Case Report

RYR2 receptor gene mutation associated with catecholaminergic polymorphic ventricular tachycardia in children: a case report & literature review

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Background: Ryanodine receptor 2 (*RYR2*) gene mutation causing catecholaminergic polymorphic ventricular tachycardia (CPVT) is one of the identified causes of sudden death in adults and children.

Case Description: We report a case of *RYR2* gene mutation presented with cardiac arrest and recurrent syncopal attack with accidental finding of cardiac tumour. For the systematic review, we used four databases (Scopus, PubMed, Ovid and Google Scholar) to search articles with the terms "*RYR2* gene mutation" and "catecholaminergic polymorphic ventricular tachycardia (CPVT)". Fourteen studies were chosen and reviewed together with our reported patient. Most of the patients presented initially with syncopal attack and developed cardiac arrest later. Some of them presented with both syncopal attack and seizures precipitated by exercise or stress. We found that 43.8% of patients shared similar variants or coding effects in *RYR2* gene mutation. Demographically, the mean age at presentation is 11 years old with 53% of reported cases were male.

Conclusions: Refractory arrhythmias cardiac arrest not responding to adrenaline should raise the suspicion towards *RYR2* gene mutations. Recognition of this condition is important as it affects the outcome of resuscitation. Untimely diagnosis of *RYR2* gene mutations with appropriate use of pharmacological agents during resuscitation is important to ensure a better outcome.

Keywords: Ryanodine receptor 2 (*RYR2*); gene mutation; catecholaminergic polymorphic ventricular tachycardia (CPVT); case report

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Introduction

Ryanodine receptor 2 (*RYR2*) is primarily found in cardiac muscles to facilitate calcium release from sarcoplasmic reticulum, leading to muscle contractions. *RYR2* gene mutation can cause uncontrolled muscle contraction and causing arrythmias and lead to cardiac arrest. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is one of the most identified causes of cardiac arrest in paediatric populations and manifested as syncopal attack induced by exercise. CPVT is diagnosed by unexplained exercise-induced ventricular tachycardia (VT) or ventricular fibrillation (VF) in a normal heart structure and electrocardiogram (ECG). Eighty percent of cases showed positive family history with 10 index cases and each family at least experienced a case of either sudden infant death syndrome (SIDS) or drowning at time of presentation (1). CPVT was reported to contribute to about 30% of cardiac arrest by causing a spontaneous efflux of calcium ions, activating the sympatho-adrenergic system giving rise to ventricular arrythmias (2). Approximately 50–65% of CPVT-type 1 cases are associated with *RYR2* gene mutation. Petrungaro *et al.* found that CPVT can also give cardiac rhythm disturbances and be associated with overlap syndromes with non-compact myocardium in which patient presented with atrioventricular (AV) block (3). Although, intravenous adrenaline is the first choice of pharmaceutical therapy in cardiac resuscitation, the use of adrenaline in patient with *RYR2* gene receptor mutation will lead to CPVT and death. In CPVT, beta-blocker could be beneficial though treatment failure was reported mainly due to poor adherence (4).

Another known complication of *RYR2* gene mutation is epilepsy which may be due to either the nature of the disease or as a complication of recurrent episodes of cardiac arrest leading to hypoxic ischaemic encephalopathy (HIE). In 2021, a study in China demonstrated a Benign Epilepsy of childhood of Centrotemporal Spike (BECTS) associated with *RYR2* gene missense mutation. Five of the subjects had onset of childhood-onset focal seizures with two probands with family history of arrythmias (5). On the other hand, recent studies showed association of *RYR* gene mutation with tumours, particularly in adults. There is no case reported in children so far. Tumour mutational burden (TMB) was found higher in those with *RYR* gene mutations, mainly in *RYR2* gene mutations (6). Till date, only two types of cancer have been reported which are oesophageal cancer and lung cancer (7,8). *RYR2* gene mutation is known to be mostly expressed in the epithelial cells, which can cause either adenocarcinoma or squamous cell carcinoma (9).

In this article, we report a case of *RYR2* gene mutation presenting with cardiac arrest, eventually had multiple episodes of syncopal attack and seizure, with an interesting accidental finding of cardiac tumour. Subsequently, we proceed to systematically review the literature for cases of CPVT with documented RYR2 mutations among paediatric population, focusing on the main clinical manifestation and their genetic mutation profile. We present this article in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-255/rc).

Highlight box

Key findings

- In this systemic review of 14 articles, all reported patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) presented with syncopal attack, seizure, or sudden death. Ryanodine receptor 2 (*RYR2*) gene mutation detected in all cases with few articles reported association with family history of *RYR2* gene mutation.

What is known and what is new?

- *RYR2* gene mutation is a rare gene mutation commonly associated with CPVT.
- With regards to our patient, she has *RYR2* gene mutation with cardiac tumour which can be another triggering factor for her CPVT.

What is the implication and what should change now?

- In recent years, *RYR2* gene mutation identification associated with CPVT has been well recognised. It helps in terms of choice of treatment in the event where patient with *RYR2* gene mutation develops cardiac arrest. Nevertheless, it will reduce the rate of mortality and morbidity of patient with *RYR2* gene mutations.

Case presentation

A 1-year-old girl with no previous medical illness was found unconscious at home by her father after playing with her sister. There was no choking episode or seizure witnessed prior to the event. This was her first cardiac arrest episode and no history of syncopal attack before. Her father initiated the cardio-pulmonary resuscitation (CPR) with rescue breath at home and brought her immediately to the hospital. It took 25 minutes to reach the hospital and the child did not regain consciousness in between. Upon her arrival in resus zone, her Glasgow Coma Scale (GCS) was 3/10 (E1V1M1). She was immediately intubated, and VF

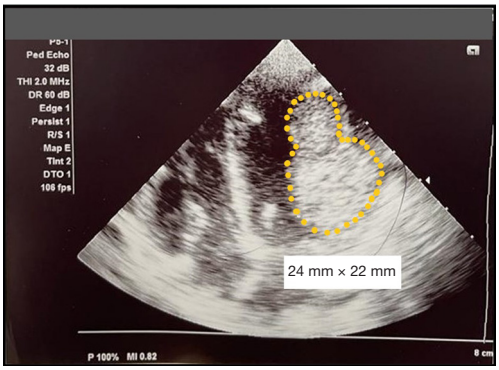

Figure 1 Echo finding of the cardiac tumour, size 24 mm × 22 mm, sessile tumour. The yellow dashed circle showed cardiac tumor margin.

was noted in the cardiac monitoring. Direct current (DC) shock of 50 Joules with six times intravenous Adrenaline 0.1 mg/kg and total bolus of intravenous Normal Saline 40 mL/kg were given. CPR was commenced for 20 minutes with return of spontaneous circulation (ROSC), and was haemodynamically unsupported. During the acute period, she developed multiple episodes of focal seizure. Neurological examination revealed power of at least 3/5 bilateral upper and lower limbs with brisk knee jerk reflexes. Subsequent assessment with computed tomography (CT) brain showed generalised cerebral sulci effacement and loss of grey-white matter differentiation, although electroencephalography (EEG) showed no epileptiform changes. Cerebral spinal fluid examination was not suggestive of infection and other blood investigations were normal. Chest radiography showed clear lungs field bilaterally. As she continued to had seizures, she was started on syrup levetiracetam 20 mg BD.

Her echocardiogram assessment revealed presence of two large tumours at the posterior wall of left ventricle with the largest size of 24 mm × 22 mm (*Figure 1*) otherwise with good ventricular contractility. Brain magnetic resonance arteriogram/venogram (MRA/MRV) and cardiac magnetic resonance imaging (MRI) showed profound hypotensive type of HIE and two intramyocardial masses largest 37 mm × 30 mm along lateral wall of left ventricle suggestive of rhabdomyomas or fibromas. She was discharged home after 23 days of admission with both the parents were educated with basic life support (BLS) in the event of cardiac arrest. Since discharged, she was admitted several times with multiple episodes of syncopal attack at home precipitated by crying and was documented of VT upon presentation to the emergency department. She was then initiated on oral amiodarone of 5 mg/kg/dose twice daily to control the arrythmias. Whole exome sequencing (WES) was performed, and *RYR2* gene mutation was found in the patient and her father. She is currently on Gross Motor Function Classification (GMFCS) level 5 with swallowing incoordination requiring nasogastric Ryle's tube feeding assistance. Despite on the medication, she still had two episodes of VT per week precipitated by triggers such as crying, anger, or stress. The decision for conservative management for the index case was made after a discussion in a multidisciplinary meeting, taking into consideration of risk outweigh the benefit in this age group.

We report a patient based on retrospective review of information via electronic medical record, digital laboratory system, and digital radiological, image and reports in Hospital Pakar Kanak-Kanak (HPKK), National University of Malaysia. For systemic review, four large databases: PubMed, Ovid, Scopus and Google Scholar were used to find articles with keywords "*RYR2* gene mutations" and "CPVT" up to December 2022. Selected articles based on title and abstract included are: (I) case reports and articles on children 18 years old and below with (II) treatment response on CPVT and (III) written in English only. We excluded reports of asymptomatic patients with *RYR2* gene mutations and articles written in other languages.

We have summarised the results of the literature search using PRISMA flow diagram (*Figure 2*). The data of clinical presentation, clinical findings, radiology modalities and findings, laboratory results, confirmatory tests, and treatments were collected and tabulated.

Following inclusion and exclusion criteria, 14 articles were selected, summarised in *Table 1*. A total of 90 patients were included in the review, including our patients. The patients' age ranged from 4 weeks old to 18 years old, with the mean age at presentation 11±4 years old. Only 3 patients (3.3%) presented below the age of 1 year old.

Forty-six of the reviewed cases were males, 42 were females and 2 were unspecified. 13 of the patients (14.4%) presented with both syncopal attack and seizure during the initial presentation; 72 patients (80%), including our patient presented with typical syncopal attack. Only 4 (4.4%) patients presented with CPVT without exercise or stress-induced event. Three of them (3.3%) presented with sudden cardiac arrest and were diagnosed with *RYR2* gene mutation post-mortem.

Thirteen genetic variants or coding effects were detected to be associated with CPVT and considered as pathogenic. *Figure 3* showed the top 15 variants/coding effect that

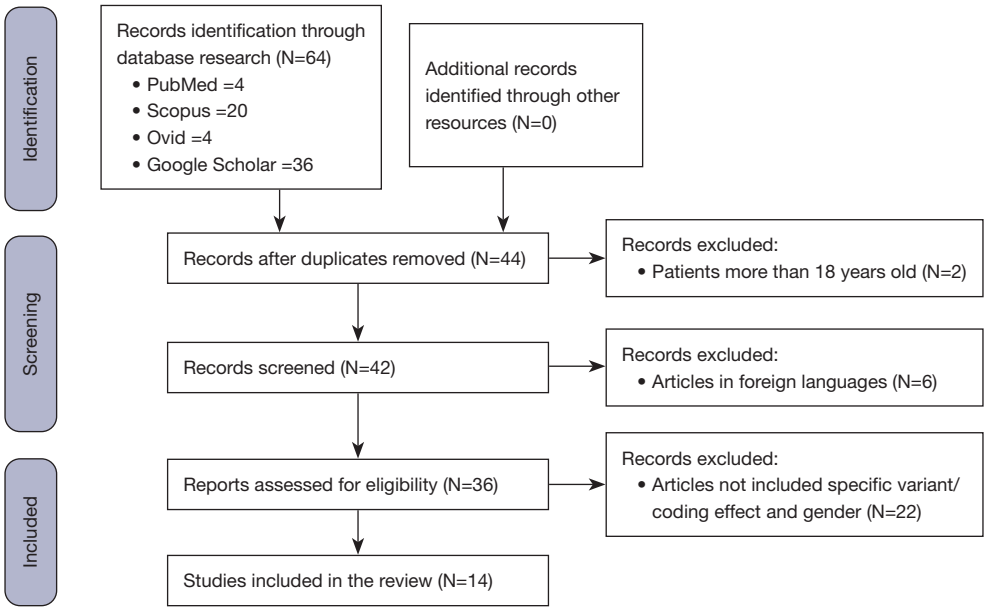

Figure 2 PRISMA flow chart of literature review.

represents nearly 45% of the total cases reviewed. To date, none of the literature review showed similar *RYR2* gene mutation with c.294+3A>G variant as in our patient. The nucleotide mutation results are shown in *Figure 4*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the legal guardians for publication of this case report and accompanying images. A copy of written consent is available for review by the editorial office of this journal.

Discussion

RYR2 receptor gene mutation leading to CPVT has been documented in several cases reported in children and adult, and their manifestations may range from benign to severe life-threatening conditions. Nonetheless, the choice of pharmacological treatment may need adjustment in patients with *RYR2* gene mutation. In this review, we will focus on characteristics of pathogenic *RYR2* gene mutation and its variants among paediatric population.

Ohno *et al.* has described in 2015, several gene receptors which can cause cardiac arrest in a young patient namely, *RYR2*, *CASQ2*, *KCNJ2*, *TRDN* and *CALM1* with more than 60% of CPVT patients carry mutations in *RYR2* (9). *RYR2* gene mutation can be autosomal dominant (AD) or autosomal recessive (AR) in which the receptor functions primarily in controlling the calcium release from sarcoplasmic reticulum in each cardiac cycle (39). In our patient, she has heterozygotes condition of *RYR2* gene mutation with c.294+3A>G variant. According to the latest International Guidelines on Sudden Cardiac Death, CPVT can be diagnosed with either: (I) exercise or emotion-induced bidirectional or polymorphic VT with normal heart structure and normal baseline ECG at rest, or (II) based on heterozygous state that causes pathogenic (or likely pathogenic) variants in *RYR2*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, or *KCNJ2* or biallelic pathogenic (or likely pathogenic) variants in *CASQ2*, *TECRL*, or *TRD* (40). Our patient fulfilled both diagnostic criteria of CPVT.

Phenotypes of *RYR2* gene mutation has been described by Leung *et al.* in 2022, which the group reported as mainly occurring in female gender with the median age of presentation of eight years old, clinically presenting with syncopal attack (41). Koponen *et al.* showed similar results with predominantly CPVT occurring in female gender. This study focused on *RYR2 p2328S* gene mutation which resulted on cardiac arrest in 5% of patients and 25% of patients had syncopal attack due to exercise or stress (42). Based on the cardiac abnormality reported, presence of VT or VF was one of the commonest cardiac manifestations in patients with *RYR2* gene mutation (4). Furthermore, the same study also reported in nine patients who had positive

Table 1 *RYR2* gene mutation with pathogenic coding variants and its phenotypes

Case No.	Mutation	Gender	Exercise-induced	Syncope	Seizure	Age*	Reference
1	A2254V	Female	Yes	Yes	Not documented	8	Postma *et al*. (10)
2	A2387T	Female	Yes	Yes	Not documented	18	Tester *et al.* (1)
3	A2394G	Female	Yes	Yes	Yes	9	Postma *et al.* (10)
4	A2403T	Female	Yes	Yes	Not documented	14	Choi *et al.* (11)
5	A2403T	Male	Yes	Yes	Not documented	7	Choi *et al.* (11)
6	A2403T	Female	Yes	Yes	Not documented	16	Tester *et al.* (1)
7	A4510T	Male	Yes	Yes	Not documented	15	Choi *et al*. (11)
8	A4510T	Male	Yes	Yes	Not documented	11	Tester *et al.* (1)
9	A4860G	Female	Yes	Yes	Not documented	7	Priori *et al.* (12)
10	A169G	Male	Yes	Yes	Not documented	18	Hsueh *et al*. (13)
11	c. 6800G>A	NS	Yes	SIDS	Not documented	6 months	Tester *et al.* (1)
12	c. 6800G>A	NS	Yes	SIDS	Not documented	4 weeks	Tester *et al.* (1)
13	c.7580T>G	Male	Yes	Yes	Yes	9	Duan *et al.* (14)
14	c.7580T>G	Male	Yes	Yes	Yes	3 months	Duan *et al.* (14)
15	c.12244G>C	Male	Yes	Yes	Not documented	12	Nathani *et al.* (15)
16	c.12470G>A	Female	Yes	Yes	Not documented	15	Del Franco *et al.* (16)
17	c.12520T>A	Male	Yes	Yes	Not documented	17	Seildmayer *et al.* (2)
18	c.12670G>T	Male	Yes	Yes	Yes	3	Hu *et al.* (17)
19	c.1458A>C	Male	Yes	Sudden death	Not documented	17	Larsen (18)
20	c.6497G>A	Female	Yes	Yes	Not documented	13	Mahlke *et al.* (19)
21	c.6800G>A	Male	No	No	Not documented	15	Kohli *et al.* (20)
22	c.7169c > t	Male	Yes	Yes	Yes	11	Watanabe *et al.* (21)
23	c.7210C>A	Female	Yes	Sudden death	Not documented	13	Beckmann *et al.* (22)
24	c.9872A>T$^{=}$	Female	Yes	Yes	Not documented	9	Blancard *et al*. (23)
25	D3291V	Female	Yes	Yes	Not documented	10	Blancard *et al*. (23)
26	E1724K	Female	Yes	Yes	Not documented	9	Postma *et al.* (10)
27	E2311D	Male	Yes	Yes	Not documented	8	Priori *et al.* (12)
28	E243K	Male	Yes	Yes	Not documented	13	Roston *et al.* (4)
29	E4076K	Male	Yes	Yes	Not documented	10	Postma *et al.* (10)
30	E4950K	Male	Yes	Yes	Not documented	10	Priori *et al.* (12)
31	F4020L	Male	Yes	Yes	Yes	4	Postma *et al.* (10)
32	G14876A	Male	Yes	Yes	Not documented	10	Allouis *et al.* (24)
33	G14876A	Male	Yes	Yes	Not documented	6	Allouis *et al.* (24)
34	G14876A	Female	Yes	Yes	Not documented	11	Allouis *et al.* (24)
35	G14876A	Male	No	Yes	Not documented	12	Allouis *et al.* (24)

Table 1 (*continued*)

Table 1 (*continued*)

Case No.	Mutation	Gender	Exercise-induced	Syncope	Seizure	Age*	Reference
36	G14876A	Female	Yes	Yes	Not documented	15	Allouis *et al.* (24)
37	G14876A	Female	Yes	Yes	Not documented	13	Allouis *et al.* (24)
38	G375S	Male	Yes	Yes	Not documented	14	Heiner *et al.* (25)
39	G3946A	Male	Yes	Yes	Not documented	6	Pizzale *et al.* (26)
40	G3946S	Male	Yes	Yes	Not documented	14	Priori *et al.* (12)
41	G3946S	Male	Yes	Yes	Not documented	9	Priori *et al.* (12)
42	G3946S	Male	Yes	Yes	Not documented	11	Wilde *et al.* (27)
43	G4076L	Female	Yes	Yes	Not documented	10	Wilde *et al.* (27)
44	G4671R	Male	Yes	Yes	Not documented	11	Choi *et al.* (11)
45	G4671R	Male	Yes	Yes	Not documented	10	Tester *et al.* (1)
46	G4936L	Male	Yes	Yes	Not documented	17	Itoh *et al.* (28)
47	H4108N	Female	Yes	Yes	Yes	4	Postma *et al.* (10)
48	H4108Q	Female	Yes	Yes	Not documented	6.5	Postma *et al.* (10)
49	H4762P	Female	Yes	Yes	Yes	13	Postma *et al.* (10)
50	I4756S	Female	Yes	Yes	Not documented	16	Letsas *et al.* (29)
51	I4848V	Female	Yes	Yes	Not documented	14	Choi *et al.* (11)
52	I4848V[1]	Female	Yes	Yes	Not documented	16	Choi *et al.* (11)
53	I4848V	Female	Yes	Yes	Not documented	14	Tester *et al.* (1)
54	I4855M	Female	No	No	Not documented	10	Roston *et al.* (4)
55	I4867M	Male	Yes	Yes	Not documented	9	Priori *et al.* (12)
56	L2534V	Male	Yes	Yes	Not documented	13	Hasdemir *et al.* (30)
57	L3778F	Male	Yes	Yes	Not documented	10	Priori *et al.* (12)
58	M4109R	Male	Yes	Yes	Not documented	15	Nof *et al.* (31)
59	M4109R	Female	No	Yes	Not documented	12	Nof *et al.* (31)
60	n.A12476C	Female	No	No	Not documented	2	Di Pino *et al.* (32)
61	N4104I	Male	Yes	Yes	Yes	7	Postma *et al.* (10)
62	N4104K	Male	Yes	Yes	Not documented	9	Priori *et al.* (12)
63	N4895D	Male	Yes	Yes	Not documented	9	Priori *et al.* (12)
64	NS	Female	Yes	Yes	Not documented	13	Bhuiyan *et al.* (33)
65	NS	Female	Yes	Yes	Not documented	12	Roston *et al.* (34)
66	NS	Female	Yes	Yes	Not documented	9	Saito *et al.* (35)
67	NS	Male	Yes	Yes	Not documented	16	Saito *et al.* (35)
68	P164S	Male	Yes	Yes	Not documented	17	Choi *et al.* (11)
69	P4511L	Male	Yes	Yes	Not documented	17	Wilde *et al.* (27)
70	P466A	Male	Yes	Yes	Not documented	9	Tester *et al.* (1)

Table 1 (*continued*)

Table 1 (*continued*)

Case No.	Mutation	Gender	Exercise-induced	Syncope	Seizure	Age*	Reference
71	P4902S	Female	Yes	Yes	Not documented	13	Postma *et al.* (10)
72	R169Q	Female	Yes	Yes	Not documented	6	Nozaki *et al.* (36)
73	R169Q	Female	Yes	Yes	Not documented	5	Nozaki *et al.* (36)
74	R169Q	Female	Yes	Yes	Yes	7	Nozaki *et al.* (36)
75	R176Q	Male	Yes	Yes	Not documented	12	Tester *et al.* (1)
76	R2474S	Male	Yes	Yes	Not documented	8	Priori *et al.* (12)
77	R414L	Male	Yes	Yes	Not documented	11	Choi *et al.* (11)
78	R414L	Male	Yes	Yes	Not documented	17	Tester *et al.* (1)
79	R4959Q	Female	Yes	Yes	Not documented	12	Tester *et al.* (1)
80	R4959Q	Female	Yes	Yes	Yes	11	Roston *et al.* (4)
81	S2246L	Male	Yes	Yes	Not documented	2	Priori *et al.* (12)
82	S2246L	Female	Yes	Yes	Not documented	9	Priori *et al.* (12)
83	S2246L	Female	Yes	Yes	Not documented	11	Aizawa *et al.* (37)
84	S4124T	Female	Yes	Yes	Not documented	14	Tester *et al.* (1)
85	V4471I	Female	Yes	Yes	Not documented	8	Roston *et al.* (4)
86	V4471I	Female	Yes	Yes	Yes	18	Roston *et al.* (4)
87	V4771I	Male	Yes	Yes	Not documented	6	Priori *et al.* (12)
88	V4771I	Female	Yes	Yes	Yes	12	Postma *et al.* (10)
89	230 C>T	Male	Yes	Sudden death	Not documented	17	d'Amati *et al.* (38)
90	c.294+A>G	Female	Yes	Yes	Yes	1	Abdullah and Ali

*, the unit of Age is "year" unless otherwise specified. SIDS, sudden infant death syndrome.

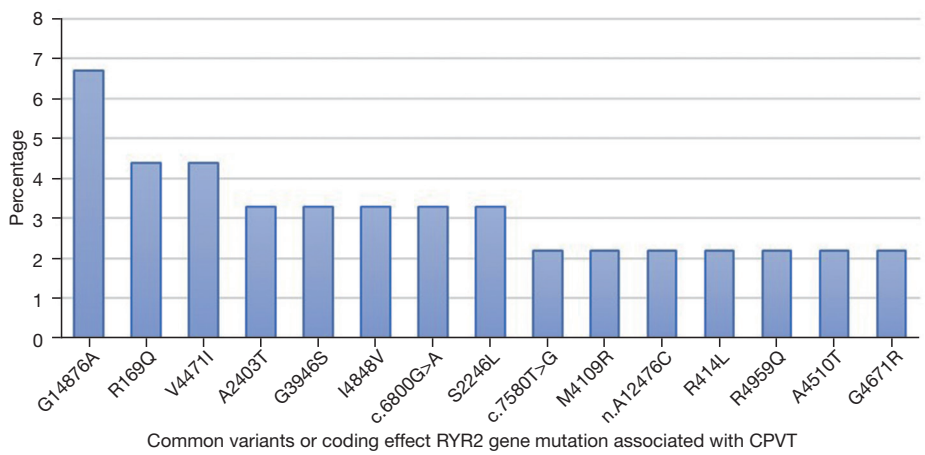

Figure 3 Bar graph of top 15 variants/coding effect from 90 cases reviewed. CPVT, catecholaminergic polymorphic ventricular tachycardia.

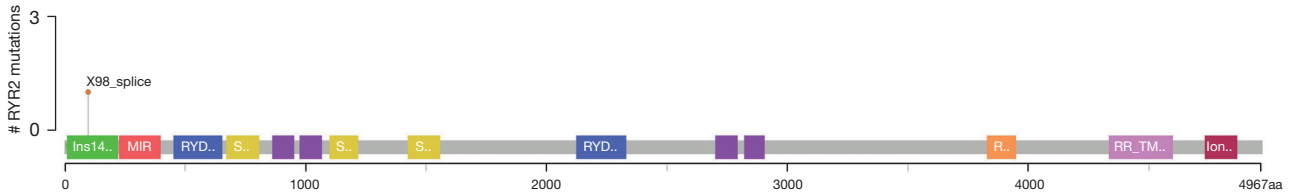

Figure 4 Nucleotide mutation of *RYR2* gene with c.294+3A>G variant. The sequence change falls in intron 4 of the *RYR2* gene. It does not directly change the encoded amino acid sequence of RYR gene protein. It affects nucleotide within the consensus splice site. RYR2, ryanodine receptor 2.

respond to adrenaline or epinephrine challenge test after inducing VT. Similarly in a case series reported by Bellamy *et al.*, they also demonstrated in three different patients (age range, 4–10 years old), a positive response to epinephrine challenge test by inducing arrythmias in patients with *RYR2* gene mutation, which successfully reverted by nadolol and flecainide (43).

In comparison to our patient, she had two precipitating factors that can provoke her CPVT episode which are the underlying *RYR2* gene mutation and the incidental finding of the cardiac tumour. Generally, in paediatrics population, rhabdomyoma is the commonest cardiac tumour in children, commonly associated with tuberous sclerosis, with other possible differential diagnoses of cardiac tumour being fibroma and myxoma. In our study and Miyake *et al.* study in 2011 showed out of 173 patients in Children's Boston Hospital, rhabdomyoma contributed the highest numbers of patients with cardiac tumour. On the other hand, fibroma demonstrated highest total number of patients presented with VT (16 patients) or cardiac arrest (2 patients) (44). Hypothetically, the cardiac tumour can further complicate the underlying condition caused by *RYR2* gene mutation and resulted in uncontrolled CPVT. In cases with the size of the cardiac tumour is significant and/or in haemodynamically unstable patient, surgical resection will be the best choice to control the symptoms (44). Till date, our patient is the only reported case of *RYR2* gene mutation manifesting with concomitant CPVT and cardiac tumour, which may lead for her recalcitrant arrythmias.

Choices of pharmacological treatment depend on individual response. Most of the literature review reported beta blocker as the treatment of choice in CPVT. According to American College of Cardiology nadolol, a non-selective beta-1-receptor blocker in heart and vascular smooth muscle is suggested as the first line treatment in CPVT, combined with flecainide (45), though this treatment it is not easily accessible in most part of the world. Other choices of beta-blocker include propranolol (non-selective beta blocker), atenolol, bisoprolol and metoprolol (selective beta-1 receptor blocker). The main reason of using beta-blocker as the main choice in CPVT due to the longer half-life with once daily dose and less potential central nervous side effects (46). The next step to consider after pharmacological therapy is the implantable cardiac defibrillator (ICD). ICD can be implanted either via epicardial or transvenous approach. Epicardial is the best approach in our patient due to her young age and small size. Primary indication in our patient is channelopathy disease with high risk factors; (I) onset at young age; (II) previous history of cardiac arrest; and (III) genetic variants (47).

Conclusions

The patients reviewed in this article showed similar clinical presentations and complications with the previously reported patients with *RYR2* gene mutation. *RYR2* gene mutation with c.294+3A>G variant may be another novel mutation which uniquely associated the formation of cardiac tumour. In our case, it could be speculated that her CPVT may also be provoked by underlying cardiac tumour with early onset at the age of 1 year old. The mean age for the onset usually at 2 years old.

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Footnote

Reporting Checklist: The authors have completed the CARE

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-255/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the legal guardians for publication of this case report and accompanying images. A copy of written consent is available for review by the editorial office of this journal.

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