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Impact of cascade screening for catecholaminergic polymorphic ventricular tachycardia type 1

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ABSTRACT

Objective Human cardiac *ryanodine receptor 2* (*RYR2*) shows autosomal-dominant inheritance in catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1); however, *de novo* variants have been observed in sporadic cases. Here, we investigated CPVT1-related *RYR2* variant inheritance and its clinical significance between familial and *de novo* cases.

Methods We enrolled 82 independent CPVT1 probands (median age: 10.0 (7.0–13.0) years; 45 male) carrying the *RYR2* variants and whose biological origin could be confirmed by parental genetic analysis: assured familial inheritance (familial group: n=24) and *de novo* variants (*de novo* group: n=58). We examined the clinical characteristics of the probands and their family members carrying the *RYR2* variants.

Results In the *de novo* group, the *RYR2* variants were more likely located in the C-terminus domain and less likely in the N-terminus domain than those in the familial group. The cumulative incidence of the first cardiac events (syncope and cardiac arrest (CA) or CA only) of the probands at the age of 5 and 10 years was higher in the *de novo* group than in the familial group. Nearly half of the probands in both groups experienced CA events before diagnosis. Only 37.5% of their genotype-positive parents had symptoms; however, at least 66.7% of the genotype-positive siblings were symptomatic.

Conclusions CPVT1 probands harbouring *de novo* *RYR2* variants showed an earlier onset of symptoms than those with assured familial inheritance. Cascade screening may enable early diagnosis, risk stratification and prophylactic therapeutic intervention to prevent sudden cardiac death of probands and potential genotype-positive family members.

INTRODUCTION

Variants of the human cardiac ryanodine receptor 2 gene (*RYR2*) are known arrhythmogenic underliers responsible for catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1),[1–4] identified in ~60% of patients with catecholaminergic polymorphic ventricular tachycardia (CPVT)[4–7] and clinically characterised as exercise-induced or emotional stress-induced polymorphic ventricular tachycardia (VT) capable of leading to sudden cardiac death, especially in young patients.[8] The cardiac ryanodine receptor channel controls Ca^{2+} release from the sarcoplasmic reticulum to the cytosol during the plateau phase of the action potential responsible for myocardial contraction, and CPVT1-related *RYR2* variants have been reported to cause abnormal Ca^{2+} leak from sarcoplasmic reticulum, which may induce arrhythmias under elevated adrenergic tone.[9–11]

Autosomal-dominant inheritance of the CPVT1-related *RYR2* variants was initially identified from a large family cascade screening.[1 4] *De novo* variants have also been found in 35%–92% of CPVT1 probands,[12–14] but the phenotypic differences between *de novo* and familial cases remain unclear. Generally, mutation-specific genetic testing for family members is recommended if a disease-causative *RYR2* variant is identified in the CPVT proband.[15 16] However, limited evidence exists as to whether inheritance can be assessed by the phenotypes and who would benefit from genetic testing. Moreover, as genetic testing sometimes raises sensitive discussion and some family members are hesitant to undergo testing, further clinical data to support cascade screening are required. Hence, we aimed to investigate the inheritance of CPVT1-related *RYR2* variants, their clinical significance between *de novo* and familial probands, and clinical features of family members in the familial group.

METHODS

Settings and participants

Among 346 Japanese patients (probands) with suspected CPVT and had undergone *RYR2* genetic screening at the National Cerebral and Cardiovascular Center, Japan (2006–2021), or Shiga University of Medical Science, Japan, (2005–2020), 170 *RYR2*-negative probands and 13 probands who did not meet the CPVT criteria (n=12) or whose parents had an apparent mosaic *RYR2* variant (n=2) were excluded. Probands who had a compound heterozygous variant inherited from both parents (n=1) and had a double mutation of maternal origin (n=1) were excluded. Furthermore, 72 probands whose family screening had not been completely performed were excluded. Therefore, in this retrospective study, we enrolled 82 sets of independent family lines whose probands were clinically diagnosed with CPVT carrying *RYR2* variants based on the 2013 expert consensus recommendation

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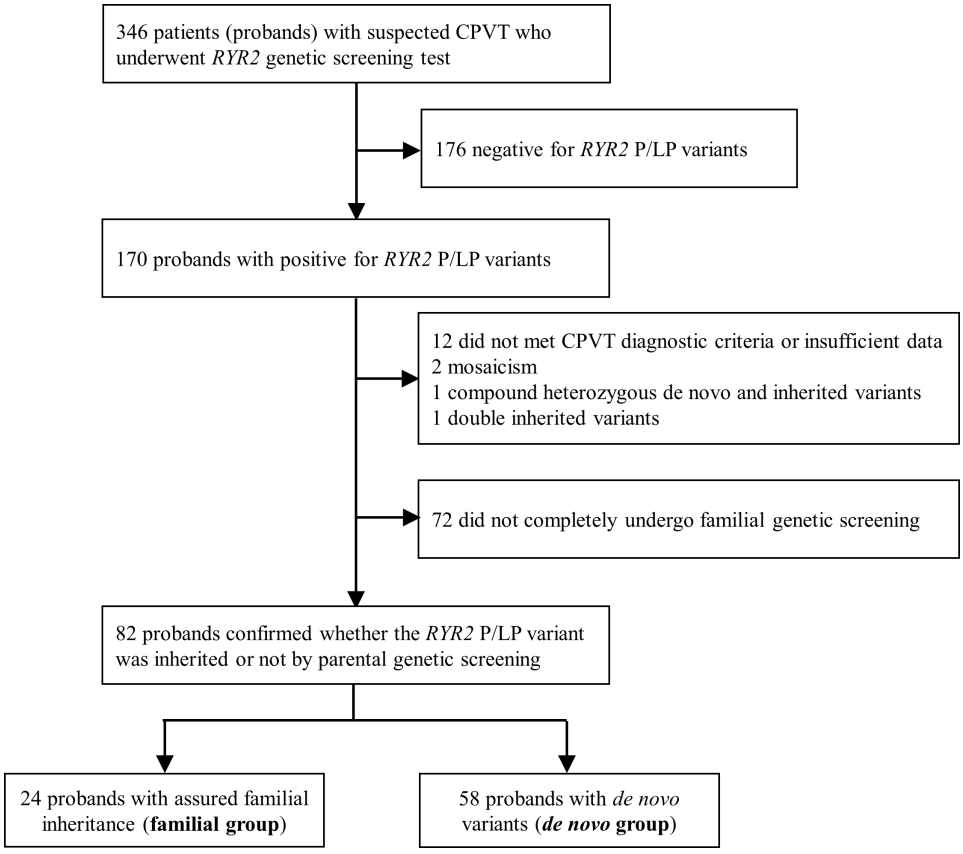

Figure 1 Study profile. Study flowchart showing patients (probands) with CPVT with *RYR2* pathogenic (P) or likely pathogenic (LP) variants and those in which *RYR2* variants were determined to have or have not originated from either parents. CPVT, catecholaminergic polymorphic ventricular tachycardia.

(figure 1).[8] For the *RYR2* variants, we included only pathogenic or likely pathogenic variants according to the American College of Medical Genetics and Genomics guideline (online supplemental table 1).[17]

Written informed consent was obtained from the subjects before genetic testing at each institute. Affirmative agreement for genetic and clinical studies from subjects and permission of their parents were obtained for child subjects. Some probands were previously described in studies from 2015, 2016 and 2018.[14 18]

When only one of the parents was identified as carrying the same *RYR2* variant as the child (proband), we included him/her in the familial inheritance group, even if the other parent did

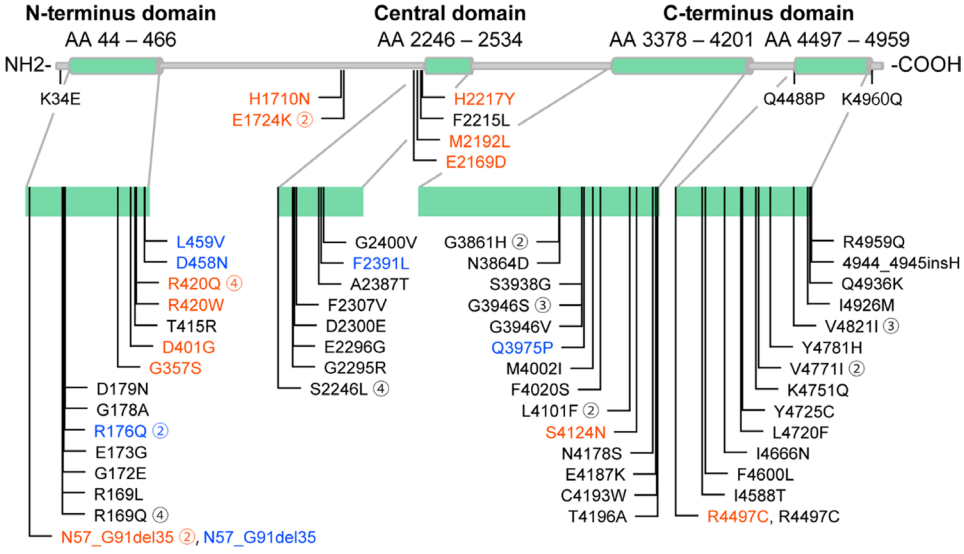

Figure 2 Location of the *RYR2* variants. The *RYR2* variants of the probands in this study. Red characters, maternal-originated variants; blue characters, paternal-originated variants and black characters, *de novo* variants. The encircled number adjacent to each variant shows the number of probands who had the same variant.

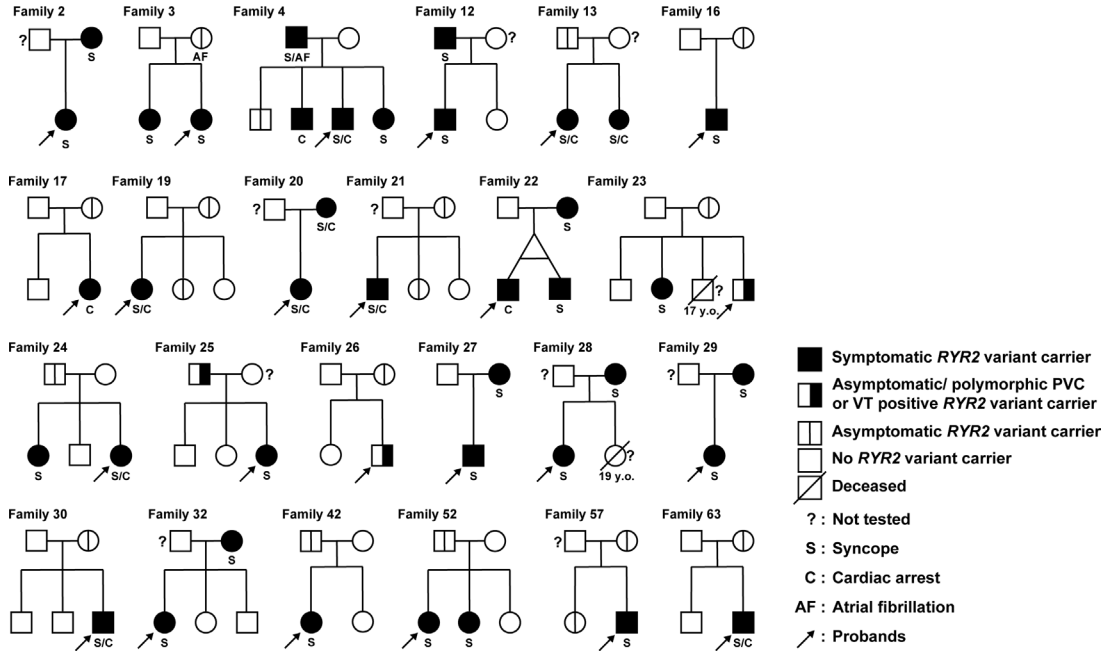

Figure 3 Family pedigrees of familial CPVT. Among 24 pedigrees of familial CPVT1 cases, 14 families underwent complete genetic screening for both parents. In the remaining 10 families, there was only one parent confirmed as genotype-positive, and the other was not completely confirmed as genotype-negative. CPVT, catecholaminergic polymorphic ventricular tachycardia.

not undergo genetic testing. Contrastingly, when neither parent carried the same *RYR2* variant, we included them in the *de novo* group. In the inherited families, the genotype and phenotype of the siblings were also examined. The clinical characteristics of the *de novo* and familial groups, maternal-originated or paternal-originated variants, were assessed for all probands.

Clinical findings

Clinical information of the probands and family members were obtained from their medical records, and cardiac arrest (CA) and syncopal events were investigated. Syncope was defined as a transient loss of consciousness with or without seizures or confirmed ventricular arrhythmia that did not require resuscitation or defibrillation. The QT interval was corrected (QTc) for the heart rate using Bazett's formula. We defined bradycardia as heart rate below the second percentile for age.[19 20] Bidirectional VT was defined as beat-to-beat alternation of the QRS axis present for more than four beats on any ECG recording.[21]

Genetic testing and location classification

Genetic screening of all probands and families was performed by combining the conventional Sanger method, multiplex ligation-dependent probe amplification and next-generation sequencing using MiSeq (Ilumina, San Diego, California, USA), as previously described.[18] Variants detected with next-generation sequencing were further reconfirmed by Sanger sequencing for accuracy in results. We assessed the *RYR2* variant location distribution by classifying four groups based on the known disease-related variant cluster domain: (1) N-terminal domain (amino acid (AA) 44–466), (2) central domain (AA 2256–2434), (3) C-terminal domain (AA 3778–4201 and 4497–4959) and (4) others outside the three domains.[9 22 23] As for missense variants, genetic significance was confirmed using information from public databases to exclude normal variation. This information was gathered in May 2021.

Statistical analysis

Quantitative variables are expressed as median (IQR). The Mann-Whitney U test was employed to compare continuous variables. Categorical variables are presented as number (n) and percentage (%) and compared using the χ^2 test or Fisher's exact test. To evaluate eccentricity distribution of *RYR2* variant locations, multiplicity-adjusted p values were calculated using the Bonferroni procedure. Gray's test was used to examine the equality of cumulative incidence for first syncope, first CA and any first cardiac event before CPVT diagnosis in probands among the familial and *de novo* groups, and multiplicity-adjusted p values were calculated using the Bonferroni procedure. We treated diagnosis and medication therapy initiation as competing risks in order to analyse the probands' event rate and diagnosis of probands or their siblings to analyse the siblings' event rate. The OR with a 95% CI was estimated using univariable and multivariable logistic regression analyses and adjusted for sex to evaluate parent-predictive factors responsible for CA events in a proband. Results with a $p<0.05$ based on a two-sided test were considered statistically significant. Statistical analyses were performed using EZR (V.1.51; Saitama Medical Center, Jichi Medical University, Saitama, Japan),[24] a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and SAS software (V.9.4; SAS Institute, Cary, North Carolina, USA).

Patients and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

RYR2 variants and clinical phenotypes of probands

Among 82 CPVT1 probands, 45 (54.9%) were men, 61 (74.4%) had a history of syncope and 41 (50.0%) suffered from CA mainly triggered by exercise or emotional stress before diagnosis.

Sixty-two *RYR2* variants were identified, 59 of which were missense variants. The location of the *RYR2* variants and the clinical background of each proband are shown in figure 2 and online supplemental table 2. Most of the variants were located in the N-terminus (AAs 44–466), central (AAs 2246–2534) and C-terminus (AAs 3378–4201 and 4497–4959) domains, which are CPVT1 hotspots.[23] Information regarding missense variants, such as in silico prediction and allele frequency, obtained from public databases is shown in online supplemental tables 3 and 4.

Differences between *de novo* and familial probands

Fifty-eight probands formed the *de novo* group. Twenty-four probands were confirmed as the familial group, with the same *RYR2* variants identified in the father (n=7) or mother (n=17). Details of the family pedigree of familial cases are shown in figure 3.

The percentages of subjects with initial symptoms, either syncope or CA, and those with the worst symptoms before clinical diagnosis of CPVT did not differ between groups (table 1). However, age at occurrence of the first symptom, CA and clinical diagnosis were significantly lower, and bidirectional VT was more frequently documented in the *de novo* group than in the familial group. Neurological phenotypes such as epilepsy and intellectual disability did not significantly differ between the two groups and were not related to clinical phynotypes (table 1, online supplemental table 5). Distribution of variant location in *RYR2* differed between groups (p<0.001), with variants in the *de novo* group more likely to be located in the C-terminus domain (33/57 (57.9%) vs 3/24 (12.5%), adjusted p<0.001) and less likely located in the N-terminus domain (10/57 (17.5%) vs 14/24 (58.3%), adjusted p<0.001) than those in the familial group.

Figure 4 shows the cumulative cardiac incidence before diagnosis, and table 2 shows actual event rates at different ages and their differences between the groups. The cumulative incidence of syncope or CA was higher in the *de novo* group than in the familial group at 5 and 10 years of age. However, the total event rate at 15 years of age and the overall cumulative incidence were not significantly different between groups (adjusted p=0.36 and p=0.10) (figure 4A,B). The cumulative incidence of the first cardiac event was higher in the *de novo* group than in the familial group at 5, 10 and 15 years of age and cumulative incidence differed between groups (adjusted p=0.002) (figure 4C). This indicates earlier occurrence of the first event in the *de novo* group than in the familial group.

Table 1 Clinical characteristics and variant locations between *de novo* and familial probands

	De novo group	Familial group	P value
Number of probands, n	58	24	
Male sex, n (%)	34 (58.6)	11 (45.8)	0.34
Age at first symptom, years	6.5(5.0, 9.0)	10.0(8.3, 12.8)	<0.001
Age at clinical diagnosis, years	9.0(5.3, 12.0)	13.0(11.0, 14.8)	<0.001
Syncope*, n (%)	41 (70.7)	20 (83.3)	0.28
Syncope age, years	7.0(5.0, 9.0)	10.0(8.0, 13.0)	0.001
CA*, n (%)	31 (53.4)	10 (41.7)	0.47
CA age, years	8.0(5.0, 12.0)	12.0(11.0, 13.8)	0.010
Initial symptom: syncope/CA, n (%)	41/17 (70.7/29.3)	18/4 (81.8/18.2)	0.40
Worst symptom: syncope/CA, n (%)	27/31 (46.6/53.4)	12/10 (54.5/45.5)	0.62
Reason for the genetic test: syncope/CA/ polymorphic VT on exercise stress ECG, n (%)	27/31/0 (46.6/53.4/0)	14/8/2 (58.3/33.3/8.3)	0.036
ECG parameters			
Heart rate, beats per minute	63(55, 77)	59(54, 73)	0.34
QT, ms	402(380, 441)	411(400, 432)	0.42
QTc, ms	421(397, 440)	410(396, 447)	0.95
Bidirectional VT†, n (%)	26 (44.8)	4 (16.7)	0.023
Bradycardia for age, n (%)	16 (27.6)	4 (16.7)	0.40
Atrial fibrillation†, n (%)	6 (10.3)	0 (0)	0.17
Epilepsy, n (%)	13 (22.4)	2 (8.3)	0.21
Intellectual disability, n (%)	8 (13.8)	0 (0)	0.097
Variant location‡, n (%)			
N-terminus domain	10 (17.5)	14 (58.3)	<0.001
Central domain	10 (17.5)	1 (4.2)	
C-terminus domain	33 (57.9)	3 (12.5)	
Other area	4 (7.0)	6 (25.0)	

Data are represented as n (%) and median (IQR).
*All syncope and CA events before clinical diagnosis were counted on the list and some probands have both events.
†Documentation on any ECG recordings
‡Splicing error is not included.
CA, cardiac arrest; VT, ventricular tachycardia.

Effects of *RYR2*-variant-carrying parents on probands

Online supplemental table 6 shows the clinical characteristics of genotype-positive parents. Among 24 parents, including 7 (29.2%) fathers and 17 (70.8%) mothers, only 9 (37.5%) cases experienced syncope, including 1 (4.2%) concomitant history of CA. To investigate whether parental history of syncope or CA affected the total incidence of probands before diagnosis, we compared the probands with and without a parental history of syncope or CA (online supplemental table 7). Proband age at the first symptom was significantly lower in probands whose parents had a history of syncope or CA than in those without any symptoms in their parents (7.5 years vs 13.0 years, p=0.016). However, we observed no significant difference in other clinical features between groups. Logistic regression analysis revealed that parental clinical or genetic factors were not always associated with CA events in the CPVT1 probands (online supplemental table 8).

We further investigated how paternal or maternal origin affects the phenotype of probands, but we observed no significant difference in clinical findings between probands with paternal-originated or maternal-originated *RYR2* variants (online supplemental table 9).

Clinical manifestation of genotype-positive siblings

All family pedigrees of the familial group are shown in figure 3. Two individuals had died at ages 17 and 19, respectively, (families 23 and 28, respectively) before genetic screening. Twenty-eight siblings belonging to the familial group (10 brothers and 18 sisters) underwent genetic testing, with 12 of them (3 brothers and 9 sisters) identified as carrying the same *RYR2* variants as their probands.

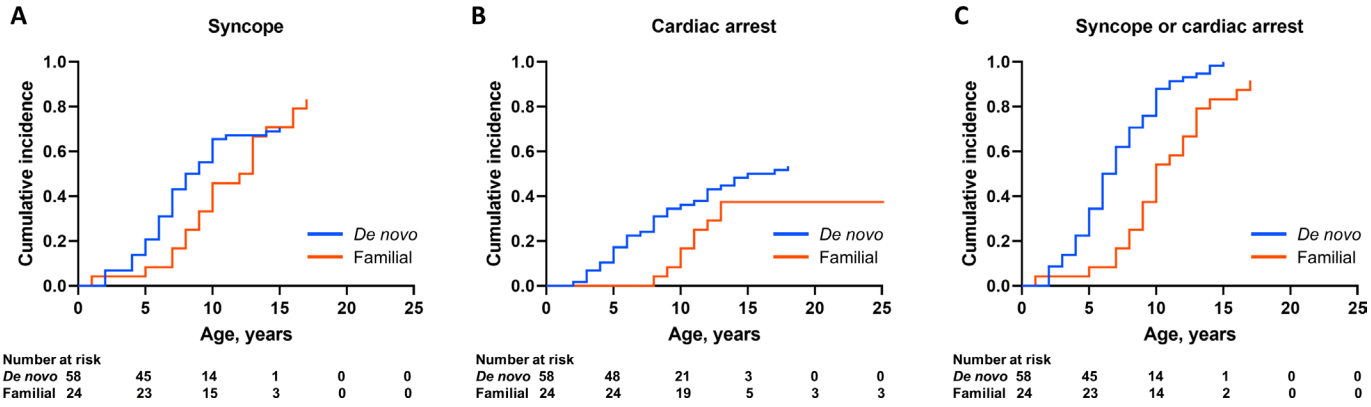

Figure 4 Cumulative cardiac incidence before diagnosis of CPVT in probands with *RYR2* variants. Cumulative cardiac events of first syncope (A), first CA (B) and any of the first cardiac event (C) in probands harbouring *RYR2* variants inherited from the parent or those with *de novo* cases. CA, cardiac arrest; CPVT, catecholaminergic polymorphic ventricular tachycardia.

Among 12 siblings with the same *RYR2* variants as the probands, 8 (66.7%) were symptomatic, 6 (families 3, 4, 22, 23, 24 and 52) had a history of syncope, 1 (family 4) had a history of CA and 1 (family 13) had experienced both CA and syncope. Figure 5 shows the cumulative first cardiac incidence of syncope (figure 5A) and CA (figure 5B) and any of the cardiac events (figure 5C) in genotype-positive siblings. None received medical treatment during genetic testing.

DISCUSSION

This is the first study that demonstrated complete trio genetic analysis of inheritance in CPVT1 probands. The main findings are the following: (1) age of any first cardiac event or CA was lower in the *de novo* group than in the familial group; (2) syncope comprised more than half of the first symptoms, and nearly half of the probands in both groups experienced a CA event before diagnosis; (3) one-third of genotype-positive parents were symptomatic; (4) two-thirds of genotype-positive siblings were symptomatic during genetic testing and (5) the locations of the *RYR2* variants differed between familial and *de novo* group.

Relationship between inheritance and clinical manifestation of CPVT1

Among the CPVT-causative genes, *RYR2* is the most common causative underlier and exhibits autosomal-dominant inheritance. Patients with CPVT1 are usually diagnosed by the age of 40 but can also be identified by genetic screening for idiopathic ventricular fibrillation.[7 25 26] In the present study, >70% of the CPVT1 probands had a syncopal episode and ~50% had experienced CA before diagnosis. The age of event onset was lower in the *de novo* group than in the familial group, aligning with a previous study.[14] Since many parents carrying the same *RYR2* variants as probands were asymptomatic without any medication, the *RYR2* variants in the familial group may be less pathogenic than those in the *de novo* group, resulting in a concealed phenotype or CA event at an older age. One presumption is that lethality prior to reproductive age may result in a more severe phenotype in the *de novo* cases than familial cases. Furthermore, more than half of the probands were *de novo* cases, which is relatively higher compared with the past report;[2] however, we could not directly assess the familial/*de novo* ratio given the different genetic testing enquiry of parents between the studies. The popularity of large family cascade screening in CPVT-1 could have led to a more frequent diagnosis of the familial cases in the initial phase or a more aggressive recent genetic screening of asymptomatic families facilitated the diagnosis of the *de novo* cases.

RYR2 variants are associated with CPVT1 clusters in certain domains. Their structure-function analysis suggests that these loci are predominantly associated with intra-*RYR2* domain interactions and cytoplasmic Ca^{2+}-dependent channel modulation.[2] An association exists between *RYR2* variant location and the clinical phenotype of CPVT1, as patients harbouring variants in the C-terminus domain have an increased risk of non-sustained VT than those with variants in the N-terminus.[12] However, the CA

Table 2 Estimated cumulative cardiac incidence rate in probands and differences between *de novo* and familial cases at each age point

Age point	5 years old	10 years old	15 years old
Syncope, % (95% CI)			
De novo group	20.7	65.5	70.7
Familial group	8.3	45.8	70.8
Difference	12.4 (0.6 to 23.4)	19.7 (22.9 to 36.2)	−0.1 (−14.6 to 17.3)
CA, % (95% CI)			
De novo group	17.2	36.2	50
Familial group	0.0	8.3	37.5
Difference	17.2 (8.9 to 23.5)	27.9 (14.9 to 39.8)	12.5 (−4.3 to 30.9)
Syncope or CA, % (95% CI)			
De novo group	34.5	87.9	100.0
Familial group	8.3	54.1	83.3
Difference	26.2 (12.9 to 37.0)	33.8 (17.6 to 48.5)	16.7 (8.2 to 30.2)

CA, cardiac arrest; CI, confidence interval.

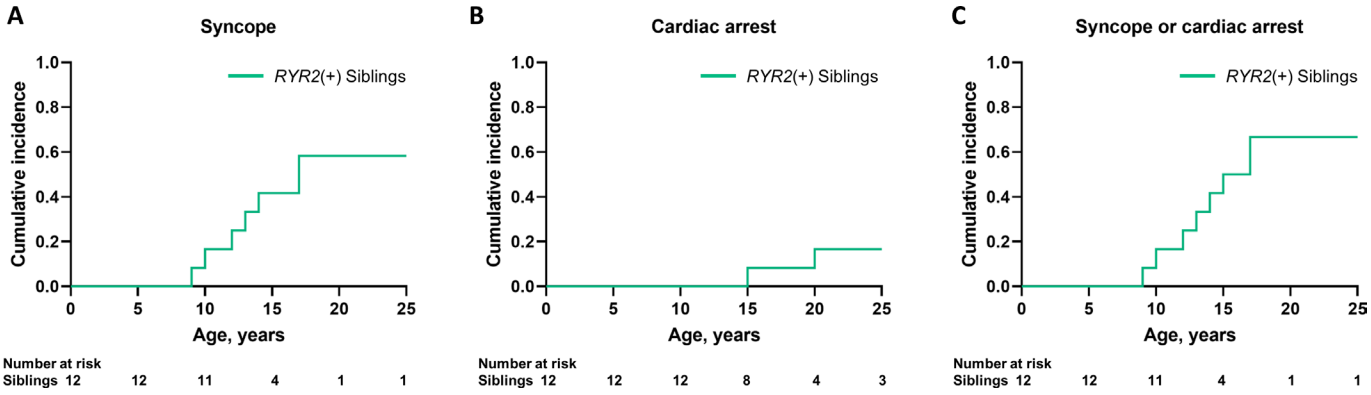

Figure 5 Cumulative cardiac incidence in siblings carrying the same *RYR2* variants as their probands. Cumulative cardiac events of first syncope (A), first CA (B) and any of the first cardiac event (C) in siblings harbouring *RYR2* variants (*RYR2*(+)) inherited from their parents. CA, cardiac arrest.

rate and age of the event in all probands did not differ between variants located in the N-terminus and C-terminus domains (online supplemental table 10). This suggested that variants within the same domain vary in severity and that the severity of each variant may determine its heritability.

Because mutational hotspots are largely related to loci prone to mutation during replication or DNA repair,[27] it is reasonable to identify the same variant in different probands. However, in the present study, most variants did not overlap between groups, even if they existed within the same hotspots. This maldistribution may have resulted from different family lines having the same ancestral origin, whereas many of the variants found in the *de novo* group were not inheritable by the next generation.

Clinical implications of genetic screening for family members

Familial CPVT1 probands exhibited a late onset of symptoms than the *de novo* group; however, there were similar levels of CA risk if they had no proper medication before diagnosis, thus highlighting the difficulty in diagnosis without symptoms at any age. As a beta-blocker, flecainide and left cardiac sympathetic denervation can decrease the risk of life-threatening cardiac events in CPVT.[3 13 26 28] An active attempt to diagnose and introduce early therapy would reduce CA risk. Although a burst-exercise test can reveal typical ventricular arrhythmias related to CPVT, an ECG cannot fully estimate cardiac event risk.[29 30] Therefore, our results support the idea that cascade screening should be recommended for all family members, even if they have no symptoms.[8 15 16] Indeed, genetic screening for asymptomatic families is sometimes a sensitive issue from the standpoint of potential ethical, emotional and social consequences of the test results, and careful genetic counselling and explaning the purpose of the examination are necessary before the genetic test.

Generally, relatives carrying the *RYR2* variant exhibit a considerable phenotypic difference.[12] In the present study, syncope or CA was only documented in 37.5% of genotype-positive parents, indicating that inheritance cannot be predicted based on symptoms. The symptomatic rate among genotype-positive siblings was relatively high (66.7%). The actual frequency may have been considerably higher if the two siblings who died before genetic diagnosis had been included. Additionally, because a previous study demonstrated that CPVT phenotype prevalence in family members increases up to 20 years of age,[12] more asymptomatic genotype-positive siblings in the present study are expected to manifest the CPVT phenotype during the follow-up periods. Disease-modifier genes from the genotype-negative parent may also be a possible factor that results in phenotype presentation between the parents and their children. Thus, for children, early genetic screening may be strongly beneficial in preventing sudden cardiac death. Furthermore, considering the possibility of parents with genetic mosaicism, which was reported in one of the 63 patients with CPVT1 with *RYR2* variants in a previous study,[23] a genotype-negative result in both parents does not always guarantee the negative genotype in siblings. Therefore, comprehensive genetic screening should be recommended for all family members in order to enable early diagnosis and initiation of therapeutic intervention (online supplemental file 2).

Limitations

First, only a small number of probands and their families were enrolled and there may be some selection bias in the enrolment. Several factors led to the small sample size of both groups, as *de novo* cases were difficult to be diagnosed, and familial cases were not included if their genotype-positive parents were deceased before cascade screening. However, given the lack of difference in rate of cardiac events rate, age of the events and bidirectional VT between the probands enrolled in this study and those excluded due to a lack of parental genetic test results (data not shown), selection bias based on the complete familial genetic screening would be limited. Second, cases of mosaicism cannot completely be ruled out by PCR-based Sanger sequencing[30] and germline mosaicism by testing other organs. Third, not all probands who have had their *RYR2* variants identified by Sanger sequencing underwent comprehensive genetic screening for other potential pathogenic variants. Fourth, not all probands and family members underwent exercise-stress testing to elucidate arrhythmogenic potential, especially the probands who had already suffered with VT or a ventricular fibrillation-storm episode, asymptomatic family members and younger children who could not undergo stress testing. Finally, this is a retrospective study and we could not fully follow up with patients after their diagnosis of CPVT1. As such, the prognostic difference between *de novo* and familial cases of CPVT1 after pharmacological and non-pharmacological therapies remains unclear. Further investigation with larger samples is required.

CONCLUSION

De novo CPVT1 cases demonstrated earlier onset of initial symptoms as compared with familial-inherited cases. Because two-thirds of the genotype-positive parents were asymptomatic and inheritance could not be predicted by their symptoms, genetic screening of parents and siblings in all CPVT1 cases may

enable early diagnosis and prophylactic therapeutic intervention to prevent sudden cardiac death.

Key messages

What is already known on this subject?

⇒ Catecholaminergic polymorphic ventricular tachycardia (CPVT), an inherited arrhythmia that is potentially fatal in children, is difficult to diagnose, because the resting ECG is mostly normal.

⇒ *RYR2* variants are identified in ~60% of clinically affected patients with CPVT, and genetic testing for probands and family members is recommended.

⇒ However, *de novo* variants are also identified in sporadic cases of CPVT probands and the phenotypic differences between *de novo* and familial cases of CPVT remain unclear.

What might this study add?

⇒ This is the first study demonstrating trio analysis of inheritance using a large number of CPVT probands.

⇒ CPVT probands harbouring *de novo RYR2* variants as compared with those with assured familial inheritance showed an earlier onset of initial symptoms.

⇒ The distribution of the *RYR2* variant location differed between the two groups.

⇒ Because not all genotype-positive parents were symptomatic and inheritance cannot be confirmed by parental symptoms, genetic screening of family members may help in risk stratification and early therapeutic strategies for CPVT.

How might this impact on clinical practice?

⇒ This study highlights the importance of why advancing genetic screening is necessary for families of CPVT probands.

⇒ To disclose the inheritance pattern, either *de novo* or familial, proband siblings should consider early genetic screening to prevent sudden cardiac death.

⇒ This study is clinically important for personalised risk stratification of patients with CPVT and families and particularly for child and adolescent health.

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Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

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Contributors All authors take full responsibility for data collection, analysis and interpretation; research conduct and manuscript submission. KS, SO, MH and TA contributed to study conception and design. SO, KS and NI performed genetic analysis. KK, KT, KS, MF, TM, YK, HS, TK, MW, KY, KI, YI, KM and SN collected the extracted data from patient records. SO and KA performed statistical analysis of all data. KS and TA drafted the manuscript, and SO, MH, TA and KK critically revised the manuscript. TA accepts full responsibility for the work as a guarantor.

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Supplemental Materials

Impact of cascade screening for catecholaminergic polymorphic ventricular tachycardia type 1

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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.

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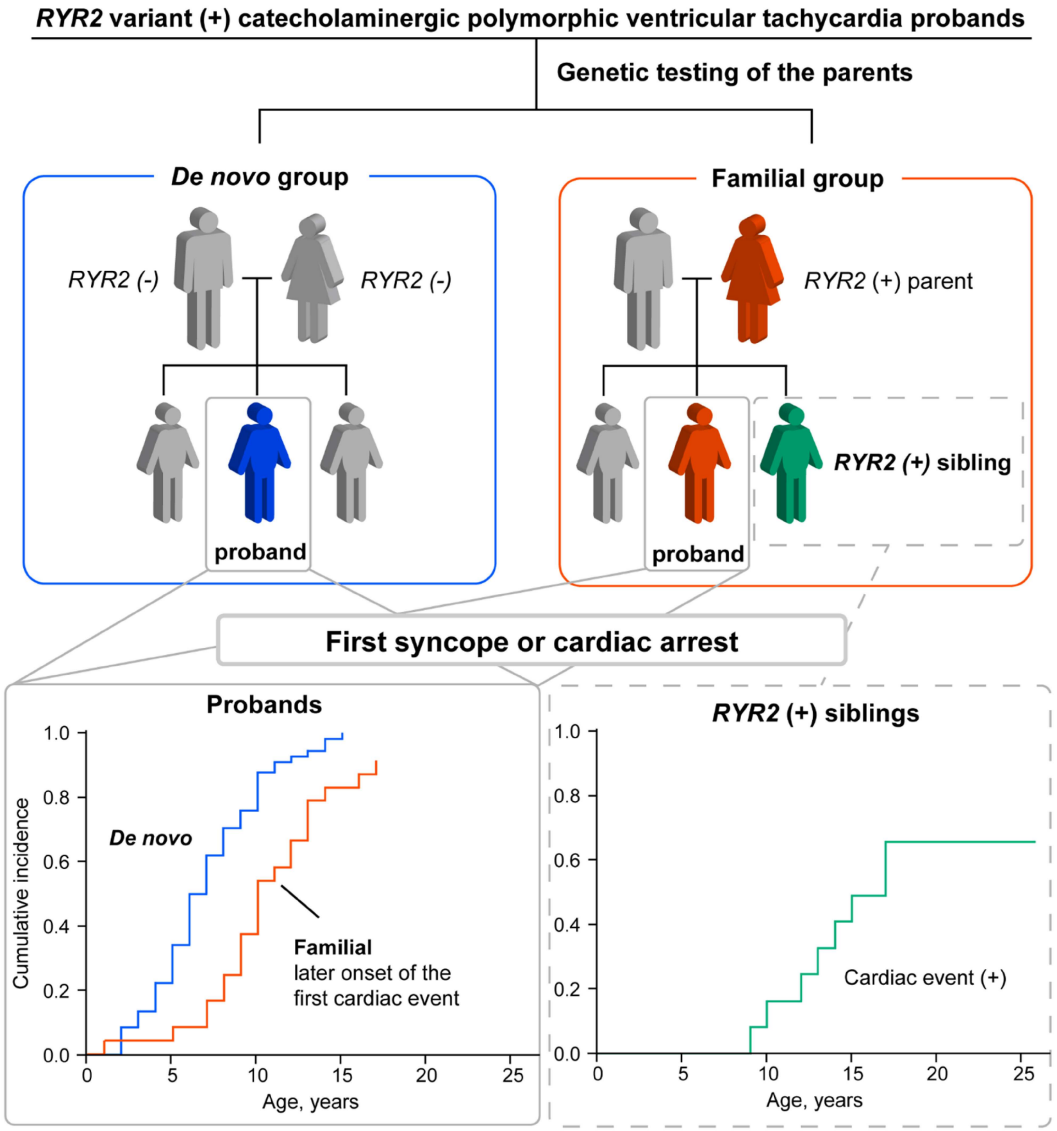
RYR2 variant (+) catecholaminergic polymorphic ventricular tachycardia probands
Genetic testing of the parents
De novo group
RYR2 (-)
RYR2 (-)
proband
Familial group
RYR2 (+) parent
RYR2 (+) sibling
proband
First syncope or cardiac arrest
Probands
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
De novo
Familial
later onset of the
first cardiac event
0
5
10
15
20
25
Age, years
RYR2 (+) siblings
Cardiac event (+)