Supplemental Materials

Impact of cascade screening for catecholaminergic polymorphic ventricular tachycardia type 1

Shimamoto, et al

Supplemental Table 1. *RYR2* variant classification according to the American College of Medical Genetics (ACMG) guideline.

Variants		PVS1	PS1	PS2	PS3	PS4	PM1	PM2	PM3	PM4	PM5	PM6	PP1	PP2	PP3	PP4	PP5	ACMG
c.100A>G	p.K34E			1				1							1	1		LP
exon 3 deletion	p.N57_G91del35				1		1	1		1			1		1			P
c.506G>A	p.R169Q			1			1	1			1				1	1		P
c.506G>T	p.R169L		1	1			1	1			1					1	1	P
c.515G>A	p.G172E			1			1	1			1				1	1	1	P
c.518A>G	p.E173G			1			1	1							1	1		P
c.527G>A	p.R176Q						1	1			1				1	1	1	LP
c.533G>C	p.G178A			1			1	1							1	1		P
c.535G>A	p.D179N			1			1	1			1				1	1		P
c.1069G>A	p.G357S						1	1					1		1	1	1	LP
c.1202A>G	p.D401G						1	1					1		1	1		LP
c.1244C>G	p.T415R			1			1	1			1				1	1		P
c.1258C>T	p.R420W		1		1		1	1			1		1		1	1	1	P
c.1259G>A	p.R420Q		1				1	1			1		1		1	1	1	P
c.1372G>A	p.D458N						1	1					1		1	1		LP
c.1375C>G	p.L459V						1	1					1		1	1		LP
c.5128C>A	p.H1710N						1	1							1	1		LP
c.5170G>A	p.E1724K						1	1					1		1	1	1	LP
c.6507G>T	p.E2169D						1	1					1		1	1		LP
c.6574A>T	p.M2192L						1	1					1		1	1		LP
c.6645T>G	p.F2215L			1			1	1							1	1		P
c.6649C>T	p.H2217Y						1	1							1	1	1	LP
c.6737C>T	p.S2246L			1			1	1							1	1	1	P
c.6883G>A	p.G2295R		1	1			1	1							1	1		P
c.6887A>G	p.E2296G			1			1	1							1	1		P

c.6900C>G	p.D2300E			1			1	1							1			LP
c.6919T>G	p.F2307V		1	1			1	1							1	1		P
c.7159G>A	p.A2387T			1			1	1			1				1		1	P
c.7171T>C	p.F2391L						1	1					1		1	1		LP
c.7199G>T	p.G2400V			1			1	1							1	1		P
c.11583G>C	p.Q3861H			1			1	1							1	1		P
c.11583G>T	p.Q3861H			1			1	1							1	1		P
c.11590A>G	p.N3864D			1			1	1							1	1		P
c.11812A>G	p.S3938G			1			1	1							1	1		P
c.11836G>A	p.G3946S			1			1	1			1				1	1	1	P
c.11837G>T	p.G3946V			1			1	1							1	1	1	P
c.11924A>C	p.Q3975P						1	1					1		1	1		LP
c.12006G>T	p.M4002I		1	1			1	1							1	1		P
c.12059T>C	p.F4020S			1			1	1							1	1		P
c.12301C>T	p.L4101F			1			1	1							1	1	1	P
c.12371G>A	p.S4124N						1	1							1	1	1	LP
c.12533A>G	p.N4178S			1			1	1							1	1	1	P
c.12559G>A	p.E4187K			1			1	1							1	1		P
c.12579C>G	p.C4193W			1			1	1							1			LP
c.12586A>G	p.T4196A			1			1	1							1	1	1	P
c.13463A>C	p.Q4488P			1				1							1			LP
c.13489C>T	p.R4497C			1			1	1					1		1	1	1	P
c.13763T>C	p.I4588T			1			1	1							1	1	1	P
c.13800T>G	p.F4600L			1			1	1							1	1		P
c.13997T>A	p.I4666N			1			1	1							1	1		P
c.14158C>T	p.L4720F			1			1	1							1	1	1	P
c.14174A>G	p.Y4725C			1			1	1			1				1	1	1	P
c.14251A>C	p.K4751Q			1			1	1			1				1	1	1	P

c.14311G>A	p.V4771I			1			1	1							1	1	1	P
c.14341T>C	p.Y4781H			1			1	1							1		1	P
c.14461G>A	p.V4821I			1			1	1							1	1		P
c.14778A>G	p.I4926M			1			1	1							1	1	1	P
c.14806C>A	p.Q4936K			1			1	1							1	1		P
c.14832_14834dupTCA	p.4944_4945insH			1			1	1		1					1			P
c.14876G>A	p.R4959Q			1			1	1							1	1	1	P
c.14878A>C	p.K4960Q			1				1							1			LP
c.6023 –2 A>G	Splicing Error	1		1												1		P

Evidence of pathogenicity; Very strong (PVS1), Strong (PS1~4), Moderate (PM1~6) and Supporting (PS1~5) were referred to the Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology Genetics in medicine[1].

1: corresponds to the criteria, LP: likely pathogenic, P: pathogenic

Supplemental Table 2. *RYR2* variants and clinical characteristics of the probands.

Family lines	Sex	Variants		Trio*	Heredity	Age at the first symptom, year	Age at clinical diagnosis, years	History of Syncope	History of CA	Bidirectional VT	Symptom or arrhythmia of the parents	Reference
1	M	c.100A>G	p.K34E	(+)	*de novo*	7	9	(+)	(–)	(+)	NA	
2	F	exon 3 deletion	p.N57_G91del35	(–)	maternal	1	11	(+)	(–)	(–)	Syncope	[2]
3	F	exon 3 deletion	p.N57_G91del35	(+)	maternal	16	17	(+)	(–)	(–)	AF	[2]
4	M	exon 3 deletion	p.N57_G91del35	(+)	paternal	17	30	(+)	(+)	(–)	Syncope/AF	[2]
5	F	c.506G>A	p.R169Q	(+)	*de novo*	5	5	(+)	(+)	(+)	NA	[2-4]
6	F	c.506G>A	p.R169Q	(+)	*de novo*	7	9	(+)	(+)	(+)	NA	[2-4]
7	F	c.506G>A	p.R169Q	(+)	*de novo*	4	4	(–)	(+)	(+)	NA	[2-4]
8	M	c.506G>A	p.R169Q	(+)	*de novo*	6	6	(–)	(+)	(+)	NA	[2-4]
9	F	c.506G>T	p.R169L	(+)	*de novo*	9	9	(+)	(–)	(+)	NA	[2]
10	F	c.515G>A	p.G172E	(+)	*de novo*	6	8	(+)	(+)	(+)	NA	[3]
11	M	c.518A>G	p.E173G	(+)	*de novo*	2	4	(+)	(+)	(–)	NA	
12	M	c.527G>A	p.R176Q	(–)	paternal	9	9	(+)	(–)	(–)	Syncope	[5]
13	F	c.527G>A	p.R176Q	(–)	paternal	9	22	(+)	(+)	(–)	(–)	[5]
14	M	c.533G>C	p.G178A	(+)	*de novo*	12	12	(–)	(+)	(–)	NA	[2]
15	M	c.535G>A	p.D179N	(+)	*de novo*	4	4	(+)	(–)	(+)	NA	[6]
16	M	c.1069G>A	p.G357S	(+)	maternal	13	13	(+)	(–)	(+)	(–)	[3]
17	F	c.1202A>G	p.D401G	(+)	maternal	11	11	(–)	(+)	(–)	(–)	
18	F	c.1244C>G	p.T415R	(+)	*de novo*	8	42	(+)	(–)	(–)	NA	[6]
19	F	c.1258C>T	p.R420W	(+)	maternal	12	13	(+)	(+)	(–)	(–)	[7]
20	F	c.1259G>A	p.R420Q	(–)	maternal	7	12	(+)	(+)	(–)	Syncope/VF	[2, 6, 8, 9]
21	M	c.1259G>A	p.R420Q	(–)	maternal	13	14	(+)	(+)	(+)	(–)	[2, 6, 8, 9]
22	M	c.1259G>A	p.R420Q	(+)	maternal	10	11	(–)	(+)	(–)	Syncope	[2, 6, 8, 9]
23	M	c.1259G>A	p.R420Q	(+)	maternal	NA	14	(–)	(–)	(–)	(–)	[2, 6, 8, 9]

24	F	c.1372G>A	p.D458N	(+)	paternal	10	11	(+)	(+)	(–)	(–)	
25	F	c.1375C>G	p.L459V	(–)	paternal	10	37	(+)	(–)	(+)	PVC	
26	M	c.5128C>A	p.H1710N	(+)	maternal	NA	8	(–)	(–)	(–)	(–)	
27	M	c.5170G>A	p.E1724K	(+)	maternal	8	11	(+)	(–)	(–)	Syncope	2, 6, 7, 9
28	F	c.5170G>A	p.E1724K	(–)	maternal	10	25	(+)	(–)	(–)	Syncope/PVC	2, 6, 7, 9
29	F	c.6507G>T	p.E2169D	(–)	maternal	7	7	(+)	(–)	(+)	Syncope	2, 6, 7, 9
30	M	c.6574A>T	p.M2192L	(+)	maternal	13	13	(+)	(+)	(–)	(–)	2, 6
31	F	c.6645T>G	p.F2215L	(+)	*de novo*	5	7	(+)	(+)	(–)	NA	
32	F	c.6649C>T	p.H2217Y	(–)	maternal	5	7	(+)	(–)	(–)	Syncope	6
33	M	c.6737C>T	p.S2246L	(+)	*de novo*	13	13	(–)	(+)	(+)	NA	2-4, 6
34	F	c.6737C>T	p.S2246L	(+)	*de novo*	3	3	(–)	(+)	(–)	NA	2-4, 6
35	M	c.6737C>T	p.S2246L	(+)	*de novo*	3	3	(–)	(+)	(–)	NA	2-4, 6
36	M	c.6737C>T	p.S2246L	(+)	*de novo*	2	2	(–)	(+)	(+)	NA	2-4, 6
37	F	c.6883G>A	p.G2295R	(+)	*de novo*	8	13	(+)	(+)	(–)	NA	
38	M	c.6887A>G	p.E2296G	(+)	*de novo*	11	12	(+)	(+)	(–)	NA	
39	F	c.6900C>G	p.D2300E	(+)	*de novo*	6	6	(–)	(+)	(–)	NA	
40	F	c.6919T>G	p.F2307V	(+)	*de novo*	7	13	(+)	(+)	(+)	NA	
41	M	c.7159G>A	p.A2387T	(+)	*de novo*	10	10	(–)	(+)	(–)	NA	3, 4, 10
42	F	c.7171T>C	p.F2391L	(+)	paternal	14	14	(+)	(–)	(–)	(–)	
43	M	c.7199G>T	p.G2400V	(+)	*de novo*	10	15	(+)	(+)	(–)	NA	2, 4
44	F	c.11583G>C	p.Q3861H	(+)	*de novo*	14	14	(–)	(+)	(–)	NA	2, 4
45	F	c.11583G>T	p.Q3861H	(+)	*de novo*	8	8	(+)	(–)	(+)	NA	2
46	F	c.11590A>G	p.N3864D	(+)	*de novo*	11	11	(–)	(+)	(–)	NA	2, 6
47	M	c.11812A>G	p.S3938G	(+)	*de novo*	4	5	(+)	(–)	(+)	NA	6
48	F	c.11836G>A	p.G3946S	(+)	*de novo*	6	16	(+)	(–)	(+)	NA	2, 6
49	M	c.11836G>A	p.G3946S	(+)	*de novo*	6	9	(+)	(+)	(+)	NA	2, 6
50	M	c.11836G>A	p.G3946S	(+)	*de novo*	5	7	(+)	(–)	(+)	NA	2, 6
51	F	c.11837G>T	p.G3946V	(+)	*de novo*	7	8	(+)	(–)	(+)	NA	
52	F	c.11924A>C	p.Q3975P	(+)	paternal	12	19	(+)	(–)	(–)	(–)	

53	M	c.12006G>T	p.M4002I	(+)	*de novo*	2	3	(+)	(–)	(+)	NA	[2]
54	M	c.12059T>C	p.F4020S	(+)	*de novo*	9	13	(+)	(–)	(+)	NA	
55	F	c.12301C>T	p.L4101F	(+)	*de novo*	2	3	(+)	(–)	(–)	NA	
56	M	c.12301C>T	p.L4101F	(+)	*de novo*	5	5	(–)	(+)	(–)	NA	
57	M	c.12371G>A	p.S4124N	(–)	maternal	9	11	(+)	(–)	(–)	(–)	[2]
58	M	c.12533A>G	p.N4178S	(+)	*de novo*	4	7	(+)	(–)	(–)	NA	[2, 3, 10]
59	M	c.12559G>A	p.E4187K	(+)	*de novo*	7	7	(+)	(–)	(–)	NA	[2, 3, 6, 10]
60	F	c.12579C>G	p.C4193W	(+)	*de novo*	6	6	(–)	(+)	(–)	NA	[2, 6]
61	M	c.12586A>G	p.T4196A	(+)	*de novo*	7	9	(+)	(–)	(–)	NA	
62	M	c.13463A>C	p.Q4488P	(+)	*de novo*	10	10	(+)	(–)	(–)	NA	[2]
63	M	c.13489C>T	p.R4497C	(+)	maternal	8	14	(+)	(+)	(–)	(–)	[2, 5, 6, 11]
64	M	c.13489C>T	p.R4497C	(+)	*de novo*	8	8	(–)	(+)	(+)	NA	[5, 6, 11]
65	M	c.13763T>C	p.I4588T	(+)	*de novo*	3	3	(–)	(+)	(+)	NA	
66	F	c.13800T>G	p.F4600L	(+)	*de novo*	9	11	(+)	(–)	(–)	NA	[2]
67	M	c.13997T>A	p.I4666N	(+)	*de novo*	5	6	(+)	(–)	(–)	NA	
68	M	c.14158C>T	p.L4720F	(+)	*de novo*	6	15	(+)	(–)	(+)	NA	
69	M	c.14174A>G	p.Y4725C	(+)	*de novo*	10	28	(+)	(–)	(–)	NA	[2]
70	F	c.14251A>C	p.K4751Q	(+)	*de novo*	6	9	(+)	(–)	(+)	NA	[2, 4, 9]
71	M	c.14311G>A	p.V4771I	(+)	*de novo*	10	11	(+)	(–)	(–)	NA	[2-5, 9]
72	M	c.14311G>A	p.V4771I	(+)	*de novo*	10	12	(+)	(–)	(+)	NA	[2-5]
73	F	c.14341T>C	p.Y4781H	(+)	*de novo*	2	2	(+)	(–)	(–)	NA	
74	F	c.14461G>A	p.V4821I	(+)	*de novo*	6	10	(+)	(–)	(+)	NA	[6]
75	M	c.14461G>A	p.V4821I	(+)	*de novo*	10	14	(+)	(+)	(–)	NA	[6]
76	F	c.14461G>A	p.V4821I	(+)	*de novo*	8	11	(+)	(–)	(–)	NA	[6]
78	M	c.14778A>G	p.I4926M	(+)	*de novo*	5	5	(–)	(+)	(+)	NA	
79	M	c.14806C>A	p.Q4936K	(+)	*de novo*	14	17	(+)	(+)	(–)	NA	[2]
80	M	c.14832_1483 4dupTCA	p.4944_4945insH	(+)	*de novo*	5	5	(–)	(+)	(–)	NA	[2]
81	M	c.14876G>A	p.R4959Q	(+)	*de novo*	7	9	(+)	(+)	(–)	NA	

82	F	c.14878A>C	p.K4960Q	(+)	*de novo*	15	18	(+)	(+)	(–)	NA	
83	M	c.6023 –2 A>G	Splicing Error	(+)	*de novo*	4	9	(+)	(–)	(–)	NA	[6]

*Trio (+): Both of the parents underwent genetic testing, (): One parent has been confirmed to have same variants with probands , proving heritability, but the other has not been tested.

AF: atrial fibrillation, CA: cardiac arrest, PVC: premature ventricular contraction, NA: not applicable, VT: ventricular tachycardia

Supplemental Table 3. *In silico* prediction of *RYR2* variants

Variants		Mutation accessor*	Poly-Phen-2†	CADD Score‡	ClinVar§	VarSome‖
c.100A>G	p.K34E	Medium	Possibly damaging	24.9	VUS	VUS/LP
c.506G>A	p.R169Q	Medium	Probably damaging	29.2	P/LP	P
c.506G>T	p.R169L	Medium	Probably damaging	29	P	LP
c.515G>A	p.G172E	Medium	Probably damaging	27.3	LP	LP
c.518A>G	p.E173G	Medium	Probably damaging	28.3		VUS/P
c.527G>A	p.R176Q	Medium	Probably damaging	26.3	P	P
c.533G>C	p.G178A	Medium	Probably damaging	25.9		VUS/P
c.535G>A	p.D179N	Medium	Probably damaging	28.9	VUS	LP
c.1069G>A	p.G357S	Medium	Probably damaging	26.6	P	LP
c.1202A>G	p.D401G	Medium	Possibly damaging	23		VUS/P
c.1244C>G	p.T415R	Medium	Probably damaging	23.6		LP
c.1258C>T	p.R420W	Medium	Probably damaging	27	P	P
c.1259G>A	p.R420Q	Medium	Probably damaging	25.3	P	P
c.1372G>A	p.D458N	Medium	Probably damaging	25.3	VUS	VUS/LP
c.1375C>G	p.L459V	Medium	Probably damaging	21.5	VUS	VUS/LP
c.5128C>A	p.H1710N	Medium	Probably damaging	26		VUS/P
c.5170G>A	p.E1724K	Medium	Probably damaging	29.6	P/LP	LP
c.6507G>T	p.E2169D	Medium	Probably damaging	25		VUS/P
c.6574A>T	p.M2192L	Low	Probably damaging	24.9		VUS/P
c.6645T>G	p.F2215L	Medium	Probably damaging	27.7		VUS/P
c.6649C>T	p.H2217Y	Medium	Probably damaging	29	LP	LP
c.6737C>T	p.S2246L	Medium	Probably damaging	28.9	P	P
c.6883G>A	p.G2295R	Medium	Probably damaging	32	LP	LP
c.6887A>G	p.E2296G	Medium	Probably damaging	30		VUS/P
c.6900C>G	p.D2300E	Medium	Probably damaging	23.7		VUS/P
c.6919T>G	p.F2307V	Medium	Probably damaging	28.3		VUS/P
c.7159G>A	p.A2387T	Medium	Probably damaging	28.2	P/LP	P
c.7171T>C	p.F2391L	Medium	Probably damaging	31		VUS/P
c.7199G>T	p.G2400V	Medium	Probably damaging	28		VUS/P
c.11583G>C	p.Q3861H	High	Probably damaging	25.4	LP	VUS/LP
c.11583G>T	p.Q3861H	High	Probably damaging	25.7	LP	VUS/LP
c.11590A>G	p.N3864D	Medium	Probably damaging	28.5	VUS	VUS/LP
c.11812A>G	p.S3938G	Medium	Probably damaging	25.7		VUS/LP
c.11836G>A	p.G3946S	Medium	Probably damaging	31	P	LP
c.11837G>T	p.G3946V	Medium	Probably damaging	28.7		VUS/P
c.11924A>C	p.Q3975P	Medium	Probably damaging	27.6		VUS/LP
c.12006G>T	p.M4002I	Low	Probably damaging	25.8	LP	LP
c.12059T>C	p.F4020S	Medium	Probably damaging	31		VUS/LP
c.12301C>T	p.L4101F	Medium	Probably damaging	24.9	LP	LP

c.12371G>A	p.S4124N	Medium	Probably damaging	25.5		VUS/LP
c.12533A>G	p.N4178S	Low	Probably damaging	23.4	P/LP	LP
c.12559G>A	p.E4187K	Medium	Probably damaging	28.7		VUS/LP
c.12579C>G	p.C4193W	Medium	Probably damaging	23.8		VUS/P
c.12586A>G	p.T4196A	Low	Possibly damaging	22.7		LP
c.13463A>C	p.Q4488P	Medium	Probably damaging	26.3		VUS/LP
c.13489C>T	p.R4497C	Medium	Probably damaging	32	P/LP	P
c.13763T>C	p.I4588T	Medium	Possibly damaging	27.6	LP	LP
c.13800T>G	p.F4600L	Medium	Benign	23.2		VUS/P
c.13997T>A	p.I4666N	Medium	Probably damaging	27		VUS/LP
c.14158C>T	p.L4720F	Medium	Probably damaging	28.6		VUS/LP
c.14174A>G	p.Y4725C	Medium	Probably damaging	29.4	LP	LP
c.14251A>C	p.K4751Q	Medium	Probably damaging	29.3	P/LP	LP
c.14311G>A	p.V4771I	Low	Probably damaging	24.9	P	P
c.14341T>C	p.Y4781H	Medium	Probably damaging	26.2	LP	LP
c.14461G>A	p.V4821I	Medium	Probably damaging	24.2		VUS/LP
c.14778A>G	p.I4926M	Medium	Probably damaging	24.5		VUS/LP
c.14806C>A	p.Q4936K	Medium	Possibly damaging	32		LP
c.14876G>A	p.R4959Q	Low	Probably damaging	32	P/LP	P
c.14878A>C	p.K4960Q	Medium	Probably damaging	27.3		VUS/LP

* http://mutationassessor.org/r3

† http://genetics.bwh.harvard.edu/pph2/

‡ http://cadd.gs.washington.edu/home

§ https://www.ncbi.nlm.nih.gov/clinvar/

|| https://varsome.com/

LP: likely pathogenic, P: pathogenic, VUS: variant of unknown significance.

Supplemental Table 4. Allele frequency of *RYR2* variants

Genomic position in GRCh37*	Variant		Variant ID	Allele frequency		
				HGVD†	gnomAD browser‡	TogoVar§
1:237433848	c.100A>G	p.K34E	rs876661385	¬	¬	¬
1:237540665	c.506G>A	p.R169Q	rs397516539	¬	¬	¬
1:237540665	c.506G>T	p.R169L	rs397516539	¬	¬	¬
1:237540674	c.515G>A	p.G172E	rs1553426678	¬	¬	¬
1:237540677	c.518A>G	p.E173G	¬	¬	¬	¬
1:237540686	c.527G>A	p.R176Q	rs794728708	¬	¬	¬
1:237540692	c.533G>C	p.G178A	¬	¬	¬	¬
1:237540694	c.535G>A	p.D179N	rs794728709	¬	¬	¬
1:237604682	c.1069G>A	p.G357S	rs1401116572	¬	¬	¬
1:237608732	c.1202A>G	p.D401G	¬	¬	¬	¬
1:237608774	c.1244C>G	p.T415R	rs1288202574	¬	¬	¬
1:237608788	c.1258C>T	p.R420W	rs190140598	2/2418	3/249018	¬
1:237608789	c.1259G>A	p.R420Q	rs794728721	¬	¬	¬
1:237617770	c.1372G>A	p.D458N	rs1553458124	¬	¬	¬
1:237617773	c.1375C>G	p.L459V	¬	¬	¬	¬
1:237777556	c.5128C>A	p.H1710N	¬	¬	¬	¬
1:237777598	c.5170G>A	p.E1724K	rs794728740	¬	¬	¬
1:237794793	c.6507G>T	p.E2169D	¬	¬	¬	¬
1:237796896	c.6574A>T	p.M2192L	¬	¬	¬	¬
1:237796965	c.6645T>G	p.F2215L	¬	¬	¬	¬
1:237796971	c.6649C>T	p.H2217Y	rs1372052481	¬	¬	¬
1:237798237	c.6737C>T	p.S2246L	rs121918597	¬	¬	¬
1:237801747	c.6883G>A	p.G2295R	rs794728745	¬	¬	¬
1:237801751	c.6887A>G	p.E2296G	¬	¬	¬	¬
1:237801764	c.6900C>G	p.D2300E	¬	¬	¬	¬
1:237801783	c.6919T>G	p.F2307V	¬	¬	¬	¬
1:237804240	c.7159G>A	p.A2387T	rs794728753	¬	¬	¬
1:237804252	c.7171T>C	p.F2391L	¬	¬	¬	¬
1:237804280	c.7199G>T	p.G2400V	¬	¬	¬	¬
1:237935337	c.11583G>C	p.Q3861H	¬	¬	¬	¬
1:237935337	c.11583G>T	p.Q3861H	¬	¬	¬	¬
1:237935344	c.11590A>G	p.N3864D	rs1573887621	¬	¬	¬
1:237942002	c.11812A>G	p.S3938G	¬	¬	¬	¬
1:237942026	c.11836G>A	p.G3946S	rs794728777	¬	¬	¬
1:237942027	c.11837G>T	p.G3946V	¬	¬	¬	¬
1:237944908	c.11924A>C	p.Q3975P	¬	¬	¬	¬
1:237947018	c.12006G>T	p.M4002I	¬	¬	¬	¬

1:237947071	c.12059T>C	p.F4020S	¬	¬	¬	¬
1:237947313	c.12301C>T	p.L4101F	rs794728785	¬	¬	¬
1:237947383	c.12371G>A	p.S4124N	¬	¬	¬	¬
1:237947545	c.12533A>G	p.N4178S	rs794728787	¬	¬	¬
1:237947571	c.12559G>A	p.E4187K	rs794728790	¬	¬	¬
1:237947591	c.12579C>G	p.C4193W	¬	¬	¬	¬
1:237947598	c.12586A>G	p.T4196A	rs1174371313	¬	¬	¬
1:237951422	c.13463A>C	p.Q4488P	¬	¬	¬	¬
1:237954741	c.13489C>T	p.R4497C	rs121918600	¬	¬	¬
1:237955604	c.13763T>C	p.I4588T	rs876661386	¬	¬	¬
1:237957184	c.13800T>G	p.F4600L	¬	¬	¬	¬
1:237961377	c.13997T>A	p.I4666N	¬	¬	2/244982	¬
1:237969443	c.14158C>T	p.L4720F	¬	¬	¬	¬
1:237969459	c.14174A>G	p.Y4725C	¬	¬	¬	¬
1:237969536	c.14251A>C	p.K4751Q	rs794728802	¬	¬	¬
1:237972213	c.14311G>A	p.V4771I	rs794728804	¬	¬	¬
1:237972243	c.14341T>C	p.Y4781H	rs1553335836	¬	¬	¬
1:237982363	c.14461G>A	p.V4821I	rs1432337470	¬	¬	¬
1:237994835	c.14778A>G	p.I4926M	¬	¬	¬	¬
1:237994863	c.14806C>A	p.Q4936K	¬	¬	¬	¬
1:237995919	c.14876G>A	p.R4959Q	rs794728811	¬	¬	¬
1:237995921	c.14878A>C	p.K4960Q	¬	¬	¬	¬

* Only the first position is described on deletion or insertions variant that involves several bases.

† http://www.hgvd.genome.med.kyoto-u.ac.jp/index.html

‡ http://gnomad.broadinstitute.org We described the total allele count of all the ethnic groups in genomAD v2.1.1.

§https://togovar.biosciencedbc.jp/ We described summed up numbers of the Japanese datasets (Japanese Genotype-phenotype Archive, Human Genetic Variation Database, and ToMMo 3.5KJPNv2 Allele Frequency Panel) in TogoVar databases.

Supplemental Table 5. Characteristics of probands with or without Epilepsy or Intellectual disability

	Epilepsy* (+) n = 15	**Epilepsy* (-) n = 67**	**P-values**	**Intellectual disability (+) n = 8**	**Intellectual disability (-) n = 74**	**P-values**
Male sex, n (%)	11 (73.3)	34 (50.7)	0.15	4 (50.0)	41 (55.4)	1.00
De novo/Familial cases, n (%)	2/13 (13.3/86.7)	22/45 (32.8/67.2)	0.21	0/8 (0/100)	24/50 (32.4/67.6)	0.10
Age at first symptom, years	7.0 [5.3, 8.8]	8.0 [5.0, 10.0]	0.30	6.5 [4.8, 7.0]	8.0 [5.0, 10.0]	0.075
Age at clinical diagnosis, years	9.0 [8.5, 13.5]	10.0 [6.5, 13.0]	0.46	8.0 [5.5, 11.5]	10.5 [7.0,13.0]	0.28
Syncope†, n (%)	12 (80.0)	49 (73.1)	0.75	7 (87.5)	54 (73.0)	0.67
Syncope age, years	7.0 [5.5, 8.3]	8.0 [6.0, 10.0]	0.21	7.0 [5.5, 7.0]	8.0 [6.0, 10.0]	0.082
CA†, n (%)	7 (46.7)	34 (50.7)		3 (37.5)	38 (51.4)	0.71
CA age, years	9.0 [8.0, 11.0]	10.0 [5.3, 12.0]	0.93	8.0 [6.0,8.5]	10.0 [6.0,12.8]	0.29
Bidirectional VT‡, n (%)	8 (53.3)	22 (32.8)	0.15	3 (37.5)	27 (36.5)	1.00
Variant location § , n (%)						
N-terminus domain	3 (21.4)	21 (31.3)	0.77	1 (12.5)	23 (31.5)	0.34
Central domain	2 (14.3)	9 (13.4)		1 (12.5)	10 (13.7)	
C-terminus domain	8 (57.1)	28 (41.8)		6 (75.0)	30 (41.1)	
Other area	1 (7.1)	9 (13.4)		0 (0.0)	10 (13.7)	

Data are n (%) and median [interquartile range].

CA: cardiac arrest, VT: ventricular tachycardia.

* Epilepsy includes epilepsy and epileptic seizure

† All syncope and CA events before clinical diagnosis have counted on the list and some probands have both events.

‡ Documentation on any electrocardiogram recordings

§ Splicing error is not included.

Probands with epilepsy: R169Q, R176Q, T415R, H1710N, S2246L, F2307V, G3946S, M4002I, F4020S, N4178S, T4196A, L4720F, V4821I, I4926M, Splicing Error (c.6023–2 A>G)

Probands with intellectual disability; F2307V, E4187K, I4666N, L4720F, Y4781H, V4821I, R4959Q

Underlined variants: One proband for each variants showed both epilepsy and intellectual disability

Supplemental Table 6. Clinical characteristics of the parents carrying *RYR2* variants

	Total	Father	Mother
Number of parents, n	**24**	**7**	**17**
Syncope, n (%)	9 (37.5)*	1 (14.3)	8 (47.0)*
CA, n (%)	1 (4.2)*	0 (0)	1 (5.9)*
Atrial fibrillation, n (%)	2 (8.3)	1 (12.5)	1 (5.9)
Premature ventricular contractions, (%)	3 (12.0)	1 (12.5)	2 (11.8)

Data are n (%)

CA: cardiac arrest

* This person had both syncope and CA event.

Supplemental Table 7. Association between probands phenotype and parental syncope or aborted cardiac arrest.

	Parental history of syncope or CA (+) n = 9	Parental history of syncope or CA (-) n = 15	P-values
Male sex, n (%)	4 (44.4)	7 (46.7)	1.00
Age at first symptom, years	8.0 [7.0, 10.0]	12.0 [10.0, 13.0]	0.019
Age at clinical diagnosis, years	11.0 [9.0, 12.0]	14.0 [12.0, 15.5]	0.10
Syncope*, n (%)	8 (88.9)	12 (80.0)	1.00
Syncope age, years	7.5 [6.5, 9.3]	13.0 [10.0, 13.3]	0.016
CA*, n (%)	3 (33.3)	7 (46.7)	0.68
CA age, years	12.0 [11.0, 21.0]	12.0 [11.0, 13.5]	0.82
Initial symptom: Syncope/ CA, n (%)	8/1 (88.9/11.1)	10/3 (76.9/23.1)	0.62
Worst symptom: Syncope/ CA, n (%)	6/3 (66.7/33.3)	6/7 (46.2/53.8)	0.42
ECG parameters			
Heart rate, base per minutes	57 [53, 70]	60 [54, 73]	0.61
QT, ms	409 [400, 420]	420 [400, 441]	0.42
QTc, ms	393 [384, 441]	424 [401, 447]	0.16
Bidirectional VT, n (%)	1 (11.1)	3 (20.0)	1.00
Bradycardia for age, n (%)	3 (33.3)	1 (6.7)	0.13
Epilepsy, n (%)	0 (0)	2 (13.3)	0.51

Data are n (%) and median [interquartile range].

CA: cardiac arrest, VT: ventricular tachycardia.

* All syncope and CA events before clinical diagnosis have counted on the list and some probands have both events.

Supplemental Table 8.

Logistic regression analyses of *RYR2* variant carrying parent's factors for proband's aborted cardiac arrest.

	Univariable	Multivariable*
Variables	**OR (95% CI)**	**Adjusted OR (95% CI)**
Maternal-originated inheritance, (vs Paternal)	0.93 (0.16 – 5.54)	0.86 (0.14 – 5.41)
Parent's history of syncope or CA	0.57 (0.10 – 3.18)	0.57 (0.10 – 3.21)

*Multivariate logistic regression analysis was adjusted for proband's sex.

CA: cardiac arrest, CI: confidence interval, OR: odds ratio.

Supplemental Table 9. Characteristics of the probands by inheritance origin.

	Maternal-originated inheritance n = 17	Paternal-originated inheritance n = 7	P-values
Male sex, n (%)	9 (52.9)	2 (28.6)	0.39
Age at first symptom, years	10.0 [7.5, 12.5]	10.0 [9.5, 13.0]	0.25
Age at clinical diagnosis, years	12.0 [11.0, 14.0]	19.0 [12.5, 26.0]	0.067
Syncope*, n (%)	13 (76.5)	7 (100)	0.28
Syncope age, years	9.0 [7.0, 13.0]	12.0 [10.0, 15.0]	0.086
CA*, n (%)	7 (41.2)	3 (42.9)	1.00
CA age, years	12.0 [11.5, 13.5]	11.0 [10.0, 20.5]	0.65
Initial symptom: Syncope/ CA, n (%)	12/3 (80.0/20.0)	6/1 (85.7/14.3)	1.00
Worst symptom: Syncope/ CA, n (%)	8/7 (53.3/46.7)	4/3 (57.1/42.9)	1.00
ECG parameters			
Heart rate, base per minutes	59 [56, 72]	53 [44, 67]	0.15
QT, ms	412 [392, 428]	409 [400, 461]	0.46
QTc, ms	416 [396, 446]	404 [392, 445]	0.78
Bidirectional VT, n (%)	3 (17.6)	1 (14.3)	1.00
Bradycardia for age, n (%)	2 (11.8)	2 (28.6)	0.55
Epilepsy, n (%)	1 (5.9)	1 (14.3)	0.51

Data are n (%) and median [interquartile range].

CA: cardiac arrest, VT: ventricular tachycardia.

* All syncope and CA events before clinical diagnosis have counted on the list and some probands have both events.

Supplemental Table 10. Characteristics of the probands by variant's domain.

	C-terminus domain n = 36	N-terminus domain n = 24	P-values
De novo/ Familial cases, n (%)	33/3 (91.7/8.3)	10/14 (41.7/58.3)	<0.001
Age at first symptom, years	7.0 [5.0, 9.0]	9.0 [6.0, 11.5]	0.11
Syncope*, n (%)	28 (77.8)	18 (75.0)	1.00
Syncope age, years	7.0 [5.8, 9.0]	9.0 [6.3, 13.0]	0.12
CA*, n (%)	13 (36.1)	15 (62.5)	0.065
CA age, years	9.0 [5.0, 14.0]	10.0 [7.0, 12.0]	0.82

Data are n (%) and median [interquartile range].

CA: cardiac arrest.

* All syncope and CA events before clinical diagnosis have counted on the list and some probands have both events.

Supplemental References

1. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. ***Genetics in medicine*** May 2015;17:405-424.

2. Ohno S, Hasegawa K, Horie M. Gender Differences in the Inheritance Mode of RYR2 Mutations in Catecholaminergic Polymorphic Ventricular Tachycardia Patients. ***PLOS ONE*** 2015;10:e0131517.

3. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, Hofman N, Bikker H, van Tintelen JP, Mannens MM, Wilde AA, Ackerman MJ. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. ***Journal of the American College of Cardiology*** Nov 24 2009;54:2065-2074.

4. Kawamura M, Ohno S, Naiki N, et al. Genetic Background of Catecholaminergic Polymorphic Ventricular Tachycardia in Japan. ***Circ J*** 2013;77:1705-1713.

5. Priori SG, Chen SRW. Inherited Dysfunction of Sarcoplasmic Reticulum Ca²⁺ Handling and Arrhythmogenesis. ***Circulation Research*** 2011;108:871-883.

6. Kawata H, Ohno S, Aiba T, et al. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Associated With Ryanodine Receptor (RyR2) Gene Mutations – Long-Term Prognosis After Initiation of Medical Treatment –. ***Circ J*** 2016;advpub.

7. van der Werf C, Nederend I, Hofman N, et al. Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives. ***Circulation Arrhythmia and electrophysiology*** Aug 1 2012;5:748-756.

8. Wang YY, Mesirca P, Marqués-Sulé E, Zahradnikova A, Jr., Villejoubert O, D'Ocon P, Ruiz C, Domingo D, Zorio E, Mangoni ME, Benitah JP, Gómez AM. RyR2R420Q catecholaminergic polymorphic ventricular tachycardia mutation induces bradycardia by disturbing the coupled clock pacemaker mechanism. ***JCI insight*** Apr 20 2017;2.

9. Ozawa J, Ohno S, Fujii Y, Makiyama T, Suzuki H, Saitoh A, Horie M. Differential Diagnosis Between Catecholaminergic Polymorphic Ventricular Tachycardia and Long QT Syndrome Type 1 - Modified Schwartz Score. ***Circ J*** Aug 24 2018;82:2269-2276.

10. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia. ***Circulation*** 2009;119:2426-2434.

11. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. ***Circulation*** Jul 2 2002;106:69-74.