Supplementary Online Content

Akhtar MM, Lorenzini M, Pavlou M, et al; European Genetic Cardiomyopathies Initiative Investigators. Association of left ventricular systolic dysfunction among carriers of truncating variants in filamin C with frequent ventricular arrhythmia and end-stage heart failure. Published online May 12, 2021. *JAMA Cardiol*. doi:10.1001/jamacardio.2021.1106

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Supplementary Definitions

***Abnormal T-wave inversion*:** T-wave inversion on the electrocardiogram (ECG) beyond leads III, aVR or V_1.

Aborted SCD: Successful advanced life support resuscitation with emergent direct current (DC) cardioversion for a cardiac arrest or haemodynamically unstable ventricular tachycardia (VT).

Anti-tachycardia pacing (ATP): Pacing via an implanted ICD for the termination of ventricular tachycardia. The ICD devices were programmed as per local institutional policy in the respective specialist tertiary cardiomyopathy units and no specific 'cut-off' threshold rate was recorded.

Appropriate Implantable Cardioverter Defibrillator (ICD) Shock: Appropriate DC shock via an implanted transvenous or subcutaneous ICD for the successful termination of ventricular tachycardia or ventricular fibrillation. The ICD devices were programmed as per local institutional policy in the respective specialist tertiary cardiomyopathy units and no specific 'cut-off' threshold rate was recorded.

Arrhythmogenic cardiomyopathy: Presence of myocardial changes and phenotype that fulfils a definite diagnosis for arrhythmogenic right ventricular cardiomyopathy (ARVC) based on international recommended criteria. [1]

***Atrial tachyarrhythmias*:** Presence of atrial fibrillation (AF), atrial flutter (AFL) or atrial tachycardia (AT) that is paroxysmal, persistent or permanent in nature.

***FLNC Variant Classification*:** FLNCtv were defined as nonsense, frameshift or canonical splice-site variants. that introduce a premature stop codon, large deletions involving one or more exons in *FLNC*, or canonical splice-site variants predicted to alter gene splicing. Six software packages (MaxENT, HSF, NNSplice, SSF, GeneSplicer and dbscSNV) were used to predict the impact of splice-site variants.[2-5] Only variants for which the splice-site predictor software were unanimously predictive of pathogenicity were included. Variants were classified as pathogenic or 'likely-pathogenic' based on ACMG (American College of Medical Genetics and Genomics) guidelines. Pathogenic variants were those that have been described or published as pathogenic in previous publications associated with *FLNC* and DCM or AC. 'Likely pathogenic' variants were unpublished loss of function variants (nonsense, frameshift and canonical splice-site variants) in *FLNC* and a MAF < $1x10^{-4}$. All centres are specialist tertiary cardiomyopathy units managing all types of inherited cardiovascular diseases. Individuals recruited were consecutive and were routinely genetically tested with a next-generation sequencing DCM panel or whole-exome panel and identified to harbour pathogenic or likely pathogenic variants in *FLNC*. The presence of an additional co-inherited pathogenic or likely pathogenic variant in another DCM-causing gene resulted in exclusion from this cohort to minimise the risk of compound-hit mutation bias. The minimum NGS gene panel probands would have been tested for was 96 genes.

Frequent ventricular ectopy (VE): VE burden of ≥500/24 hours on Holter monitoring [6].

***Left ventricular dilatation*:** An absolute left ventricular end-diastolic dimension (LVEDD) >55mm on TTE or absolute LV end-diastolic volume (LVEDV) >214mls in males or >178mls in females on CMR [7].

Left Ventricular Systolic Dysfunction (LVSD): LVEF <50% on TTE or CMR. Mild to moderate and severe LVSD were defined as LVEF values of 36-49% and ≤35% respectively.

Mild non-diagnostic phenotype: Presence of a minor cardiac abnormality suggestive of gene expression on clinical evaluation [AF, abnormal T-wave inversion on ECG, isolated LV dilatation, NSVT, frequent VE or late gadolinium enhancement (LGE)] in patients without LVSD and not meeting diagnostic criteria for AC.

Non-Sustained Ventricular Tachycardia (NSVT): defined as 3 or more consecutive ventricular beats at a rate of ≥120bpm for <30 seconds.

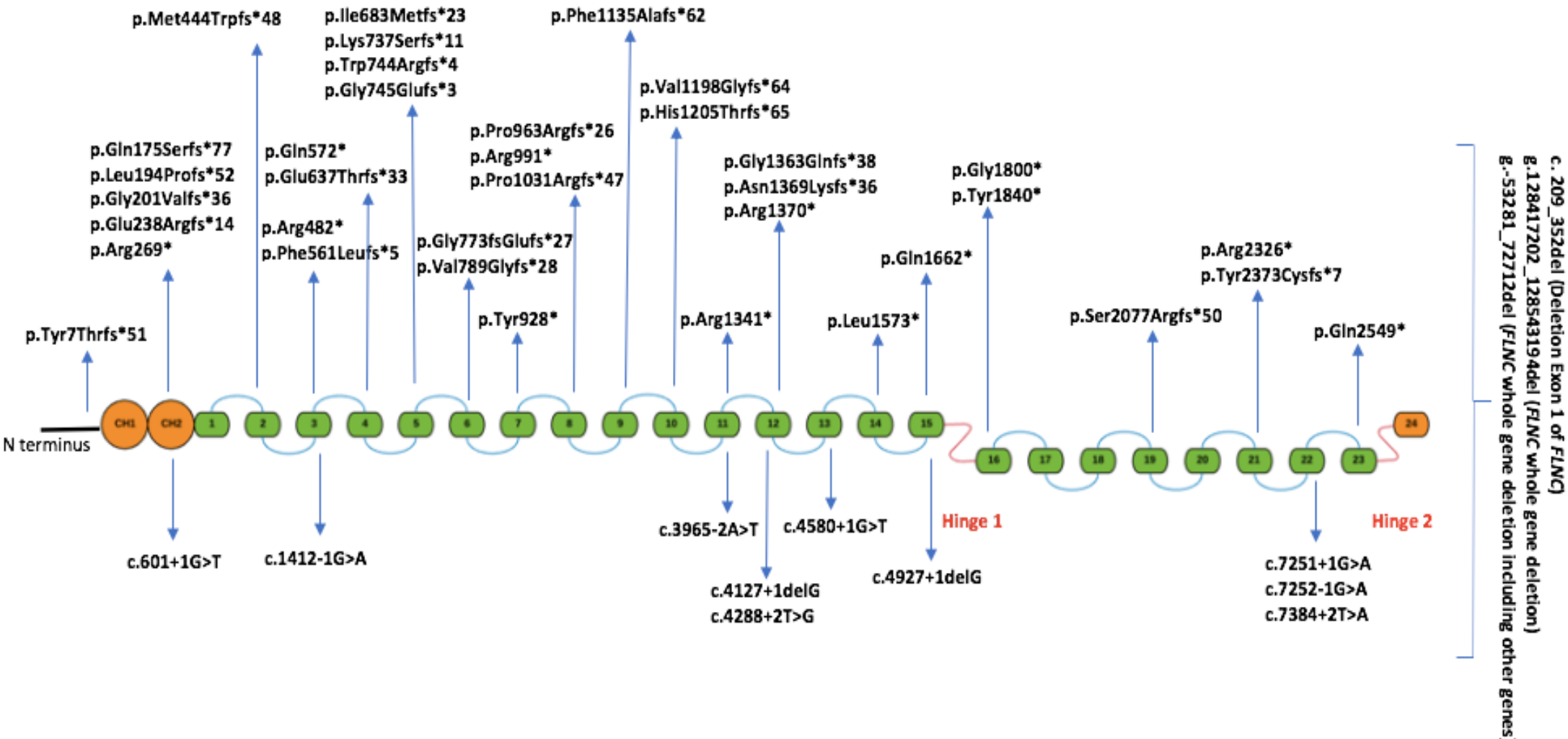
Probands: The index patient at participating institutions with a FLNCtv and left ventricular ejection fraction (LVEF) <50% or unexplained left ventricular dilatation, irrespective of the presence of a family history (FH) of SCD or DCM. Importantly, where the sole patient from a family incorporated into the cohort was phenotype negative (asymptomatic mutation carrier) due to identification of FLNCtv on molecular autopsy on a deceased relative or due to a familial history of DCM and FLNCtv identified in another non-participating centre, they were not coded as probands but as asymptomatic relatives (explaining the presence of 55 probands from 61 families).

Sudden Cardiac Death (SCD): Witnessed sudden unexplained death with or without documented ventricular fibrillation (VF), nocturnal death without worsening of symptoms or death within 1 hour of acute symptoms.

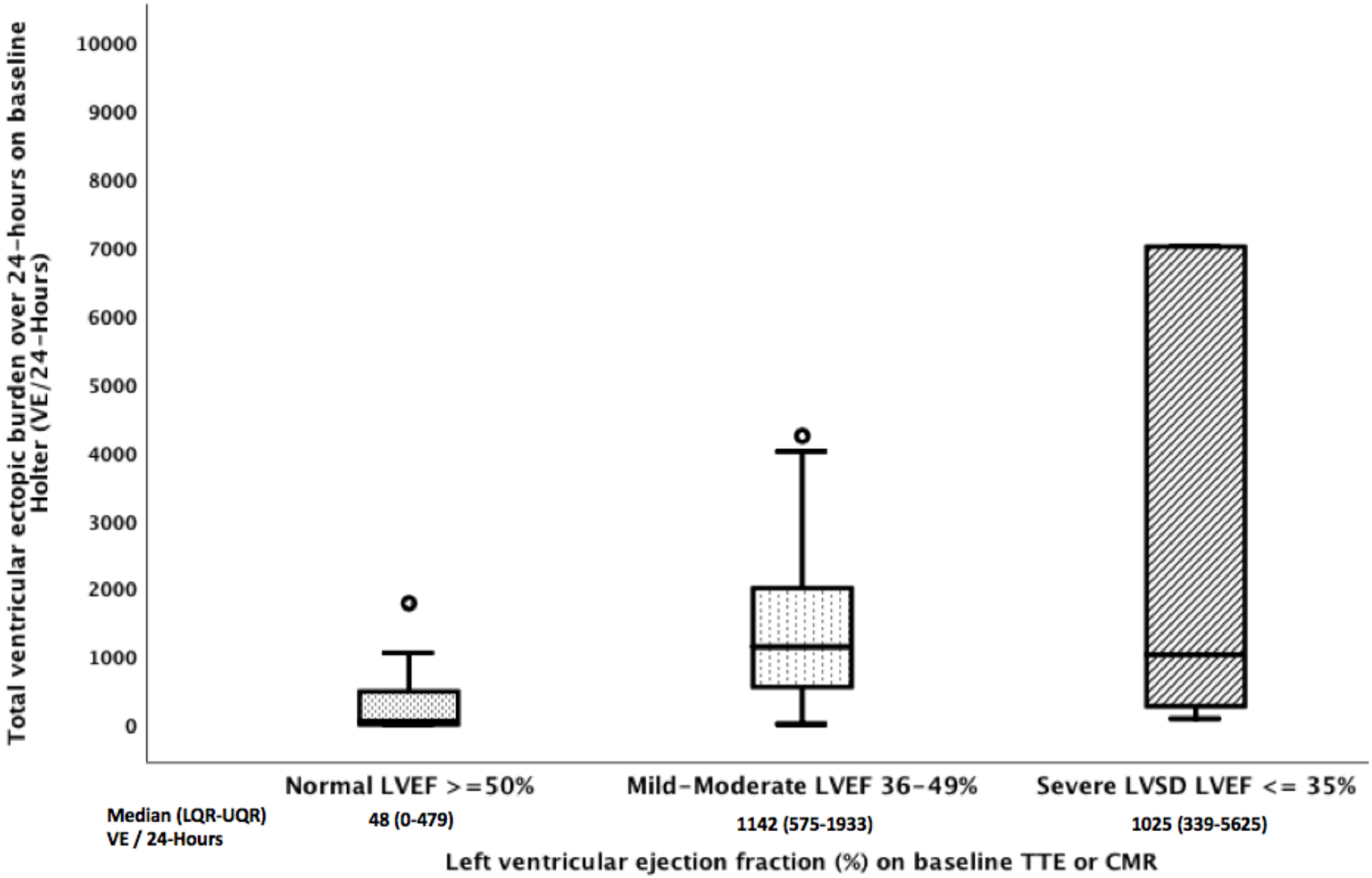
TTNtv *(Truncating variants in the TTN gene):* Nonsense or frameshift mutations that introduce a premature stop codon, or canonical splice-site variants predicted to alter gene splicing in *TTN*. Pathogenic TTNtv were defined as novel or rare [minor allele frequency (MAF) < 0.01% in control populations using gnomAD browser] variants located in constitutively-expressed exons (including *TTN* isoforms N2B and N2BA) with a percentage splice index (PSI) >90% and previously published to be associated with dilated cardiomyopathy. Likely-pathogenic TTNtv were defined as novel or rare variants located in constitutively-expressed exons but not previously published. TTNtv that were located in a non-constitutively expressed exon (PSI<90%) and/or only affected the N2B or N2BA isoform of *TTN*, were classified as variants of unknown significance (VUS) and not included in the cohort. Patients with TTNtv were recruited from the same centres and were incorporated in a previous publication on the clinical phenotypes of patients with TTNtv [8].

eFigure 1. Structure of Filamin C

The location of the variants affecting exonic regions (nonsense and frameshift) as well as canonical splice-site variants are displayed. Three large deletions were identified, one resulting in deletion of exon 1 of *FLNC* and the other two causing whole gene deletion in *FLNC*. Amino acid positions were annotated using www.uniprot.org/uniprot/Q14315.

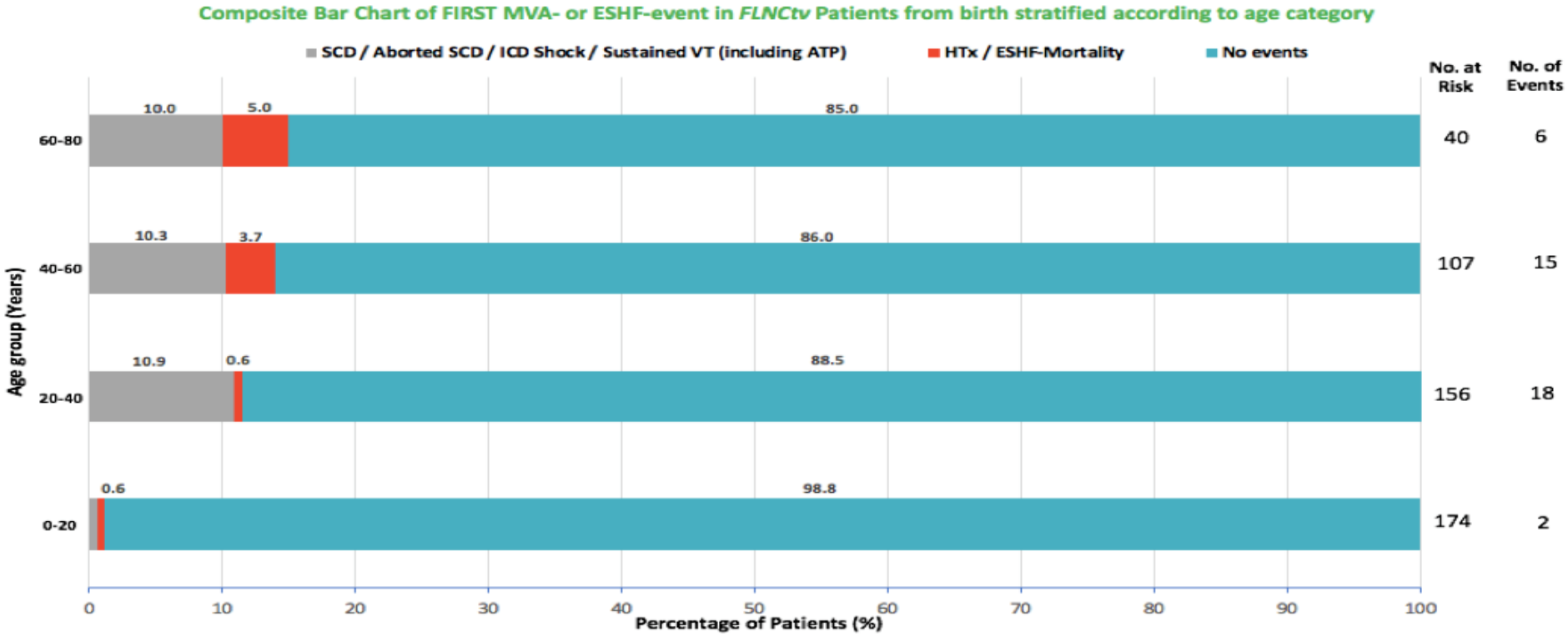


eFigure 2. Box-Plot Demonstrating the VE-Burden /24 Hours on Baseline Holter Assessment
Stratified according to baseline LVEF category (p=0.001).



eFigure 3. Bar Chart Demonstrating the Spectrum of First MVA or ESHF End Point From Birth in the Entire Cohort of 174 *FLNCtv* Carriers for Different Age Groups

Includes 167 patients with baseline and longitudinal data and 7 without baseline data due to presentation with SCD or surrogate). This chart demonstrates that it is rare for adverse events to occur before the age of 20 years. However, the frequency of SCD is approximately 10% between the ages of 20-80 years with an increasing incidence of ESHF-events over the age of 40 years. There were 3 patients in this cohort with *FLNCtv* between the ages of 80-100 years in whom one had an ESHF event (not displayed on bar chart.



eTable 1. List of Mutations in *FLNC* Incorporated into the Cohort and Predicted to Result in Protein Truncation

***FLNC* Mutation** NP_001449.3	**gnomAD MAF**	**DNA change** NM_001458.4	**ClinVar Accession number**	**Predicted Impact**
p.Tyr7Thr fs*51	Absent			Frameshift mutation stopgain
p.Gln175Serfs*77	Absent			Frameshift mutation stopgain
p.Leu194Profs*52 #	Absent			Frameshift mutation stopgain
p.Gly201Valfs*36 #	Absent			Frameshift mutation stopgain
p. Glu238Arg fs*14	Absent			Frameshift mutation stopgain
p.Arg269* #	4.005×10^{-6}	c.805C>T	VCV000539411	Nonsense mutation
p.Met444Trpfs*48	Absent			Frameshift mutation stopgain
p.Arg482*	Absent	c.1444C>T	VCV000517207	Nonsense mutation
p.Phe561Leufs*5	Absent			Frameshift mutation stopgain
p.Gln572* #	Absent			Nonsense mutation
p.Glu637Thrfs*33	Absent			Frameshift mutation stopgain
p.Ile683Metfs*23	Absent			Frameshift mutation stopgain
p.Lys737Serfs*11 #	Absent			Frameshift mutation stopgain
p.Trp744Argfs*4	Absent			Frameshift mutation stopgain
p.Gly745Glufs*3	4.069×10^{-6}			Frameshift mutation stopgain
p.Gly773fsGlufs*27	Absent			Frameshift mutation stopgain
p.Val789Glyfs*28	Absent			Frameshift mutation stopgain
p.Tyr928*	Absent			Nonsense mutation
p.Pro963Argfs*26 #	Absent			Frameshift mutation stopgain
***FLNC* Mutation** NP_001449.3	**gnomAD MAF**	**DNA change** NM_001458.4	**ClinVar Accession number**	**Predicted Impact**

p.Arg991* #	Absent	c.2971C>T	VCV000267288.2	Nonsense mutation
p.Pro1031Argfs*47	Absent			Frameshift mutation stopgain
p.Phe1135Alafs*62 #	Absent			Frameshift mutation stopgain
p.Val1198Glyfs*64	Absent			Frameshift mutation stopgain
p.His1205Thrfs*65	Absent			Frameshift mutation stopgain
p.Arg1341*	Absent	c.4021C>T	VCV000620373	Nonsense mutation
p.Gly1363Glnfs*38	Absent			Frameshift mutation stopgain
p.Asn1369Lysfs*36 #	Absent			Frameshift mutation stopgain
p.Arg1370*	Absent	c.4108C>T	VCV000842060	Nonsense mutation
p.Leu1573*	Absent			Nonsense mutation
p.Gln1662*	Absent	c.4984C>T	VCV000852214	Nonsense mutation
p.Gly1800* #	Absent			Nonsense mutation
p.Tyr1840*	Absent			Nonsense mutation
p.Ser2077Argfs*50 #	Absent			Frameshift mutation stopgain
p.Arg2326* #	$4.11x10^{-6}$	c.6976C>T	VCV000478129	Nonsense mutation
p.Tyr2373Cysfs*7	Absent			Frameshift mutation stopgain
p. Gln2549*	Absent			Nonsense mutation
c.209_352del	Absent			Deletion Exon 1 of *FLNC*
g.128417202_128543194del	Absent			Whole *FLNC* Gene Deletion
g.-53281_72712del	Absent			Whole *FLNC* Gene Deletion including *CCDC136*, *ATP6V1F* and *KCP* genes

List of mutations in *FLNC* incorporated into the cohort and predicted to result in protein truncation. Minor Allele Frequency (MAF) in genome Aggregation Database (gnomAD) is noted for the different variants as well as DNA change and ClinVar accession number for variants on ClinVar. This table includes nonsense and frameshift mutations as well as large deletions affecting one or more exons of *FLNC*. Absent MAF depicts absence in the gnomAD database. Pathogenic variants have been previously published and have a (#) next to the mutation.

eTable 2. List of splice Site Mutations in *FLNC* Identified

The variants were incorporated into the cohort as they were predicted to affect gene splicing by all applicable splice-site prediction software. Minor Allele Frequency (MAF) in genome Aggregation Database (gnomAD) and the predicted impact of splice-site mutation on protein truncation via different prediction software including MaxEnt, HSF, NNSplice, SSF, GeneSplicer and dbscSNV are reported. Adaboost and Random Forest scores range from 0 to 1, with a higher value increasing the likelihood the mutation results in aberrant splicing. Variant NM_001458.4 (FLNC):c.7251+1G>A has ClinVar accession number VCV000539340.1. The remainder splice-site variants are not reported on ClinVar and do not have an accession number.

**Pathogenic (previously published) *Likely-Pathogenic (meets ACMG criteria but not published)

Variant	gnomAD MAF	MaxEnt	HSF	NNSplice	SSF	GeneSplicer	dbscSNV		PREDICTORS	FINAL SPLICING CONCLUSION
							Adaboost	Random Forest		
*c.601+1G>T	Absent	YES	YES	YES	YES	YES	1	0.934	(6/6)	SPLICING AFFECTED
*c.1412-1G>A	$4.076x10^{-6}$	YES	YES	YES	YES	YES	1	0.94	(6/6)	SPLICING AFFECTED
**c.3965-2A>T	Absent	YES	YES	YES	YES	YES	1	0.926	(6/6)	SPLICING AFFECTED
**c.4127+1delG	Absent	YES	YES	YES	YES	YES	N/A	N/A	(5/5)	SPLICING AFFECTED
*c.4288+2T>G	Absent	YES	YES	YES	YES	YES	1	0.928	(6/6)	SPLICING AFFECTED
**c.4580+1G>T	Absent	YES	YES	YES	YES	YES	1	0.934	(6/6)	SPLICING AFFECTED
**c.4927+1delG	Absent	YES	YES	YES	YES	YES	N/A	N/A	(5/5)	SPLICING AFFECTED
**c.7251+1G>A	Absent	YES	YES	YES	YES	YES	1	0.944	(6/6)	SPLICING AFFECTED
*c.7252-1G>A	Absent	YES	YES	YES	YES	YES	0.999	0.946	(6/6)	SPLICING AFFECTED
*c.7384+2T>A	$4.092x10^{-6}$	YES	YES	YES	YES	YES	1	0.94	(6/6)	SPLICING AFFECTED

eTable 3. Baseline Demographic and Clinical Data of 167 Genotype-Positive *FLNCtv* Patients With Follow-up Data Stratified According to Proband Status

	Numbers (n) evaluated from cohort	Overall count (%) or Mean ± SD / Median [IQR]	Probands (n=55)	Relatives (n=112)	p-value
Demographics					
Male Sex	167	89 (53.3%)	36 (65.5%)	53 (47.3%)	**0.03**
Caucasian Ethnicity	164	150 (91.5%)	47 (90.4%)	103 (92.0%)	0.80
Baseline Clinical Evaluation					
Mean age (years)	167	43.2 ± 18.1	46.2 ± 16.5	41.7 ± 18.8	0.11
Aborted SCD prior to evaluation	167	9 (5.4%)	8 (14.5%)	1 (0.9%)	**0.001**
Dyspnoea:	166	39 (23.5%)	30 (55.6%)	9 (8.0%)	**<0.001**
NYHA Class III-IV		17 (10.2%)	15 (27.8%)	2 (1.8%)	
Chest Pain	165	22 (13.3%)	13 (24.5%)	9 (8.0%)	**0.004**
Syncope	165	11 (6.7%)	5 (9.4%)	6 (5.4%)	0.33
Palpitations	165	36 (21.8%)	21 (39.6%)	15 (13.4%)	**<0.001**
Baseline ECG Evaluation					
ECG Rhythm :	164				0.07
Sinus Rhythm		157 (95.7%)	49 (90.7%)	108 (98.2%)	
AF		6 (3.7%)	4 (7.4%)	2 (1.8%)	
PR Interval (ms)	151	155 ± 28	152 ± 35	156 ± 25	0.62
LBBB QRS Morphology	156	7 (4.5%)	6 (11.5%)	1 (1.0%)	**0.001**
QRS Duration (ms)	155	97 ± 20	107 ± 21	92 ± 17	**0.001**
Low QRS Voltage Limb leads	148	33 (22.3%)	10 (22.2%)	23 (22.3%)	0.99
	Numbers (n) evaluated from cohort	**Overall count (%) or Mean ± SD / Median [IQR]**	**Probands (n=55)**	**Relatives (n=112)**	**p-value**

Baseline Transthoracic Echocardiogram (TTE) Evaluation					
Maximal Wall Thickness (mm)	131	9.5 ± 2.6	9.4 ± 2.0	9.5 ± 2.9	0.99
Left Atrium Size PLAX view (mm)	111	35.8 ± 6.2	37.2 ± 7.6	35.0 ± 5.2	0.11
LV End-Diastolic Diameter (mm)	137	53.5 ± 9.7	60.3 ± 10.2	49.9 ± 7.2	**<0.001**
LV Ejection Fraction (%)	162	50.6 ± 15.2	37.3 ± 12.9	57.2 ± 11.5	**<0.001**
RV TAPSE (mm)	77	21.3 ± 3.7	19.1 ± 3.9	22.6 ± 2.9	**<0.001**
Baseline 24-Hour Holter Evaluation					
NSVT First Holter	104	33 (31.7%)	21 (56.8%)	12 (17.9%)	**<0.001**
VE Burden/24hr - Median [IQR]	64	197 [3-1216]	1496 [377-4163]	72 [0-500]	**<0.001**
Frequent VE (VE ≥ 500/24 hours)	90	36 (40.0%)	19 (67.9%)	17 (27.4%)	**<0.001**
Baseline Cardiac MRI (CMR) Evaluation					
LV End-Diastolic Volume (ml)	71	185 ± 56	222 ± 65	168 ± 43	**0.001**
LV Ejection Fraction (%)	89	50 ± 15	39 ± 16	56 ± 10	**<0.001**
RV Ejection Fraction (%)	66	55 ± 11	48 ± 16	57 ± 7	**0.04**
Late Gadolinium Enhancement	91	50 (54.9%)	28 (84.8%)	22 (37.9%)	**<0.001**
Extra-Cardiac Phenotype Baseline Evaluation					
CK (U/l) – median [IQR]	56	79 [59-124]	77 [56-104]	83 [65-143]	0.17

eTable 4. Table Summarizing Baseline and Follow-up LVEF including Contemporaneous LVEF (Where Available) of Any Arrhythmic End Points

SCD, aborted SCD, haemodynamically [HD] stable sustained VT, anti-tachycardia pacing [ATP], appropriate ICD shock) in FLNCtv patients with an arrhythmic composite event ever (prior to baseline evaluation at a participating centre or over follow-up at participating centre).

Pat. ID	PATIENT AGE AT 1st ARRHYTHMIC EVENT	BASELINE LVEF on TTE / CMR	FUTHER LVEF EVALUATION on TTE / CMR	LVEF CATEGORY AT TYPE OF ARRHYTHMIC EVENT
MILD – MODERATE LEFT VENTRICULAR SYSTOLIC DYSFUNCTION (50% < LVEF > 35%)				
1	**Aged 51.4 years:** HD unstable sustained VT requiring secondary prevention ICD implantation on 14/3/2017.	LVEF 47% on 7/4/2016	LVEF 47% on 17/5/2017	**Mild LVSD:** LVEF mildly impaired (47%) surrounding aborted SCD with haemodynamically unstable sustained VT.
4	**Aged 33.5 years:** Appropriate ICD Shock 15/7/2013 and further ATP for sustained VT 15/8/2013. Further ATP for VT (cycle length 245ms) 21/1/2019.	LVEF 49% on 20/1/2012	LVEF 46% on 10/5/2012 LVEF 55% on 3/7/2017 LVEF 50% on 4/6/2019	**Mild LVSD:** Patient had mild LVSD 14 months prior to appropriate ICD shock and surrounding ATP afterwards in 2013. LVEF 50% surrounding the time of sustained VT 2019 treated with ATP.
34	**Aged 39.4 years**: Aborted SCD 1/7/1984 requiring secondary prevention ICD implantation.	LVEF 32% on 31/5/2005		**Mild-Moderate LVSD** at time of aborted SCD. Actual LVEF not known but mildly dilated LV with mild-moderate LVSD on 1/7/1984. Subsequent HTx aged 60.4 years on 29/7/2005.
60	**Aged 21.5 years**: Sudden Cardiac death 31/3/2013.	LVEF 37% on 27/3/2013		**Moderate LVSD** (LVEF 37%) 4 days prior to sudden cardiac death at sporting event.
61	**Aged 75.1 years**: Aborted SCD on 25/4/2015; Further appropriate ICD shock 10/9/2017.	LVEF 45-50% on 20/4/2015	LVEF 47% on 22/5/2015 LVEF 54% on 16/11/2017	**Mild LVSD** (LVEF 45-50%) at time of aborted SCD and then further ICD shock on 10/9/2017 when contemporary LVEF was low-normal with LVEF 54%.
79	**Age 53.6 years**: HD stable sustained VT 4/7/2013. Aborted SCD 29/6/2016 requiring secondary prevention ICD; Further sustained VT treated with ATP 11/7/2016.	LVEF 48% on 4/7/2013	LVEF 42% on 5/7/2013 (CMR) LVEF 38% on 1/7/2016 LVEF 40% on 10/8/2017	**Mild LVSD:** Sustained VT (HD stable) 4/7/2013 with LVEF 48%. Moderate LVSD (LVEF 38%) at time of secondary prevention ICD and at time of subsequent appropriate ATP for VT.
80	**Aged 49 years**: Aborted SCD 11/6/2013 requiring secondary prevention ICD implantation.	LVEF 45% on 18/6/2013	LVEF 50% on 12/6/2013 (CMR) LVEF 59% on 4/5/2018	**Mild LVSD:** LVEF 45% at time of secondary prevention ICD 12/6/201.3

Pat. ID	PATIENT AGE AT 1st ARRHYTHMIC EVENT	BASELINE LVEF on TTE / CMR	FUTHER LVEF EVALUATION on TTE / CMR	LVEF CATEGORY AT TYPE OF ARRHYTHMIC EVENT
90	**Aged 35.5 years**: Aborted SCD 1/12/1996 requiring secondary prevention ICD implantation; subsequent appropriate ICD shock 1/1/1998.	LVEF 42% on 4/10/2011	LVEF 48% on 22/3/2018	**Mild LVSD** (actual value not known) at time of aborted SCD 1/12/1996. Mild LVSD [LVEF 45%] at the time of appropriate ICD shock 1/1/1998.
93	**Aged 29.8 years**: OOHVF arrest with aborted SCD 12/1/2013 and secondary prevention ICD implantation; Appropriate ICD shock 1/6/2016.	LVEF 40% on 15/1/2013	LVEF 37% on 24/1/2013 (CMR) LVEF 42% on 23/3/2018	**Moderate LVSD** [LVEF 40%] at presentation 12/1/2013 with OOHVF arrest. Moderate LVSD [LVEF 40%] also surrounding appropriate ICD shock on 1/6/2016.
96	**Aged 34.5 years**: Aborted SCD with HD unstable Sustained VT requiring emergent DCCV on 8/10/2015.	LVEF 45% on 2/6/2007	LVEF 43% on 22/11/2007 LVEF 48% on 8/10/2015 LVEF 51% on 3/8/2017	**Mild LVSD:** LVEF 48% on 8/10/2015 at the time of aborted SCD.
130	**Aged 41.7 years**: Appropriate ICD shock 5/9/2017 and further appropriate ICD shocks with syncope (HD unstable) on 1/8/2018 and 14/11/2018.	LVEF 29% on 15/3/2016	LVEF 29% on 21/8/2016 LVEF 40% on 18/10/2017	**Moderate LVSD** (LVEF 40%) surrounding all the appropriate ICD shocks.
159	**Aged 27.2 years**: OOHVF arrest requiring DCCV (Aborted SCD) 16/4/2018.	LVEF 40% on 16/4/2018	LVEF 54% on 20/4/2018 (CMR)	**Moderate LVSD** (40%) at the time of Aborted SCD 16/4/2018.
SEVERE LEFT VENTRICULAR SYSTOLIC DYSFUNCTION (LVEF ≤35%)				
7	**Aged 57.9 years**: Sudden Cardiac Death 15/7/2009.	LVEF 25% on 2/12/2004	LVEF 26% on 27/12/2006	**Severe LVSD:** Patient had severe LVSD surrounding sudden cardiac death 15/7/2009.
30	**Aged 33.2 years:** Haemodynamically unstable VT (Aborted SCD) and subsequent secondary prevention ICD implantation.	LVEF 23% on 27/12/2016		**Severe LVSD** surrounding timing of aborted SCD. Actual LVEF not available but known severe LVSD. Subsequent HTx aged 47.9 years on 16/8/2017.
69	**Aged 71.6 years**: Sudden Cardiac Death 26/2/2015.	LVEF 50% on 26/11/2010	LVEF 52% on 6/1/2011 LVEF 35% on 20/1/2015	**Severe LVSD** (LVEF 35%) on TTE 1 month prior to SCD 26/2/2015

Pat. ID	PATIENT AGE AT 1st ARRHYTHMIC EVENT	BASELINE LVEF on TTE / CMR	FUTHER LVEF EVALUATION on TTE / CMR	LVEF CATEGORY AT TYPE OF ARRHYTHMIC EVENT
89	**Aged 71 years**: OOHVF with aborted SCD and secondary prevention ICD implant; Further sustained VT at 225bpm requiring ATP in 2017.	LVEF 23% on 28/9/2013	LVEF 26% on 5/10/2013 LVEF 27% on 21/12/2017	**Severe LVSD:** LVEF 23% at presentation with OOHVF arrest and LVEF 27% surrounding sustained VT requiring ATP.
95	**Aged 44 years**: Aborted SCD 1/7/1998 requiring secondary prevention ICD implantation; Sustained VT treated with ATP 31/3/2014; Appropriate ICD shock 5/2/2020 for sustained VT.	LVEF 20% on 15/11/2010	LVEF 20% on 11/12/2017	**Severe LVSD:** Unknown definitive LVEF at time of aborted SCD 1998 but likely severely impaired. Severe LVSD (LVEF 15%) at time of ATP 31/3/2014 and LVEF also 15% at time of appropriate ICD shock 5/2/2020.
101	**Aged 43.5 years**: Sudden Cardiac Death 21/5/2015.	LVEF 29% on 1/6/2014	LVEF 29% on 4/2/2015	**Severe LVSD:** Sudden cardiac death 21/5/2015 with severe LVSD (LVEF 29%) 3 months prior to event.
137	**Aged 29.3 years**: Sudden Cardiac Death 1/1/2006.	LVEF 40% on 5/3/1998	LVEF 25% on 26/9/2005	**Severe LVSD:** LVEF 25% 4 months prior to SCD 1/1/2006.
140	**Aged 28.4 years**: Sustained VT and then Sudden Cardiac Death 24/4/2011.	LVEF 35% on 15/4/2011		**Severe LVSD:** Sustained VT – refused ICD and discharged. Sudden cardiac death 24/4/2011.
160	**Aged 41.8 years**: Aborted SCD with sustained VT requiring secondary prevention ICD implantation. Further sustained VT at 220bpm requiring appropriate ICD shock 3/9/2017.	LVEF 35% on 4/7/2017	LVEF 35% on 4/9/2017 LVEF 35% on 28/5/2018	**Severe LVSD:** LVEF 35% at time of aborted SCD June 2017 and at time of appropriate ICD shock 4/9/2017.
UNKNOWN LEFT VENTRICULAR SYSTOLIC FUNCTION SURROUNDING ARRHYTHMIC EVENT				
9	**Aged 37.9 years**: Sudden Cardiac Death 21/6/2010 with Left-dominant AC on autopsy.	LVEF 60% on 13/9/2000		**Unknown LVEF** contemporary to endpoint. Lost to follow-up and presented with sudden cardiac death 10 years later with extensive cardiac changes on autopsy consistent with LDAC.
125	**Aged 59.3 years**: Sudden Cardiac Death 1/3/2015.			**Unknown LVEF** surrounding SCD on 1/3/2015 as missed appointments for LVEF assessment. Normal ECG 10/12/2013.
SUDDEN CARDIAC DEATH PRESENTATION WITHOUT PRIOR EVALUATION				

Pat. ID	PATIENT AGE AT 1st ARRHYTHMIC EVENT	BASELINE LVEF on TTE / CMR	FUTHER LVEF EVALUATION on TTE / CMR
170	**Aged 39.9 years**: Sudden Cardiac Death Presentation.		Sudden Cardiac death 15/7/2008 with Left-dominant AC on post-mortem. Molecular autopsy.
171	**Aged 43 years**: Sudden Cardiac Death Presentation.		Sudden Cardiac death 15/7/2015 with Left-dominant AC on post-mortem. Obligate carrier.
172	**Aged 38.7 years**: Sudden Cardiac Death Presentation.		Sudden Cardiac death 26/10/2015 with Left-dominant AC on post-mortem. Molecular autopsy.
173	**Aged 20 years**: Sudden Cardiac Death Presentation.		Sudden Cardiac death 1/8/2003 with cardiomyopathy on post-mortem. Molecular autopsy.
174	**Aged 28 years**: Sudden Cardiac Death Presentation.		Sudden Cardiac death 1/1/2018 with biventricular arrhythmogenic cardiomyopathy on post-mortem. Molecular autopsy.
175	**Aged 28 years**: Sudden Cardiac Death Presentation.		Sudden Cardiac death 23/2/2016 with biventricular arrhythmogenic cardiomyopathy on post-mortem. Molecular autopsy.

eTable 5. Univariable and Multivariable Predictors of the Composite Primary End Point Using Baseline Clinical Data Obtained From Clinical Evaluation, TTE, CMR, and Holter

Frequent VE burden and LGE on CMR were not included in multivariable Cox-regression model. **This model incorporated 157 patients with FLNCtv and 27 composite primary-endpoint events.**

PREDICTORS OF THE COMPOSITE PRIMARY-ENDPOINT	Univariable HR	95% CI	Univariable p-value		Multivariable HR	95% CI	Multivariable p-value
Baseline evaluation Age / 10	1.03	0.82-1.28	0.83		0.88	0.70-1.12	0.31
Proband status	4.48	1.79-11.16	**0.001**		3.18	1.12-9.04	**0.03**
Male Sex	1.64	0.76-3.57	0.21				
Family History of SCD	0.79	0.34-1.85	0.59				
Syncope	0.80	0.19-3.39	0.76				
LVEF Decrement (from LVEF 50% / 10)	2.08	1.54-2.81	**<0.001**		1.83	1.30-2.57	**<0.001**
NSVT	2.31	0.81-6.61	0.12				
Frequent VE	5.05	1.09-23.40	**0.04**				
LGE on CMR	10.38	1.36-79.02	**0.02**				

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