Supplementary

Table S1 List of criteria for variant classification of the identified putative loss of function variants

Gene	NM_number	Variant	Variant type	Evidence of pathogenicity (ACMG)	Classification (ACMG)	KP/EP	Decision to return as SF
DSP	NM_004415.3	c.5327_5330del (p.Glu1776Glyfs*4)	Frameshift	PVS1, PM2	4	KP	Yes
		c.7745_7746del (p.Phe2582*)	Frameshift	PVS1_strong, PM2	4	EP	Yes
		c.8451C>A (p.Tyr2817*)	Stop_gain	PVS1_moderate, PM2	3	–	No
		c.8494G>T (p.Gly2832*)	Stop_gain	PVS1_moderate, PM2	3	–	No
		c.2323C>T (p.Gln775*)	Stop_gain	PVS1, PM2	4	KP	Yes
DSC2	NM_004949.4	c.2530_2531del (p.Leu844Aspfs*2)	Frameshift	PVS1_moderate, PM2	3	–	No
		c.2T>A	Start_lost	PVS1_moderate, PM2	3	–	No
		c.34G>T (p.Gly12*)	Stop_gain	PVS1, PM2	4	EP	Yes
		c.1777G>T (p.Glu593*)	Stop_gain	PVS1, PM2	4	EP	Yes
DSG2	NM_001943.4 NG_007072.3	c.3059_3062del (p.Glu1020Alafs*18)	Frameshift	PVS1, PP1, PS4_moderate	5	KP	Yes
		c.3G>A	Start_lost	PVS1_strong, PM2, PP1	5	KP	Yes
		c.3025C>T (p.Gln1009*)	Stop_gain	PVS1_strong, PM2	4	EP	Yes
		c.3340C>T (p.Gln1114*)	Stop_gain	PVS1-moderate, PM2	3	–	No
PKP2	NM_004572.3 NG_009000.1	c.1211dup (p.Val406Serfs*4)	Frameshift	PVS1, PM2, PP1	5	KP	Yes
		c.1664del (p.Phe555Serfs*8)	Frameshift	PVS1, PM2, PP1	5	EP	Yes
		c.2146-1G>C	Splice	PVS1, PS3, PM2, PP1	5	KP	Yes
		c.1378+1G>C	Splice	PVS1, PS4_supporting, PM2	5	KP	Yes
		c.223G>A (p.Gly75Arg)	Splice	PM2, PP3	3	–	No
		c.1138G>T (p.Glu380*)	Stop_gain	PVS1, PM2	4	KP	Yes
TMEM43	NM_024334.2	c.487C>T (p.Arg163*)	Stop_gain	PP3	3	–	No
		c.1A>G (p.Met1?)	Start_lost	PM2, PM4	3	–	No
		c.1021C>T (p.Arg341*)	Stop_gain	PM2, PP3	3	–	No
		c.351dup (p.His118Alafs*11)	Frameshift	PM2	3	–	No
		c.1120_1121del (p.Leu374Valfs*49)	Frameshift	PP3, BS1	3	–	No

Table S1 shows the criteria for classifying of the identified 24 putative LoF (loss of function) variants in 6605 next-generation sequencing (NGS) analyses in the five actionable arrhythmogenic right ventricle cardiomyopathy (ARVC) genes (*DSC2, DSG2, DSP, PKP2, TMEM43*). Variant type (frameshift, splice, start lost, stop gain), refSeq (Reference Sequence) and variant nomenclature was listed. The variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines with the 5-tier classification system: class 5 (pathogenic), class 4 (likely pathogenic), class 3 (variants of unknown significance, VUS). Evidence of pathogenicity (combining criteria for classifying) of each variant was shown. PVS1 (pathogenic criterion very strong), PM2 (pathogenic criterion moderate), PS3 (pathogenic criterion strong), PP3, PP4 (pathogenic criterion supporting). Evidence of benign impact: BS1 (benign strong). Variants within the actionable genes that have been previously reported as a cause of the disorder are listed as known pathogenic (KP) and variants that are previously unreported but are of the type which is expected to cause the disorder are listed as expected pathogenic (EP) and only EP/KP are returned as actionable secondary finding (SF).

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