SUPPLEMENTAL MATERIAL

Data S1.

Gene panel

We designed a panel of 72 gene which have been implicated in LVNC, other cardiomyopathies or ion channel disease. The panel consists of the following genes: *ABCC9, ACTC1, ACTN2, BAG3, CALR3, CASQ2, CAV3, CFL1, CFL2, CMYA5, CRIP2, CRYAB, DES, DMD, DMPK, DSC2, DSG2, DSP, DTNA, FHL1, FHL2, FLNC, GPD1L, HCN4, JPH2, JUP, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNQ1, LAMP2, LDB3, LMNA, MIB1, MYBPC3, MYH6, MYH7, MYL2, MYLK3, MYOM1, MYOM2, MYOZ1, MYOZ2, MYPN, NEXN, NNT, OBSCN, PDLIM3, PKP2, PLEC, PLN, PRDM16, PRKAG2, RBM20, RYR2, SCN5A, SGCD, SGCG, SLC25A4, SNTA1, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL.*

Table S1. Criteria for classifying pathogenic variants according to ACMG guideline

Evidence of pathogenicity		Category
Very strong	PVS1	null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where loss-of-function is a known mechanism of disease
Strong	PS1	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change
	PS2	De novo (both maternity and paternity confirmed) in a patient with the disease and no family history
	PS3	Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product
	PS4	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls
Moderate	PM1	Located in a mutational hot spot and/or critical and well-established functional domain without benign variation
	PM2	Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium
	PM3	For recessive disorders, detected in trans with a pathogenic variant
	PM4	Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants
	PM5	Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before
	PM6	Assumed de novo, but without confirmation of paternity and maternity
Supporting	PP1	Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease
	PP2	Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease
	PP3	Multiple lines of computational evidence support a deleterious effect on the gene or gene product
	PP4	Patient’s phenotype or family history is highly specific for a disease with a single genetic etiology
	PP5	Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation

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PVS, very strong; PS, strong; PM, moderate; PP, supporting.

Table S2. Rules for combining criteria for pathogenic and likely pathogenic variants

Pathogenic	(i) 1 Very strong (PVS1) AND (a) ≥1 Strong (PS1–PS4) OR (b) ≥2 Moderate (PM1–PM6) OR (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) OR (d) ≥2 Supporting (PP1–PP5)
	(ii) ≥2 Strong (PS1–PS4)
	(iii) 1 Strong (PS1–PS4) AND (a)≥3 Moderate (PM1–PM6) OR (b)2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR (c)1 Moderate (PM1–PM6) AND≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) AND 1 moderate (PM1–PM6)
	(ii) 1 Strong (PS1–PS4) AND 1–2 moderate (PM1–PM6)
	(iii) 1 Strong (PS1–PS4) AND ≥2 supporting (PP1–PP5)
	(iv) ≥3 Moderate (PM1–PM6)
	(v) 2 Moderate (PM1–PM6) AND ≥2 supporting (PP1–PP5)
	(vi) 1 Moderate (PM1–PM6) AND ≥4 supporting (PP1–PP5)

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PVS, very strong; PS, strong; PM, moderate; PP, supporting.

Table S3. Primers used for Sanger sequencing confirmation

	Forward primer	Reverse primer
ACTC1-1	ACTTAATTGATTTCTTACCGT	GTGTCAACTCAGGGTTAAATG
ACTC1-2	TACGGCCAGAAGCATACAGGG	CTTGACTTGGGCAGTTAGATA
DMD	ATATTTATGGGGTTATTACTA	CGAGCAGGGTCCAATTGTATC
DSC2	GCAACCTTGCATCTAGCCATA	GGCCTCATTTCAACATTGTTC
DSP-1	CCCGGACCTGCGCTACGAGGT	CGGGAAGTTCTTTCGGGACCT
DSP-2	CATAGATTTGCAACCTTGCCA	CTGGAGCCCCTTCAGGTATGC
DSP-3	ACAGAACGCTCCCGATATCAG	GCAGATGCTCCAGCGATAGAT
LAMP2-1	GCCATTACGAGCTTGTTATGC	GAGGGACACAGCAATATCAAA
LAMP2-2	TGTTCCGGTTGCAGAGTATAT	TATGCCCTTTAAAATGATAAT
LMNA	CCGAGATCGCGCCACTACACT	AAACAAACAGAAGCGCCACAA
MYBPC3-1	ATGTGCAGCACCTCAACTGGC	ACCTCCAGTGGGGGGCTCTGC
MYBPC3-2	CAGGATCCATTCGGCATTATA	GCTAACAGGATCCCGAAACTC
MYBPC3-3	CTGGAATGGGAGTGGGTTCAA	GGATTACAGGCGTCTGGCCTT
MYBPC3-4	ACATTATATTCTTTCGAGGAG	TGGTGCTCAGGCAATTATGTA
MYH7-2	GGGTCCCAACTCACATCGAAG	AGTGGGCAATGAGTACGTCAC
MYH7-3	TCTCTGTCCACCCAGGTGTAC	GGAAGGGACTCACTGGTAACT
MYH7-4	GAGAAAGACACCTAGCCATG	GACCGTCCGGAACGACAACTC
MYH7-5	GAGGAGGAATAGCAGTTGAAG	GACCAAGAACCCACCAATTCC
MYH7-6	GAGCAAGGTCAGCAAGGGTCC	CTCTTGCTGGGCTCCTTAATG
KCNE1-1	TCATGGGGAAGGCTTCGTCTC	AGCAGGGTGGCAACATGTCGG
KCNE1-2	GTGTGTTGGGTTGTTCTATGG	AGCTGCAGCAGTGGAACCTTA

NNT	AGAGAATGCTGGACATGTTCA	AAGAGAATGCTCAGTTTGACC
SCN5A	CCTGCCTCAGCCTTCCGAGTA	CCCCACTCCCTACAAGCTTTA
TNNT2	TTCCCAGTAATTATATCACAT	TGTCCTGACTTCTAACACCGT
TPM1	AGTCACAGGGGCAGGACTGAT	CCCCCACCCAGCAATATTAGA
TTN-1	GGCGTTCCACTTGTAGGTGA	GAGACTCCTGGAAAGGCCAC
TTN-2	GTTACTGGACCTGGCCTTCC	CCTGCTCCACCTAGGAGACT
TTN-3	ATTAACGGCCACAGACCGAG	GTGAACCAGTCCCTGCAAGA
TTN-4	AGGAGGTTGTGGCACTTCTG	TGTGAGAGTTCTGGACACGC
TTN-5	TGGAAGGGGTTTGCCAAGAA	CCAAGCCTACCATCAGAGCC
TTN-6	AAGGCAAGCTTGGTTCTCCA	AAAATAGGCACAGGGCCTCC
TTN-7	AGGTTTTCAGGCTCACCTGG	GGTCCGAGAAAAGAGGGTGG
TTN-8	AGGTTTTCAGGCTCACCTGG	GCACAGCACAATGGAACAGG
TTN-9	TACCGGCTGCATTGGAAACT	TTGAAAAGATCCCCCAGGGC
TTN-10	TGAAGGCTTGCTGACTCCTG	GTATTGGCCCACCTGTGGAA
TTN-11	TTTCAACAGGAGGGCCACAG	GGGGAGCTGGATAAAGACCG
TTN-12	AGACTGGGCCAAACATACCA	GAACCAGTTCAGGCCTCTCC
TTN-13	TGACAAAGGAGATGAGGTTGC	CTGCAGAGCCAGAAGTTCCA
TTN-14	CCAACAGGGCAGTAAGGGAA	AAGGGGTTGCTTCAGCTGTT
TTN-15	AGCATCTGAGGGGGAGATGT	TTGGATCCCAGGTTCCCCTA

Table S4. Pathogenic and likely pathogenic variants detected in the cohort.

Gene	dbSNP	Variant type	Transcript	Transcript effect	Protein effect	Novel variant	Pathogenicity*	Evidence†	gnomAD_ALL‡	gnomAD_EAS§	Carriers ID
ACTC1	rs193922680	missense	NM_005159	c.G301A	p.E101K		P	PS1,PS3,PM2,PP5	0.00000406	NA	90
	rs730880410	missense	NM_005159	c.T986C	p.I329T		LP	PS3,PM2	NA	NA	60
DMD		stop-gain	NM_000109	c.G7875A	p.W2625X	Novel	LP	PS3,PM2	NA	NA	43
		splicing	NM_000109	c.A3579+3T			LP	PS3,PM2	NA	NA	38
DSC2	rs193922708	missense	NM_004949	c.C835T	p.R279C		P	PS1,PS3	0.00004469	NA	9
DSP		frameshift insertion	NM_001008844	c.1_2insC	p.M1fs	Novel	LP	PVS1,PM2	NA	NA	72;99;114;115
		stop-gain	NM_001008844	c.C1138T	p.Q380X	Novel	LP	PVS1,PM2	NA	NA	66
		stop-gain	NM_001008844	c.G3901T	p.E1301X	Novel	LP	PVS1,PM2	NA	NA	70
KCNE1	rs79654911	missense	NM_000219	c.G200A	p.R67H		P	PS1,PS3,PM2,PP3,PP5	0.00005774	0.00005299	80
LAMP2		frameshift deletion	NM_001122606	c.371_375del	p.T124fs	Novel	LP	PVS1,PM2	NA	NA	13

		frameshift deletion	NM_001122606	c.325delT	p.Y109fs	Novel	LP	PVS1,PM2	NA	NA	17
LMNA		missense	NM_001257374	c.T998A	p.V333E		LP	PS3,PM2,PM5	NA	NA	40
MYBPC3	rs786204339	frameshift deletion	NM_000256	c.1377delC	p.P459fs	Novel	LP	PVS1,PM2	NA	NA	86
		frameshift deletion	NM_000256	c.1352_1379del	p.E451fs	Novel	LP	PVS1,PM2	NA	NA	104
		frameshift deletion	NM_000256	c.2568delG	p.R856fs	Novel	LP	PVS1,PM2	NA	NA	114
	rs397515887	missense	NM_000256	c.C1112T	p.P371L		LP	PS3,PM2	0.00002466	NA	43
MYH7	rs121913637	missense	NM_000257	c.C2155T	p.R719W		P	PS1,PS3,PM2,PP5	0.00003231	NA	105
	rs3218713	missense	NM_000257	c.G746A	p.R249Q		P	PS1,PS3,PM2,PP5	NA	NA	112
	rs730880161	missense	NM_000257	c.G2785A	p.E929K		P	PS1,PS3,PM2	NA	NA	48
	rs397516089	missense	NM_000257	c.G1106A	p.R369Q		P	PS1,PS3,PM2,PP5	NA	NA	64
	rs730880852	missense	NM_000257	c.C745G	p.R249G		P	PS1,PS3,PM2,PP5	NA	NA	51
NEXN	rs756273801	missense	NM_001172309	c.T488C	p.L163S		P	PS1,PS3	0.00001626	0.00017399	61

NNT		frameshift insertion	NM_012343	c.1770dupC	p.D590fs	Novel	LP	PVS1,PM2	NA	NA	105
SCN5A	rs45546039	missense	NM_000335	c.G665A	p.R222Q		P	PS1,PS3,PM2,PP3,PP5	NA	NA	72
	rs199473054	missense	NM_000335	c.G283A	p.V95I		P	PS1,PS3,PP3,PP5	0.00002886	0.00015898	27
TNNT2	rs121964856	missense	NM_000364	c.G305A	p.R102Q		P	PS1,PS3,PM2,PP3,PP5	NA	NA	9
TPM1	rs397516387	missense	NM_000366	c.C725T	p.A242V		LP	PS3,PM2	0.00000406	NA	41
TTN		frameshift insertion	NM_001256850	c.55176dupA	p.E18393fs	Novel	LP	PVS1,PM2	NA	NA	79
		frameshift deletion	NM_001256850	c.50906_50907del	p.P16969fs	Novel	LP	PVS1,PM2	NA	NA	81
		frameshift deletion	NM_001256850	c.8228delA	p.N2743fs	Novel	LP	PVS1,PM2	NA	NA	86
		splicing	NM_001256850	c.G13141+1A		Novel	LP	PVS1,PM2	NA	NA	92
		stop-gain	NM_001256850	c.C72093G	p.Y24031X	Novel	LP	PVS1,PM2	NA	NA	93
		stop-gain	NM_001256850	c.C56939A	p.S18980X	Novel	LP	PVS1,PM2	NA	NA	100

		frameshift deletion	NM_001256850	c.98135delA	p.H32712fs	Novel	LP	PVS1,PM2	NA	NA	102
		splicing	NM_001256850	c.40222+2insAATA		Novel	LP	PVS1,PM2	NA	NA	104
		stop-gain	NM_001256850	c.C80167T	p.R26723X	Novel	LP	PVS1,PM2	NA	NA	116
		frameshift deletion	NM_001256850	c.58109delT	p.V19370fs	Novel	LP	PVS1,PM2	NA	NA	117
		stop-gain	NM_001256850	c.C44607A	p.Y14869X	Novel	LP	PVS1,PM2	NA	NA	120
		stop-gain	NM_001256850	c.A88642T	p.K29548X	Novel	LP	PVS1,PM2	NA	NA	45
	rs779485172	splicing	NM_001256850	c.A63605-2T	.	Novel	LP	PVS1,PM2	NA	NA	29
		frameshift deletion	NM_001256850	c.56615_56618del	p.E18872fs	Novel	LP	PVS1,PM2	NA	NA	73
		frameshift insertion	NM_001256850	c.48473_48474insGCTTT	p.F16158fs	Novel	LP	PVS1,PM2	NA	NA	34

* Determined according to criteria in Table S2

† As listed in Table S1

‡ Minor allele frequencies of variants among total population in the Genome Aggregation Database (*Nature*. 2016;536: 285-91)

§ Minor allele frequencies of variants among East Asians in the Genome Aggregation Database (*Nature*. 2016;536: 285-91)

LP, likely pathogenic; NA, not available; P, pathogenic

Table S5. Clinical characteristics of the six carriers of *DSP* variant

Patient ID	Age at onset	Sex	NYHA class	Arrythmia	Enlarged RV	Antiarrhythmics	Other treatment	Outcome
66	20	Male	III	SUVT	No	Amiodarone		HT
70	44	Male	II	SUVT	No		RFCA	
72	17	Male	II	NSVT	No	Amiodarone	ICD	
99	40	Male	II	SUVT, AF	No	Amiodarone		
114	60	Male	III	SUVT	No	Amiodarone		HF-related death
115	51	Female	II	SUVT	No	Amiodarone	ICD	

AF, atrial fibrillation; HF, heart failure; HT, heart transplantation; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; NSVT, non-sustained ventricular tachycardia; RFCA, radiofrequency catheter ablation; RV, right ventricle; SUVT, sustained ventricular tachycardia.

Table S6. Characteristics of child patients who reached the primary endpoint.

Patient ID	Sex	Age at onset	NYHA functional class	Family history	Outcome	Pathogenic variants
10	Male	16	I/II	No	SCD	
13	Male	16	III/IV	No	HF-related death	LAMP2 p.T124fs
64	Male	3	III/IV	No	Heart transplantation	MYH7 p.R369Q
84	Male	8	I/II	No	SCD	

HF indicates heart failure; NYHA, New York Heart Association; SCD, sudden cardiac death.

Table S7. Incidence of primary and secondary endpoints in child and adult patients.

Endpoints	Children (n=17)	Adult (n=83)	*P*-Value
Death and heart transplantation, n (%)	4 (23.5)	28 (33.7)	0.411
All-cause death, n (%)	3 (17.6)	24 (28.9)	0.549
Sudden cardiac death, n (%)	2 (11.8)	4 (4.8)	0.269
Heart failure-related death, n (%)	1 (5.9)	19 (16.6)	0.182
Cardiovascular death, n (%)	3 (17.6)	24 (28.9)	0.549
Heart transplantation, n (%)	1 (5.9)	4 (4.8)	1.000

Table S8. Characteristics of adult patients who reached the primary endpoint.

Patient ID	Sex	Age at onset	NYHA functional class	Family history	Outcome	Pathogenic variants
14	Male	42	III/IV	No	HF-related death	
15	Female	39	III/IV	No	HF-related death	
17	Female	19	III/IV	Yes	HF-related death	LAMP2 p.Y109fs
18	Male	44	III/IV	No	HF-related death	
19	Male	43	III/IV	No	HF-related death	
22	Female	70	III/IV	No	HF-related death	
27	Male	50	III/IV	No	HF-related death	SCN5A p.V95I
32	Male	52	III/IV	No	HF-related death	
34	Male	18	III/IV	No	HF-related death	TTN p.F16158fs
41	Male	44	III/IV	Yes	HF-related death	TPM1 p.A242V
43	Male	59	III/IV	No	HF-related death	DMD p.W2625X;MYBPC3 p.P371L
45	Male	39	III/IV	No	HF-related death	TTN p.K29548X
51	Female	31	III/IV	Yes	HF-related death	MYH7 p.R249G
55	Female	26	III/IV	No	HF-related death	
57	Male	34	I/II	No	SCD	
61	Male	39	I/II	Yes	SCD	NEXN p.L163S
66	Male	20	III/IV	No	Heart transplantation	DSP p.Q380X
67	Male	37	III/IV	No	HF-related death	
68	Female	52	I/II	No	SCD	

73	Male	78	I/II	No	HF-related death	TTN p.E18872fs; TTN p.G4397D
77	Male	66	I/II	No	Other cardiovascular death	
80	Male	40	III/IV	No	Heart transplantation	KCNE1 p.R67H
93	Male	28	I/II	No	Heart transplantation	TTN p.Y24031X
99	Male	40	I/II	No	HF-related death	DSP p.M1fs
102	Male	23	III/IV	No	Heart transplantation	TTN p.H32712fs
105	Female	46	I/II	No	HF-related death	MYH7 p.R719W; NNT p.D590fs
110	Female	41	III/IV	No	SCD	
114	Male	60	III/IV	No	HF-related death	DSP p.M1fs; MYBPC3 p.R856fs

HF indicates heart failure; NYHA, New York Heart Association; SCD, sudden cardiac death.