-Onset Cardiac Disease

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Abstract

Background: Genetic variants in *LMNA* may cause cardiac disease but population-level contributions of variants to cardiac disease burden are not well-characterized.

Objectives: We sought to determine the frequency and contribution of rare *LMNA* variants to cardiomyopathy and arrhythmia risk among ambulatory adults.

Methods: We included 185,900 UK Biobank participants with whole-exome sequencing. We annotated rare loss-of-function and missense *LMNA* variants for functional effect using 30 *in silico* prediction tools. We assigned a predicted functional effect weight to each variant and calculated a score for each carrier. We tested associations between the *LMNA* score and arrhythmia (atrial fibrillation, bradyarrhythmia, ventricular arrhythmia) or cardiomyopathy

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outcomes (dilated cardiomyopathy and heart failure). We also examined associations for variants located upstream versus downstream of the nuclear localization signal (NLS).

Results: Overall, 1,167(0.63%) participants carried a *LMNA* variant and 15,079(8.11%) had an arrhythmia or cardiomyopathy event during a median follow-up of 10.9 years. The *LMNA* score was associated with arrhythmia or cardiomyopathy (odds ratio [OR]=2.21, P<0.001) and the association was more significant when restricting to variants upstream of the NLS (OR=5.05, P<0.001). The incidence rate of arrhythmia or cardiomyopathy was 8.43 per 1000 person-years (95%CI, 6.73–10.12) among *LMNA* variant carriers and 6.38 (95%CI, 6.27–6.50) among non-carriers. Only 3(1.2%) of the variants were reported as pathogenic in ClinVar.

Conclusions: Middle-aged adult carriers of rare missense or loss-of-function *LMNA* variants are at increased risk for arrhythmia and cardiomyopathy.

Condensed Abstract:

Genetic variants in *LMNA* may cause cardiac disease. We tested the population-level contribution of rare missense or loss-of-function variants in *LMNA* to cardiac disease in ambulatory adults from the UK Biobank. We observed that a score for *LMNA* variants informed by their predicted functional effect was significantly associated with arrhythmias and cardiomyopathy. Despite the complex pleiotropic nature of *LMNA*, the rod domain upstream of the nuclear localization signal independently associated with arrhythmia and cardiomyopathy, underscoring the clinical relevance of this region. Middle-aged adult carriers of rare missense or loss-of-function *LMNA* variants are at increased risk for arrhythmia and cardiomyopathy.

Keywords

LMNA; missense; loss-of-function; atrial fibrillation; heart failure; population-based genetics

INTRODUCTION

The *LMNA* gene encodes A-type nuclear lamins that are expressed in differentiated somatic cells. Lamins A/C provide structural support to the nucleus, mediate chromatin organization, and gene expression, among other functions (1–4). Due to the pleiotropic nature of lamins A/C, dysfunctional variants in the gene cause a heterogenous group of disorders that are collectively referred to as laminopathies (5). In particular, rare genetic variants in *LMNA* are known to cause dilated cardiomyopathy in isolation or concomitant with conduction defects, and in some cases the only presentation is conduction delay, atrial arrhythmia, or ventricular arrhythmia (6). Yet many rare genetic variants in *LMNA* exist in the general population, and their contributions to cardiovascular disease have not been defined. There is a critical need to understand the extent to which unclassified rare missense variants in *LMNA* contribute to cardiac disease in ambulatory adults.

Large-scale genetic sequencing of population-based biobanks has made it possible to interrogate the natural history of genetic variants and how they contribute to disease susceptibility (7–9). Additionally, despite advances in our understanding of variant pathogenicity using publicly aggregated databases of variant assertions such as ClinVar, the pleiotropic nature of such variants may not be accurately reflected using existing assertions

(10,11). We therefore leveraged data from the UK Biobank to examine the contributions of rare loss-of-function and missense *LMNA* variants to arrhythmia and cardiomyopathy susceptibility.

METHODS

Study population

The UK Biobank is a population-based prospective cohort study of 502,629 individuals aged 40–69 living in England, Wales, and Scotland who underwent detailed phenotyping and genetic assessment (12). The UK Biobank resource was approved by the UK Biobank Research Ethics Committee (reference #11/NW/0382) and all participants provided written informed consent to participate. Use of UK Biobank data was performed under application #17488 and approved by the Massachusetts General Brigham Institutional Review Board.

Disease phenotypes

Our analyses focused on a composite outcome of arrhythmias and cardiomyopathies including atrial fibrillation, bradyarrhythmia, ventricular arrhythmia, dilated cardiomyopathy, and heart failure. In addition, we investigated the specific incidence of pacemaker insertion (which was a subset of the bradyarrhythmia outcome), implantable cardioverter defibrillators, and overall mortality. The disease outcomes were defined using reports from medical history interviews, inpatient International Classification of Diseases (ICD)-9 and −10 diagnosis codes, operation codes, and death registry records (Online Table I). For analyses of incident disease, participants with disease evident at the baseline assessment were omitted.

Exome sequencing, data processing, and variant analysis

The current analysis is focused on UK Biobank participants who underwent whole exome sequencing and passed internal quality controls (WES, Figure 1). WES was previously performed using the IDT xGen Exome Research Panel v1.0 exome capture panel, targeting 19,396 genes. Sequencing was performed in an initial tranche of 49,884 individuals, and a second tranche of 150,453 individuals. On average, coverage at 95% of sites was over 20X. Detailed description on the genotype and variant quality control methods implemented can be found in the Online material. Analyses were restricted to samples that were high-quality and had no duplicates. Of the 200,643 individuals in the UK Biobank with WES who passed the internal quality-control, we excluded 306 samples that did not pass our additional quality-control, leaving 200,337 individuals for analysis. We additionally restricted our analysis to unrelated individuals (no first, second or third degree relationships), resulting in 185,990 individuals for analysis. Detailed description of the sample level quality control can be found in the Online material.

Predicted functional effect weights and LMNA score

We assigned each variant a predicted functional effect weight based on information from dbNSFP and the Loss-of-Function Transcript Effect Estimator (LOFTEE) plug-in implemented in the Variant Effect Predictor (VEP) (13,14). Only variants with a MAF <0.1% (and <0.1% in each major continental population in gnomAD (15)) were included

in the analysis; additional information about the variants included can be found in the online material. Missense variants were annotated utilizing VEP incorporated 30 in-silico prediction tools from the dbNSFP4.1a database (14) including: qualitative prediction algorithms (SIFT, SIFT4G, Polyphen2 HDIV, Polyphen2 HVAR, LRT, MutationTaster, FATHMM, PROVEAN, MetaSVM, MetaLR, MCAP, PrimateAI, DEOGEN2, BayesDel addAF, BayesDel noAF, ClinPred, LIST-S2, fathmm-MKL coding, fathmm-XF coding, MutationAssessor, and Aloft), and quantitative algorithms (VEST4, REVEL, MutPred, MVP, MPC, DANN, CADD, Eigen, and Eigen-PC).

For each variant, we collapsed the information from the 30 prediction tools into a single weighted value. The weighted value represented the proportion of prediction tools that predicted a given variant to be deleterious or not (i.e., each tool could assign either a 1 'deleterious' or 0 'not deleterious'). The *predicted functional effect weight* was the sum of all the prediction annotations divided by the total number of prediction tools included (with a maximum of 30 prediction tools). Missense variant weights ranged from 0 – 1, and loss-of-function variants were assigned a predicted functional effect weight of 1. All variants had a minimum of 11 annotations from the total 30 prediction tools included in the study. An individual's *LMNA* score was the summed product of the predicted functional effect weight by the number of alleles carried by that individual across the number of *LMNA* variants carried.

In addition, we calculated the score both upstream and downstream of the nuclear localization signal (NLS). Variants upstream of the NLS (exons 1–6) have been associated with cardiac and skeletal muscle disorders while downstream variants (exons 7–12) have been associated with partial lipodystrophy and progeria syndrome (16).

Variant pathogenicity assertions

We identified variants submitted to ClinVar from clinical genetic testing laboratories with the most recent assertion after 2015 and downloaded entries from https://ftp.ncbi.nlm.nih.gov/pub/clinvar/ on 11/28/2020. We utilized American College of Medical Genetics (ACMG) variant pathogenicity assertions that were submitted from commercial genetic testing laboratories for further analysis. Pathogenicity categories included "benign", "likely benign", "likely pathogenic", and "pathogenic". Variants classified in ClinVar as "benign/likely benign" or "pathogenic/likely pathogenic" were reclassified into their respective ACMG categories based on the most recent assertion. Variants in ClinVar classified as "conflicting" due to multiple assertions with conflicting interpretations and "variants of uncertain significance" were classified as such. In the final set of missense and loss-of-function variants found in the UK Biobank, there were no variants with the benign or likely benign classification.

Statistical analysis

We assessed associations between the *LMNA* score and the composite arrhythmia or cardiomyopathy outcome, as well as each component individually (atrial fibrillation, bradyarrhythmia, ventricular arrhythmia, dilated cardiomyopathy, and heart failure) using multivariable logistic regression with Firth's penalized likelihood approach. Models were

adjusted for age, sex, hypertension, diabetes mellitus, coronary artery disease, smoking status, sequencing batch, and the first five principal components of ancestry. Sensitivity analyses were performed in a homogenous subset of European ancestry. Additionally, we explored the association with a restricted *LMNA* score that included variants found upstream versus downstream of the NLS fitted using Firth's penalized likelihood approach and adjusted for age, sex, hypertension, diabetes mellitus, coronary artery disease, smoking status, sequencing batch, and the first five principal components of genetic ancestry. We also performed unweighted single variant association tests with the saddle-point approximation test to determine whether individual variants were associated with arrhythmia or cardiomyopathy, adjusting for the same covariates as above; variants with a minor allele count >5 were included (N=66) (17–19).

Using a time-to-event approach, we estimated the relations between the *LMNA* score and the composite outcome of incident arrhythmia or cardiomyopathy by fitting multivariable Cox proportional hazards regression models adjusted for age, sex, hypertension, diabetes mellitus, coronary artery disease, smoking status, sequencing batch, and the first five principal components of genetic ancestry. We further examined associations between the score and each outcome separately, and additionally investigated the relations between the *LMNA* score and incident implantable cardioverter defibrillator insertion, pacemaker insertion, and mortality. We estimated the unadjusted cumulative incidence of outcomes stratified by carrier status using the Kaplan-Meier method and compared risks for carriers and non-carriers using the log-rank method. We calculated the incidence rate per 1,000 person years for each outcome. Person-time for time-to-event models was calculated by taking the difference between the enrollment date and censor date which would be earliest of death, loss to follow-up, an outcome event, or the administrative censoring date (March 31, 2020) in all analyses. Lastly, we determined the association between the ClinVar variant categories and incident arrhythmia or cardiomyopathy using non-carriers as the referent group by fitting a multivariable Cox proportional hazards regression model with adjustment for the same covariates as above. If participants carried more than one variant, we classified them using the following hierarchy: pathogenic/likely pathogenic > conflicting interpretation > variants of uncertain significance > not in reported in ClinVar.

For regression models involving the *LMNA* score, effect estimates were expressed per 1-unit change of the score. P values and 95%-confidence intervals presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible. All statistical analyses were completed using R version 4.0 (packages: 'data.table', 'ggplot2', 'survival', 'survminer', 'base', 'MASS', 'foreign', 'prodlim', 'logistf', 'GENESIS', 'GWASTools', 'dplyr', 'SeqVarTools', 'SeqArray', 'qqman') (20).

RESULTS

Baseline characteristics

Of the 185,990 unrelated UK Biobank participants included, the mean age at enrollment was 57 ± 8 years and 55% were female. Baseline characteristics are described by exposure status in Table 1 and by cardiomyopathy and arrhythmia case status in Online Table 2. We use

the terms “carrier” and “non-carrier” to refer to individuals who are positive and negative, respectively, for a *LMNA* rare variant.

LMNA variant frequency

A total of 1,149 (0.62%) individuals carried one rare *LMNA* variant with a maximum of 2 variants carried by 18 (0.01%) individuals. Overall, 235 missense (n= 1,147 carriers) and 6 loss-of-function (n=20 carriers) variants were identified in the entire cohort with a minor allele frequency of <0.1% (Online Table 3). Most variants were singletons and doubletons, except missense variants rs142191737 (Arg545His) and rs267607563 (Arg399His), which were seen in 125 and 52 participants, respectively. Of the 241 rare *LMNA* variants, 3 (1.2%) had been reported in the ClinVar database as pathogenic (there were 0 likely pathogenic variants), 29 (12.0%) had conflicting interpretations of pathogenicity, and 95 (39.4%) additional variants were of uncertain clinical significance; the remainder 114 (47.3%) had no clinical classification (Online Table 3). On average, each missense variant was scored by 28 of the 30 missense prediction tools utilized. The *LMNA* predicted functional effect weight for the 241 loss-of-function or missense variants was right skewed (median [Q1-Q3]=0.55 [0.38–0.72]). The distribution of the predicted functional effect weights is displayed in Online Table 4. Unweighted single variant associations with arrhythmia or cardiomyopathy are displayed in Online Table 5.

LMNA score association with arrhythmia and cardiomyopathy

In total, 15,079 (8.11%) participants had at least 1 arrhythmia or cardiomyopathy event. Of the 1,167 *LMNA* variant carriers, 132 (11.31%) had at least 1 arrhythmia or cardiomyopathy event. The *LMNA* score was associated with greater odds of the composite outcome of arrhythmia or cardiomyopathy (odds ratio [OR], 2.21 [95% confidence interval [CI], 1.60–3.02], P<0.001; Table 2). Additionally, we found that the *LMNA* score was associated with each disease separately: atrial fibrillation (OR, 1.95 [95% CI, 1.34–2.78], P<0.001), bradyarrhythmia (OR, 2.23 [95% CI, 1.31–3.62], P=0.004), ventricular arrhythmia (OR, 4.01 [95% CI, 1.43–9.30], P=0.01), dilated cardiomyopathy (OR, 4.64 [95% CI, 1.06–13.85], P=0.04), and heart failure (OR, 3.04 [95% CI, 1.84–4.81], P<0.001). When we performed a sensitivity analysis restricted to participants of European ancestry (N=161,853), associations between the *LMNA* score and both the composite outcome, as well as each component outcome, were consistent (Online Table 6).

Variants upstream of the nuclear localization signal are strongly associated with cardiac phenotypes

Next, we sought to determine whether variants localized upstream of the NLS (encoded in exon 7) were associated with cardiac disease compared with variants found downstream. We created a *LMNA* score comprising variants upstream of the NLS and another comprising variants located downstream. The distribution of both scores can be found in Online Table 4. In total 427 (0.23%) individuals carried a rare *LMNA* variant localized upstream of the NLS, of which 67 (15.69%) had an arrhythmia and cardiomyopathy event. We observed a strong association between the upstream *LMNA* score and arrhythmia or cardiomyopathy (OR, 5.12 [95% CI, 3.14–8.17], P<0.001; Table 2). Results were similar after omitting the six loss-of-function variants from the score (Online Table 7). Conversely,

741 (0.40%) individuals carried a rare *LMNA* variant localized downstream of the NLS, of which 65 (8.77%) had an arrhythmia or cardiomyopathy event. No significant association was identified between the downstream *LMNA* score and the composite arrhythmia or cardiomyopathy outcome (Table 2).

Absolute disease risk estimates among LMNA carriers

We estimated the absolute risk of incident arrhythmia or cardiomyopathy among individuals without events at baseline. At a median follow-up of 10.9 years (Q1-Q3: 10.1–11.7), a greater *LMNA* score was consistently associated with greater incidence of arrhythmia or cardiomyopathy (hazard ratio [HR] 1.95, 95% CI, 1.41–2.71, P<0.001) (Table 3). The cumulative risk of events stratified by presence versus absence of an *LMNA* variant is depicted in Figure 2 / Central Illustration, for each cardiac disease in Online Figure 1 and stratified by *LMNA* variants found upstream versus downstream of the NLS in Figure 3. The 10-year cumulative risk of arrhythmia or cardiomyopathy was 7.71% (95% CI, 6.11–9.28) among *LMNA* variant carriers, whereas the cumulative risk among non-carriers was 5.91% (95% CI, 5.80–6.02) (Figure 2 / Central Illustration). The arrhythmia or cardiomyopathy incidence rate among carriers was 8.43 per 1000 person-years (95% CI, 6.73–10.12) compared to 6.38 (95% CI, 6.27–6.50) among non-carriers (Table 4). Carriers of *LMNA* variants without any ClinVar interpretation were associated with an increased risk of incident arrhythmia or cardiomyopathy compared to non-variant carriers (HR 1.71, 95% CI, 1.10–2.64, P=0.02) (Online Table 8). Overall, there were 2,703 incident pacemakers, 414 implantable cardioverter defibrillators, and 10,072 deaths during follow-up. The cumulative risk of events stratified by presence versus absence of a *LMNA* variant is depicted in Online Figure 2. A greater *LMNA* score was significantly associated with pacemaker insertion (HR 2.76, 95% CI, 1.52 – 5.01, $P=8.15\times10^{-4}$) but not incident implantable cardioverter defibrillator status (HR 1.71, 95% CI, 0.28 – 10.37, P=0.56) or mortality (HR 1.41, 95% CI, 0.96 – 2.07, P=0.08; (Online Table 9).

DISCUSSION

In a prospective cohort comprising over 185,000 unrelated middle-aged adults, we observed that rare coding variants in *LMNA* were significantly associated with atrial fibrillation, bradyarrhythmias, ventricular arrhythmias, dilated cardiomyopathy, and heart failure. Most of the variants identified in our sample were missense and with no pathogenic assertion. Our findings suggest that rare coding variants in *LMNA* contribute to cardiac disease susceptibility in the ambulatory middle-aged adults.

Our findings have three major implications. First, adults carrying rare missense variants in *LMNA* developed cardiac disease at higher rates than non-carriers in the UK Biobank, underscoring the important contribution of *LMNA* variation to cardiac disease susceptibility in an ambulatory cohort of middle-aged adults. Atrial fibrillation was the most common cardiac disease among *LMNA* carriers, corroborating prior findings that atrial arrhythmias are common manifestations of *LMNA* variant carriers (6). The lower overall burden of disease among *LMNA* variant carriers in our study may reflect the otherwise healthy composition of the UK Biobank cohort, as compared to prior reports in which individuals

were enrolled on the basis of *LMNA* variant carrier status (6). The present sample represents a unique and large dataset of *LMNA* variant carriers and provides absolute risk estimates for arrhythmia and cardiomyopathy among *LMNA* carriers in the general population.

Second, we identified a stronger association when we restricted the *LMNA* score to variants occurring upstream of the NLS implicating the rod region as critical for cardiac disease development. Our findings are consistent with previous observations; the upstream region primarily associated with a cluster of phenotypes that included cardiac, skeletal muscle and neurological involvement (16). In another study, 78% of dilated cardiomyopathy patients had *LMNA* variants that primarily clustered upstream of the NLS region (21). Provided the pleiotropic nature of the *LMNA* variants, identifying a region that is primarily associated with a particular type of laminopathy, could aid the development of therapeutics that can specifically target this domain. We speculate that variants upstream of the NLS region potentially destabilize the nuclear envelope, although further work will be required to test this hypothesis.

Third, our study demonstrates that despite the lack of existing pathogenicity assertions, many rare missense and loss-of-function variants in *LMNA* likely contribute to cardiac disease risk in middle-aged adults. Furthermore, variants with uncertain significance or conflicting pathogenicity interpretations may be associated with cardiac disease, highlighting a limitation of current variant classification schemes (22). A comprehensive scoring approach accounting for predicted functional impact of a variant might facilitate understanding of the potential contribution of *LMNA* variants to cardiac disease risk. Future refinement of pathogenicity assertions and potential accounting for the number of variants an individual carries is warranted.

This study included middle-aged adult participants of predominantly European ancestry. Hence our findings may not be generalizable to individuals of other ancestral backgrounds or ages, including younger individuals who might have more severe manifestations of *LMNA* variants. We relied on self-report, inpatient diagnostic, and procedural codes to determine diagnoses which may result in misclassification of exposures and outcomes. We did not examine family history of cardiac disease due to limited specificity of the family history information collected in the UK Biobank; future studies with larger pedigrees and detailed clinical information may be informative. We adjusted for hypertension, diabetes mellitus, coronary artery disease, and smoking status. Future analyses examining whether clinical or behavioral factors modify the effects of *LMNA* variants are warranted. We did not adjust for multiplicity which can limit the reproducibility of the inferences drawn from our analysis. Examination of the molecular mechanisms by which LOF and missense variants contribute to adult-onset cardiac disease is warranted.

Conclusions

In conclusion, ambulatory adults with rare missense or loss-of-function *LMNA* variants are at an increased risk for arrhythmia and cardiomyopathy. Predicted functional impact and location of rare genetic variants in *LMNA* are important predictors of variant association with cardiac disease susceptibility. Our findings using a genome-first approach contribute to

the understanding of the impact of *LMNA* variants to cardiac disease in ambulatory adults and may inform clinical variant interpretation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

LMNA	gene-encoding lamin A/C
NLS	nuclear localization signal

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Competency in Medical Knowledge:

Rare missense genetic variations in *LMNA*, a gene integral to nuclear structural integrity, are associated with an array of cardiac arrhythmias and cardiomyopathies such as atrial fibrillation, bradyarrhythmias, ventricular arrhythmias, dilated cardiomyopathy, and heart failure. The absolute risk of arrhythmia or cardiomyopathy is substantially higher when rare missense variants occur upstream of the nuclear localization signal in *LMNA*.

Translational Outlook:

The critical disease susceptibility properties of the rod domain upstream of the nuclear localization signal warrants further study as a potential therapeutic target.

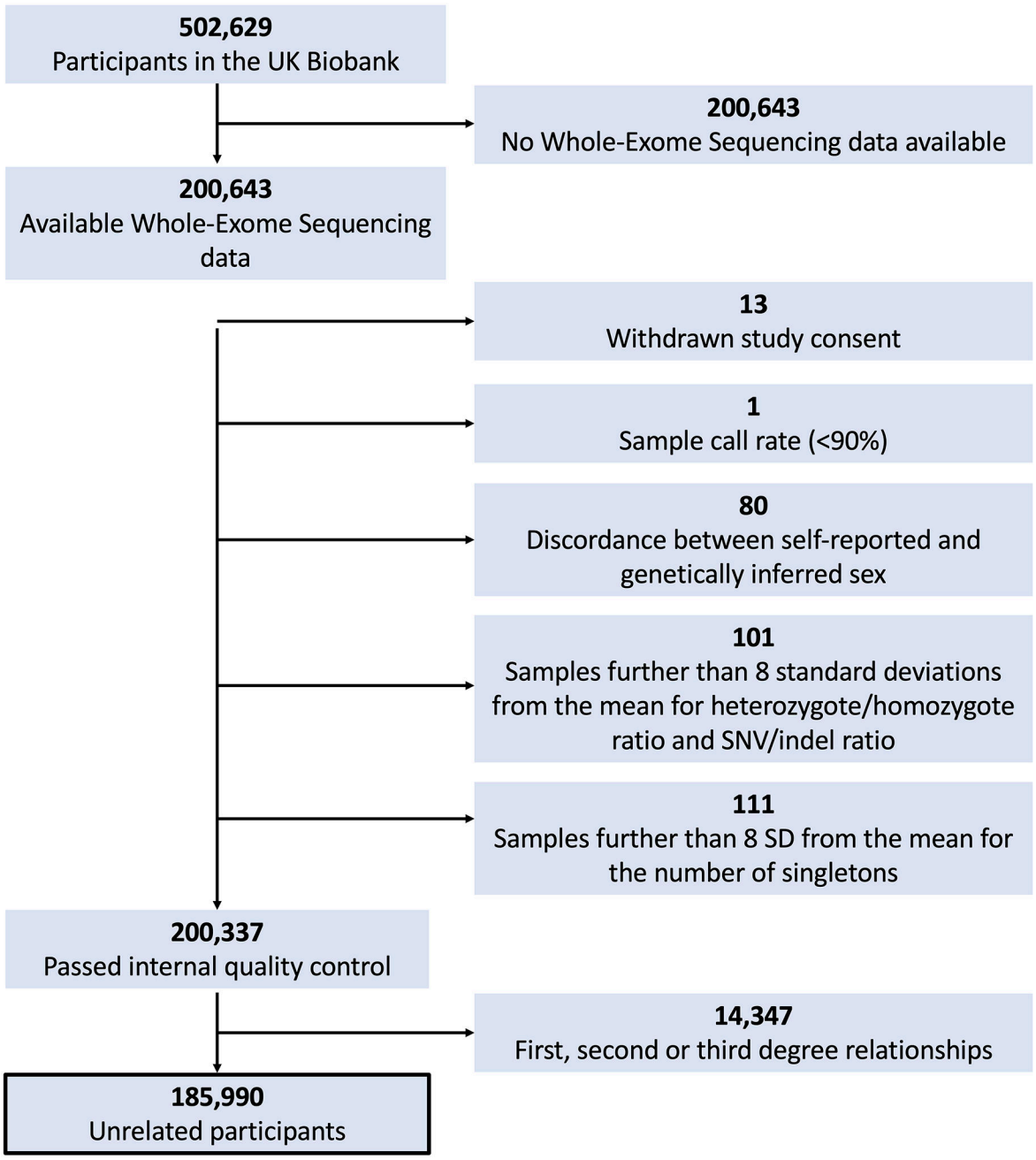

Figure 1. Participant and study flow diagram.

Diagram depicting internal quality control and kinship measures applied to UK Biobank participants with whole-exome sequencing data. The final cohort (N= 185,990) was used to assess associations between *LMNA* variants with cardiovascular outcomes.

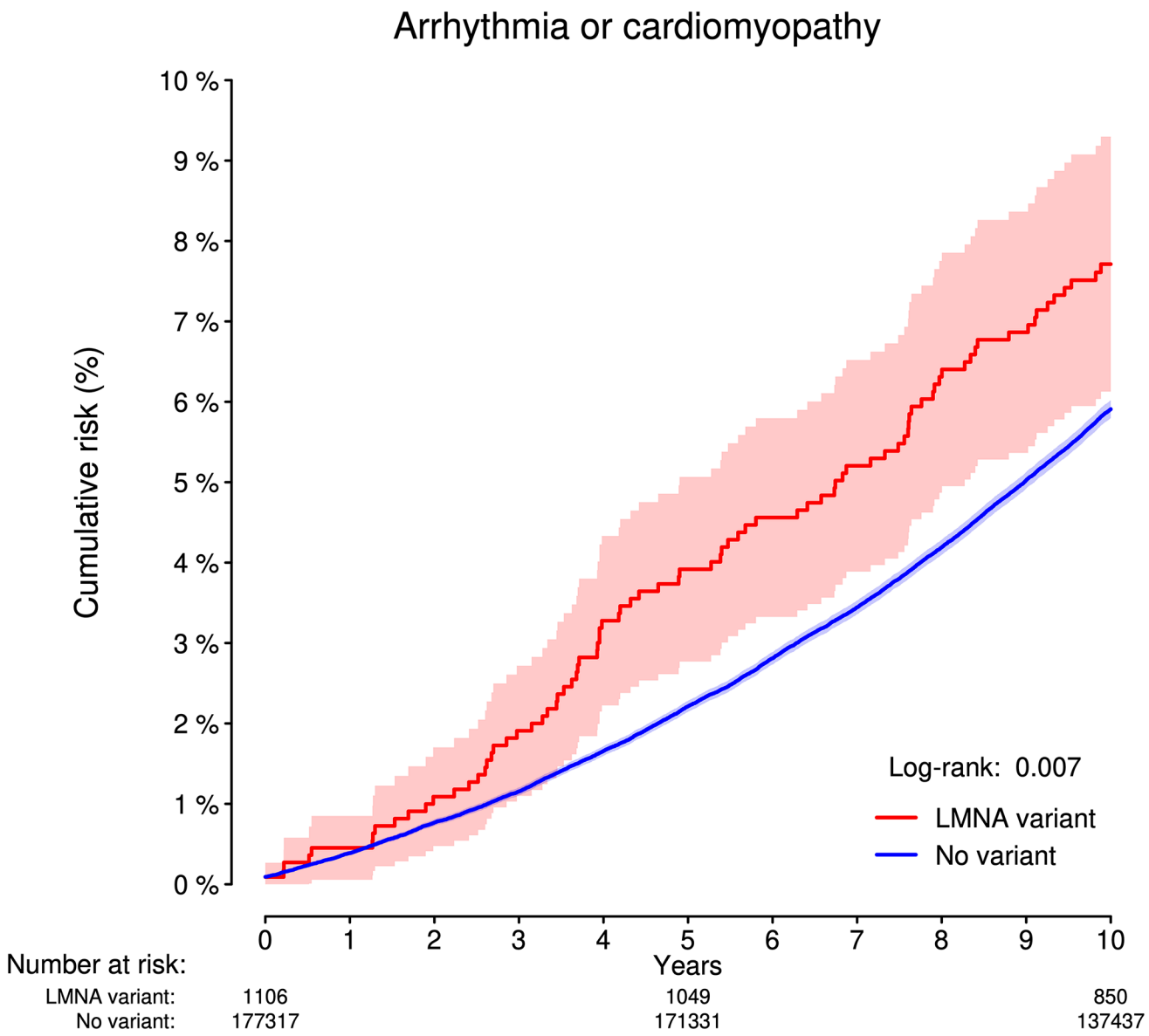

Figure 2 (Central Illustration). Risk of cardiac events by *LMNA* variant carrier status.

The cumulative incidence of arrhythmia and cardiomyopathy events is displayed among participants with and without *LMNA* rare missense or loss-of-function variants. The number at risk within each group over time is depicted below the plot.

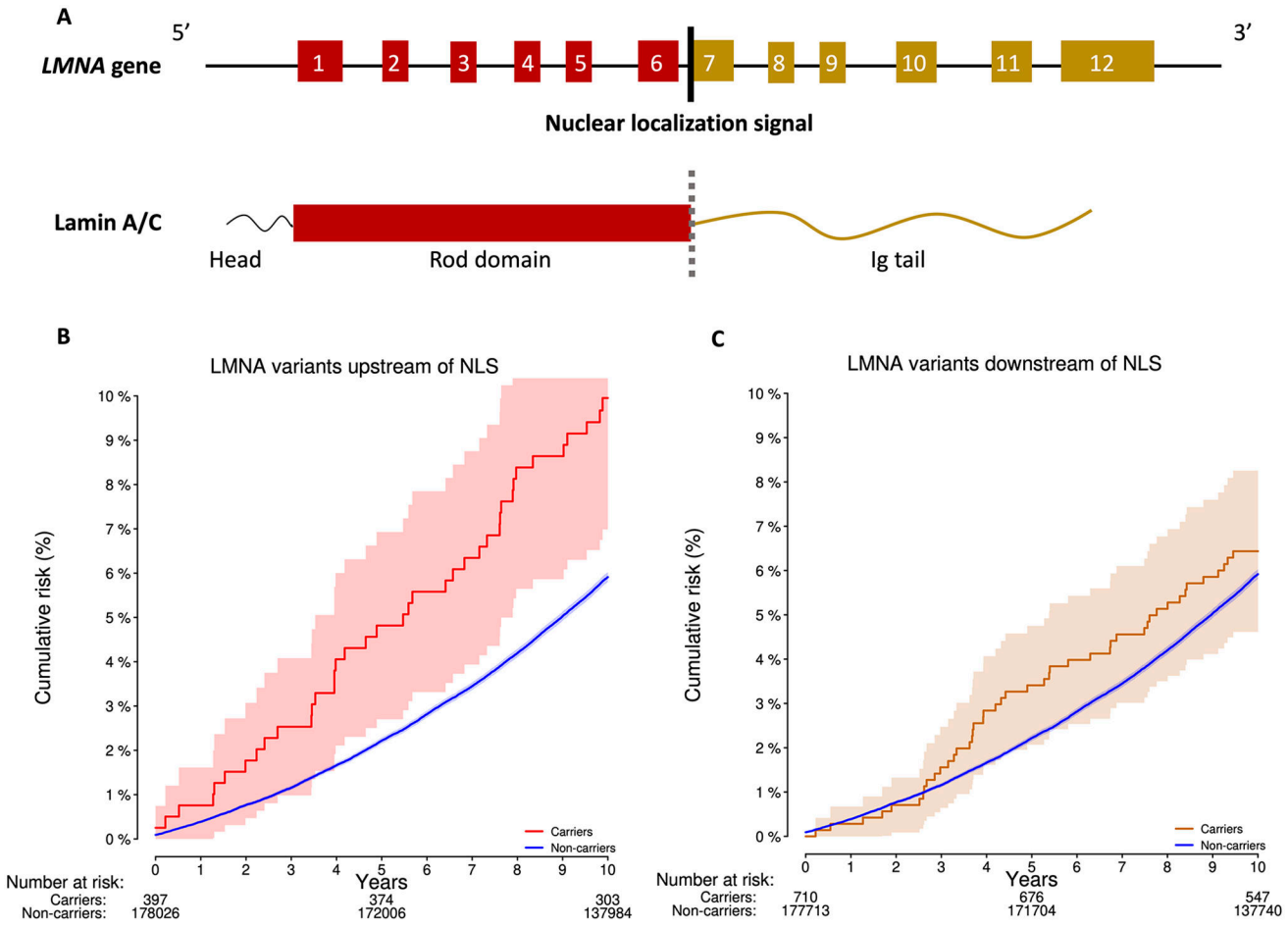

Figure 3. Risk of cardiac events in relation to *LMNA* variant location.

The *LMNA* gene and protein product are illustrated (A) and cumulative incidence curves for arrhythmia and cardiomyopathy events are displayed among participants with and without *LMNA* rare missense or loss-of-function variants upstream (B) and downstream (C) of the nuclear localization signal (NLS). The location of the NLS is depicted in a black horizontal line in the gene and in a dotted horizontal grey line in the protein product. The number at risk within each stratum over time is depicted below each plot.

Table 1.

Clinical characteristics of study samples

Characteristic	*LMNA* Carriers	Non-carriers
N (%)	1167 (0.6)	184823 (99.4)
Female (%)	641 (54.9)	101451 (54.9)
Age at enrollment, years (SD)	56.73 (8.28)	56.95 (8.09)
Age at disease onset (SD)	67.06 (8.35)	67.52 (8.11)
Race/ethnicity *		
White (%)	1072 (91.9)	173424 (93.8)
Asian (%)	36 (3.1)	4647 (2.5)
Black (%)	27 (2.3)	2991 (1.6)
White-Asian admixture (%)	4 (0.3)	324 (0.2)
White-Black admixed (%)	-	308 (0.2)
Unreported (%)	28 (2.4)	3129 (1.7)
Hypertension (%)	417 (35.7)	68481 (37.1)
Diabetes Mellitus, type 2 (%)	90 (7.7)	13462 (7.3)
Coronary artery disease (%)	53 (4.5)	9296 (5)
Smoking status		
Current (%)	102 (8.8)	17767 (9.7)
Previous (%)	402 (34.6)	64074 (34.8)
Never (%)	659 (56.7)	102038 (55.5)

* UKBB specific categorization of ancestry.

Abbreviation: SD, standard deviation.

Table 2:

Association between the *LMNA* score (split by variant location) and arrhythmia or cardiomyopathy disease

Phenotype	Cases	LMNA Variants	OR (95% CI)	P value ‡
Arrhythmia or cardiomyopathy †	15079	Entire gene	2.21 (1.60 – 3.02)	<0.001
		Upstream of NLS	5.12 (3.14 – 8.17)	<0.001
		Downstream of NLS	1.32 (0.84 – 2.00)	0.22
Atrial fibrillation	11366	Entire gene	1.95 (1.34 – 2.78)	<0.001
		Upstream of NLS	4.55 (2.62 – 7.63)	<0.001
		Downstream of NLS	1.14 (0.68 – 1.85)	0.61
Bradyarrhythmia	4680	Entire gene	2.23 (1.31 – 3.62)	0.004
		Upstream of NLS	5.85 (2.80 −11.24)	<0.001
		Downstream of NLS	1.13 (0.50 – 2.26)	0.75
Ventricular arrhythmia	933	Entire gene	4.01 (1.43 – 9.30)	0.01
		Upstream of NLS	7.44 (1.43 −25.14)	0.02
		Downstream of NLS	3.17 (0.82 – 9.04)	0.09
Dilated cardiomyopathy	359	Entire gene	4.64 (1.06 – 13.85)	0.04
		Upstream of NLS	17.24 (3.43 – 56.45)	0.002
		Downstream of NLS	1.13 (0.03 – 8.05)	0.92
Heart failure	4929	Entire gene	3.04 (1.84 – 4.81)	<0.001
		Upstream of NLS	6.28 (2.95 – 12.28)	<0.001
		Downstream of NLS	1.99 (1.01 – 3.65)	0.05

† Data presented as: atrial fibrillation, bradyarrhythmia, ventricular arrhythmia, dilated cardiomyopathy, and heart failure.

‡ No corrections for multiple testing were applied.

Abbreviation: NLS, nuclear localization signal, OR, odds ratio; CI, confidence interval.

Total variants included in the entire gene= 241, upstream of NLS= 112, and downstream of NLS= 129.

Table 3.

Association between *LMNA* score and incident disease

Phenotype	N at risk	Events	HR (95% CI)	P value ‡
Arrhythmia or cardiomyopathy †	178,423	11830	1.95 (1.41 – 2.71)	<0.001
Atrial fibrillation	182,915	8291	1.48 (0.97 – 2.26)	0.06
Bradyarrhythmia	185,380	4070	2.04 (1.20 – 3.47)	0.008
Ventricular arrhythmia	185,865	808	4.48 (1.78 – 11.26)	0.001
Dilated cardiomyopathy	181,588	275	3.79 (0.81 – 17.82)	0.09
Heart failure	185,056	4029	2.98 (1.83 – 4.84)	<0.001

† Data presented as: atrial fibrillation, bradyarrhythmia, ventricular arrhythmia, dilated cardiomyopathy, and heart failure.

‡ No corrections for multiple testing were applied.

Abbreviation: N, number; HR, hazard ratio; CI, confidence interval.

Table 4.

Incidence rate per 1000 person-years stratified by *LMNA* carrier status and incident disease

Group	Carrier status	Number of events	Person-time	Incidence rate (95% CI)
Arrhythmia or cardiomyopathy[†]	*Non-carriers*	11,735	1,838,124	6.38 (6.27 – 6.50)
	LMNA carriers	95	11,272	8.43 (6.73 – 10.12)
Atrial fibrillation	*Non-carriers*	8,233	1,954,405	4.21 (4.12 – 4.30)
	LMNA carriers	58	12,061	4.81 (3.57 – 6.05)
Bradyarrhythmia	*Non-carriers*	4033	2,010,037	2.01 (1.94 – 2.07)
	LMNA carriers	37	12,583	2.94 (1.99 – 3.89)
Ventricular arrhythmia	*Non-carriers*	796	2,029,653	0.39 (0.36 – 0.42)
	LMNA carriers	12	12,763	0.94 (0.41 – 1.47)
Dilated cardiomyopathy	*Non-carriers*	271	1,922,460	0.14 (0.12 – 0.16)
	LMNA carriers	4	12,173	0.33 (0.01 – 0.65)
Heart failure	*Non-carriers*	3,987	2,004,345	1.99 (1.93 – 2.05)
	LMNA carriers	42	12,469	3.37 (2.35 – 4.39)

[†]Data presented as: atrial fibrillation, bradyarrhythmia, ventricular arrhythmia, dilated cardiomyopathy, and heart failure.

Abbreviation: CI, confidence interval.