Supplemental Material

Cases were screened for genetic variants in six known arrhythmia genes (*KCNE1*, *KCNE2*, *KCNH2*, *KCNQ1*, *RYR2* and *SCN5A*). Twenty-six variants were identified; two individuals were double heterozygotes (Table 1). Variants were named according to HGVS recommendations and Mutalyzer [1, 2] was used to ensure variants were named correctly. The ExAC Brower [3, 4] and The Exome Variant Server [5] were used to retrieve minor allele frequency data from the ExAC and GO-ESP databases, respectively (Table 2). Furthermore, all variants were submitted to the *in silico* predictions servers PolyPhen [6], SIFT [7, 8], MutationTaster [9, 10] and MutationAssessor [11]. Additionally, ClinVar classifications were extracted from ClinVar [12] (Table 2). Conservation was assessed by BLAST and CLUSTAL OMEGA (Table 3). Finally, variants were classified as either “pathogenic”, “likely pathogenic”, “benign”, “likely benign” or “uncertain significance” in line with ACMG guidelines [13] (Table 4).

Table 1: Mutations identified in cohort

Fluidigm	HR-ID	Gene	HGMD ID	dbSNP ID	Transcript	Coding change	Protein	Amino Acid change	References
20LW00392	9	RYR2	CM097927	rs794728721	NM_001035.2	c.1259G>A	NP_001026.2	p.R420Q	[14-19]
20OK02199	36	RYR2			NM_001035.2	c.5248G>A	NP_001026.2	p.G1750R	
20SF02201	38	RYR2	CM148846		NM_001035.2	c.13823G>A	NP_001026.2	p.R4608Q	[19, 20]
20DH02217	217	KCNH2	CM002298	rs138776684	NM_000238.3	c.1039C>T	NP_000229.1	p.P347S	[21-31]
20AM00366	306	RYR2	CM056049	rs794728756	NM_001035.2	c.7202G>A	NP_001026.2	p.R2401H	[15, 32-34]
20AM02224	314	KCNE1		rs75610894	NM_000219.5	c.142C>T	NP_000210.2	p.L48F	
20DE02235	403	RYR2			NM_001035.2	c.10681C>G	NP_001026.2	p.L3561V	[19]
20DE02243	411	KCNH2			NM_000238.3	c.2564G>A	NP_000229.1	p.S855N	
20ML02281	703	RYR2		rs117180147	NM_001035.2	c.10231-4T>C			
20NF02286	708	RYR2	CM1515197	rs201500134	NM_001035.2	c.8162T>C	NP_001026.2	p.I2721T	[35]
		SCN5A	CM004144	rs45489199	NM_198056.2	c.6016C>G	NP_932173.1	p.P2006A	[27, 28, 36-49]
20NX02292	714	KCNH2	CM057119	rs199473017	NM_000238.3	c.2903C>T	NP_000229.1	p.P968L	[21, 25, 50]
20OE02293	715	RYR2		rs117180147	NM_001035.2	c.10231-4T>C			
20PU02300	722	RYR2		rs117180147	NM_001035.2	c.10231-4T>C			
20PJ02303	725	RYR2		rs766802574	NM_001035.2	c.458C>T	NP_001026.2	p.T153I	[19]
20PT02305	727	SCN5A		rs72549411	NM_198056.2	c.2437-5C>A			
20PZ02309	731	RYR2		rs117180147	NM_001035.2	c.10231-4T>C			
20QW02316	738	SCN5A	CM086913	rs41311117	NM_198056.2	c.6010T>C	NP_932173.1	p.F2004L	[36-38, 45, 48, 51-55]
20SF02323	745	RYR2		rs117180147	NM_001035.2	c.10231-4T>C			
20TG02324	746	SCN5A	CM034060	rs36210423	NM_198056.2	c.1715C>A	NP_932173.1	p.A572D	[1, 28, 41, 55-61]
		RYR2		rs117180147	NM_001035.2	c.10231-4T>C			
20LT02271	756	KCNE2	CM003449	rs2234916	NM_172201.1	c.22A>G	NP_751951.1	p.T8A	[1, 3, 5-7, 30, 31, 47, 61-63]
20DN02274	759	RYR2	CM024349	rs794728777	NM_001035.2	c.11836G>A	NP_001026.2	p.G3946S	[12, 15, 19, 64, 65]
20SH00345	907	KCNQ1	CM139859	rs794728567	NM_000218.2	c.969G>A	NP_000209.2	p.W323*	[19]
20SH00347	910	KCNQ1		rs199472783	NM_000218.2	c.1379G>A	NP_000209.2	p.G460D	
20SH00351	914	RYR2		rs377763795	NM_001035.2	c.7458T>G	NP_001026.2	p.H2486Q	
20SH00353	916	RYR2		rs397516546	NM_001035.2	c.5825T>G	NP_001026.2	p.F1942C	
20AS02332	998	KCNH2	CM057124	rs199473420	NM_000238.3	c.211G>C	NP_000229.1	p.G71R	[50, 66]
20SC02339	1006	KCNQ1	CM078293	rs12720457	NM_000218.2	c.1179G>C	NP_000209.2	p.K393N	[1, 21, 24, 25, 50, 67-71]
20BA02345	1012	KCNQ1		rs794728542	NM_000218.2	c.1829C>A	NP_000209.2	p.T610N	
20KP02366	1034	SCN5A	CM033019	rs45620037	NM_198056.2	c.659C>T	NP_932173.1	p.T220I	[9, 21, 23, 34, 46, 47, 53, 54, 72-78]

Table 2: population frequency, in silico predictions and ClinVar classification of genetic variants

Transcript change	Amino Acid change	Minor Allele Frequency (%)				in silico prediction				ClinVar
		ExAC	GO-ESP (ALL)	GO-ESP (AA)	GO-ESP (EA)	Polyphen	MutationTaster	MutationAssessor	Sift	
KCNE1										
c.142C>T	p.L48F	0.004	0.015	0.000	0.023	probably damaging	disease causing	medium impact	Damaging	
KCNE2										
c.22A>G	p.T8A	0.380	0.492	0.114	0.686	probably damaging	disease causing	medium impact	Damaging	benign
KCNH2										
c.211G>C	p.G71R	NA	NA	NA	NA	probably damaging	disease causing	medium impact	Damaging	pathogenic, Congenital long QT syndrome, autosomal dominant
c.1039C>T	p.P347S	0.141	0.046	0.000	0.070	possibly damaging	disease causing	low impact	Tolerated	
c.2564G>A	p.S855N	NA	NA	NA	NA	benign	disease causing	neutral	Tolerated	
c.2903C>T	p.P968L	0.004	0.008	0.000	0.012	benign	polymorphism	neutral	Tolerated	
KCNQ1										
c.969G>A	p.W323*	NA	NA	NA	NA		disease causing		Tolerated	pathogenic, …
c.1179G>C	p.K393N	0.110	NA	NA	NA	possibly damaging	disease causing	medium impact	Tolerated	
c.1379G>A	p.G460D	0.006	NA	NA	NA	benign	polymorphism	neutral	Tolerated	variant of uncertain significance, sudden infant death syndrome,
c.1829C>A	p.T610N	NA	NA	NA	NA	possibly damaging	disease causing	low impact	Tolerated	variant of unknown significance
RYR2										
c.458C>T	p.T153I	0.002	NA	NA	NA	probably damaging	disease causing	low impact	Damaging	variant of unknown significance
c.1259G>A	p.R420Q	NA	NA	NA	NA	probably damaging	disease causing	medium impact	Damaging	
c.5248G>A	p.G1750R	NA	NA	NA	NA	probably damaging	disease causing	medium impact	Damaging	
c.5825T>G	p.F1942C	0.003	NA	NA	NA	benign	disease causing	medium impact	Tolerated	variant of unknown significance
c.7202G>A	p.R2401H	NA	NA	NA	NA	probably damaging	disease causing	medium impact	Damaging	pathogenic/likely pathogenic, CPVT / cardiovascular phenotype,
c.7458T>G	p.H2486Q	0.001	0.008	0.000	0.012	possibly damaging	disease causing	low impact	Tolerated	
c.8162T>C	p.I2721T	0.057	0.052	0.056	0.050	possibly damaging	disease causing	low impact	Tolerated	variant of unknown significance, CPVT
c.10231-4T>C		0.115	0.017	0.055	0.000	unknown				
c.10681C>G	p.L3561V	NA	NA	NA	NA	possibly damaging	disease causing	medium impact	Damaging	
c.11836G>A	p.G3946S	NA	NA	NA	NA	probably damaging	disease causing	medium impact	Damaging	pathogenic, …
c.13823G>A	p.R4608Q	NA	NA	NA	NA	probably damaging	disease causing	medium impact	Tolerated	
SCN5A										
c.659C>T	p.T220I	0.101	0.032	0.000	0.048	probably damaging	disease causing	medium impact	Damaging	Benign/Likely benign/Pathogenic/Uncertain significance, SSS/DCM/BrS
c.1715C>A	p.A572D	0.430	0.169	0.025	0.239	benign	polymorphism	low impact	Tolerated	benign/likely benign, LQT/BRS/SSS/LVNC/PFHB/DCM
c.6010T>C	p.F2004L	0.202	NA	NA	NA	benign	polymorphism	neutral	Tolerated	benign/likely benign/variant of uncertain significance, BrS/LQT
c.6016C>G	p.P2006A	0.134	0.113	0.025	0.155	benign	polymorphism	neutral	Tolerated	likely benign/uncertain significance, BrS
c.2437-5C>A		0.035	0.054	0.023	0.070	unknown				

Table 3: HGMD classification and conservation summary

Transcript change	Amino Acid change	HGMD Variant Classification	Conservation
KCNE1			
c.142C>T	p.L48F		p.L48F - "L" is 94% conserved among 17 species: 100% conserved among 14 mammalian species and 67% conserved among 3 non-mammalian species. Carp carry a "C" at this residue. The 21 amino acids surrounding the residue were 87 % conserved in 14 mammalian species and 45 % conserved in 3 non-mammalian species.
KCNE2			
c.22A>G	p.T8A	Disease-associated polymorphism	p.T8A -" T" is 100% conserved across 60 species. The 21 amino acids surrounding this residue are 79% conserved across 56 mammalian species and 56% conserved across 4 non-mammalian species.
KCNH2			
c.211G>C	p.G71R	Disease causing mutation	p.G71R - "G" is 100% conserved across 45 species. The 21 amino acids surrounding this residue are 100% conserved in 40 mammalian species and 86% conserved among 6 non-mammalian species.
c.1039C>T	p.P347S	Disease causing mutation	p.P347S - "P" is conserved 100% across 48 mammalian species, this residue is not conserved in 8 non-mammalian species, and however, no species carried an "S". The 21 amino acids surrounding this residue are 99% conserved in 48 mammalian species and 65 % conserved in 8 non-mammalian species
c.2564G>A	p.S855N		p.S855N - "S" is 65% conserved among 20 species: 100% conserved among 10 mammalian species and 30% conserved among 10 non-mammalian species. Carp, Zebrafish, Chicken, Croaker, Pufferfish, Arowana fish, and King Cobra carry an "N" at this residue. The 21 amino acids surrounding the residue were 100 % conserved in 10 mammalian species and 89 % conserved in 10 non-mammalian species.
c.2903C>T	p.P968L	Disease causing mutation	p.P968L - "P" is 100% conserved in mammalian species and the 21 amino acids surrounding the residue are 87 % conserved in 28 mammalian species
KCNQ1			
c.969G>A	p.W323*	Disease causing mutation	
c.1179G>C	p.K393N	Disease causing mutation	p.K393N - "K" is 100% conserved in 17 non-mammalian species and 98% conserved in 48 mammalian species. Domestic Cat carries "N" at this position. The 21 amino acids surrounding this residue are 85% conserved in 48 mammalian species and 80% conserved in 17 non-mammalian species.
c.1379G>A	p.G460D		p.G460D - "G" is 30% conserved among 30 species (81% among 11 mammalian species), no species carried a D at this position. The 21 amino acids surrounding this residue are 49% conserved in 19 non-mammalian species and 84% conserved in 11 mammalian species.
c.1829C>A	p.T610N		p.T610N - "T" 91% conserved in 12 species (100% among 9 mammalian species). The 21 amino acids surrounding this residue were 92% conserved among 9 mammalian species and 52 % conserved among non-mammalian species.
RYR2			
c.458C>T	p.T153I		p.T153I - "T" is conserved in 77% of 22 species (90% among 10 mammalian species), no species carried and "I" at this position. The 21 amino acids surrounding the residue were 97.6% in 12 non-mammalian species and 99.5% in 10 mammalian species.
c.1259G>A	p.R420Q	Disease causing mutation	p.R420Q - "R" is 100% conserved in all species identified by BLAST search. The 21 amino acids surrounding this residue were 100% conserved in 57 mammalian species ad 92% conserved in 20 non-mammalian species.
c.5248G>A	p.G1750R		p.G1750R - "G" is conserved 100% in 21 species. The 21 amino acids surrounding this residue were 96.1% conserved in 11 non-mammalian species and 94.3% conserved in 10 mammalian species.
c.5825T>G	p.F1942C		p.F1942C - "F" is conserved 100% in 23 species. The 21 amino acids surrounding this residue were 92.3% conserved in 13 non-mammalian species and 99% conserved in 10 mammalian species.
c.7202G>A	p.R2401H	Disease causing mutation	p.R2401H - "R" is 100% conserved in all species identified by BLAST search. The 21 amino acids surrounding the residue were 97% conserved in 56 mammalian species and 94 % conserved in 24 non-mammalian species including Acorn worm
c.7458T>G	p.H2486Q		p.H2486Q - "H" is conserved 100% in 22 species. The 21 amino acids surrounding this residue were 94.8%% conserved in 12non-mammalian species and 99.5% conserved in 10 mammalian species.
c.8162T>C	p.I2721T	Disease causing mutation?	p.I2721T -"I" is 100% conserved in all species identified by BLAST search. The 21 amino acids surrounding the residue were 99% conserved in 54 mammalian species and 97 % conserved in 21 non-mammalian species
c.10231-4T>C			
c.10681C>G	p.L3561V		p.L3561V - "L" is conserved 100 % in 20 species. The 21 amino acids surrounding this residue were 63.2 % conserved in 10 non-mammalian species and 68.3 % conserved in mammalian species.
c.11836G>A	p.G3946S	Disease causing mutation	p.G3946S - "G" is 100% conserved in all species identified by BLAST search. The 21 amino acids surrounding the residue were 100 % conserved in 57 mammalian species and 100 % conserved in 22 non-mammalian species including Vase tunicate.
c.13823G>A	p.R4608Q	Disease causing mutation	p.R4608Q - "R" is 100% conserved in all species identified by BLAST search. The 21 amino acids surrounding the residue were 100 % conserved in 57 mammalian species and 99 % conserved in 22 non-mammalian species including Vase tunicate.
SCN5A			

c.659C>T	p.T220I	Disease causing mutation	p.T220I -"T" is 100% conserved in all species identified by BLAST search. The 21 amino acids surrounding the residue were 96 % conserved in 56 mammalian species and 91 % conserved in 7 non-mammalian species.
c.1715C>A	p.A572D	Disease causing mutation?	p.A572D - "A" is 73% conserved among 52 mammalian species, the surrounding 21 amino acids are 94% conserved. No non-mammalian species were identified in a BLAST search.
c.2437-5C>A			
c.6010T>C	p.F2004L	Disease causing mutation?	p.F2004L - "F" is 90% conserved among 51 mammalian species, the surrounding 21 amino acids are 96% conserved. No non-mammalian species were identified in a BLAST search. Long tailed chinchilla and dog, both carry "L" at this position.
c.6016C>G	p.P2006A	Disease causing mutation?	p.P2006A - "P" is 84% conserved among 51 mammalian species, the surrounding 21 amino acids are 91% conserved. No non-mammalian species were identified in a BLAST search. Domestic guinea pig, domestic cat, Brandt's bat, mouse-eared bat and little brown bat all carry "A" at this position.

Table 4: Variant classification

HGMD ID	dbSNP ID	Transcript change	Amino Acid change	Classification
KCNE1 (NM_000219.5/NP_000210.2)				
	rs75610894	c.142C>T	p.L48F	Uncertain significance
KCNE2 (NM_172201.1/NP_751951.1)				
CM003449	rs2234916	c.22A>G	p.T8A	Uncertain significance
KCNH2 (NM_000238.3/NP_000229.1)				
CM057124	rs199473420	c.211G>C	p.G71R	Likely pathogenic
CM002298	rs138776684	c.1039C>T	p.P347S	Uncertain significance
		c.2564G>A	p.S855N	Uncertain significance
CM057119	rs199473017	c.2903C>T	p.P968L	Uncertain significance
KCNQ1 (NM_000218.2/NP_000209.2)				
CM139859	rs794728567	c.969G>A	p.W323*	Likely pathogenic
CM078293	rs12720457	c.1179G>C	p.K393N	Uncertain significance
	rs199472783	c.1379G>A	p.G460D	Uncertain significance
	rs794728542	c.1829C>A	p.T610N	Uncertain significance
RYR2 (NM_001035.2 /NP_001026.2)				
	rs766802574	c.458C>T	p.T153I	Likely pathogenic
CM097927	rs794728721	c.1259G>A	p.R420Q	Pathogenic
		c.5248G>A	p.G1750R	Likely pathogenic
	rs397516546	c.5825T>G	p.F1942C	Uncertain significance
CM056049	rs794728756	c.7202G>A	p.R2401H	Likely pathogenic
	rs377763795	c.7458T>G	p.H2486Q	Uncertain significance
CM1515197	rs201500134	c.8162T>C	p.I2721T	Uncertain significance
	rs117180147	c.10231-4T>C		Uncertain significance
		c.10681C>G	p.L3561V	Likely pathogenic
CM024349	rs794728777	c.11836G>A	p.G3946S	Pathogenic
CM148846		c.13823G>A	p.R4608Q	Pathogenic
SCN5A (NM_198056.2/NP_932173.1)				
CM033019	rs45620037	c.659C>T	p.T220I	Likely pathogenic
CM034060	rs36210423	c.1715C>A	p.A572D	Likely benign
	rs72549411	c.2437-5C>A		Uncertain significance
CM086913	rs41311117	c.6010T>C	p.F2004L	Uncertain significance
CM004144	rs45489199	c.6016C>G	p.P2006A	Uncertain significance

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