DOI: https://doi.org/10.3329/cardio.v13i2.52963

Editorial

Sudden Cardiac Death and Catecholaminergic Polymorphic Ventricular Tachycardia: What Genetic Medicine could offer

Zahurul A. Bhuiyan

Lausanne University Hospitals, Switzerland

(Cardiovasc j 2021; 13(2): 106-111)

A panic-stricken 14-year-old boy was profusely sweating. His parents were very anxious; his three siblings, in a row, died suddenly without any obvious cause (Fig 1: III:2, III:3, III:4). He is their only son, who is still alive along with two daughters (Fig 1: III:1, III:5, III:6). With grief, panic and apprehension, the family consulted a cardiologist in Rajshahi, Bangladesh. The Cardiologist took the baseline ECG of the boy, all parameters were normal (Fig 1). He did an echocardiogram, nothing wrong. Blood chemistry did not lead to any clue. Confused, the cardiologist took the family history, which revealed the following: the family lived in a village near Ishwardi. Three children (siblings) in the family, who were completely normal, physically and mentally, died suddenly (Fig. 1, III:2, III:3, III:4). The first premature death in the family was of a boy, who died from a syncopal event at 12 years of age while playing (Fig. 1, III:2). Deceased (Fig. 1: III:2) had his first convulsion led syncope at 1 yr. of age while breastfeeding. Between 5 and 6 years of age, he had syncope three times, all during cycling and playing, from which he recovered spontaneously. Second sudden death in the family was of a girl, who died suddenly due to syncope at 15 years of age while making a bed at night (Fig 1: III:3). Her first syncope was at 7 years of age, followed by five syncopal events between 7 and 15 years of age, from which she had recovered spontaneously. All syncopal events occurred during physical activities. The third death in the family was also of a girl, who was emotionally devastated due to her sister's death (Fig 1: III:4). She was sent to her aunt's home in the village for emotional support. But she was grief stricken, she subsequently, while standing at water in a pond, had syncope and died at 13 years of age (Fig 1: III:4). She had her first syncope at 7 years during playing, followed by two more syncope during swimming and fruit picking. No ECG was available from any of the deceased three siblings, which might have been necessary in evaluating the cause of sudden deaths in three brothers and sisters.

The cardiologist prescribed propranolol as a preventive medication to his sweating patient (Fig 1: III:1) and contacted me for my opinion. While going through the case summary, striking similarities were observed with the clinical phenotypes of similar aged children from Sudan that we later termed as Catecholaminergic Polymorphic Ventricular Tachycardia type 3 (CPVT3), a new disease entity (OMIM: 614021), first reported by our team in 2007.[1] In both families, from Sudan and Bangladesh (Fig 1 and reference 1), children had syncopal events either due to physical activities, or during emotional excitement or stress, *i.e.* their clinical symptoms were always triggered by adrenaline (catecholamine), which led to the syncopal attacks and eventual deaths in most patients.[1]

We conducted genetic investigation in this Bangladeshi family and confirmed that the deceased had CPVT3.[1] CPVT3 is an autosomal recessive cardiac arrhythmia disorder, which is often fatal if not treated in time. [1-3] An autosomal recessive disease could also be referred to as a bi-allelic genetic disorder. Unlike long QT syndrome, which is usually an autosomal dominant or mono-allelic disorder, in autosomal recessive diseases, an individual who has a defect in only one gene copy does not usually suffer from the disease, but

Address of Correspondence: Dr. Zahurul A. Bhuiyan, Genetic and Genomic Laboratory Medicine Specialist, Senior Lecturer and Privat Docent, Cardiogenetics Division of Genetic Medicine, Lausanne University Hospitals (CHUV), Switzerland. Email: z.a.bhuiyan@chuv.ch

he/she is a carrier for the disease. Though he/she does not suffer from the disease, he/she still is able to transmit the defective allele (mutation) to his or her offspring. We have found that both parents in this family (Fig 1: II:3 and II:4) were heterozygous carriers for the disease and they had no symptoms of arrhythmia. Three children, who died suddenly in this family, all supposedly inherited two copies of the defective (pathogenic) genetic variants, one from each parent and thus had homozygous or bi-allelic genetic defects and suffered from CPVT3 (Fig 1: III:2, III:3 and III:4 and Fig 2). The profusely sweating boy (Fig 1: III:1), who consulted the cardiologist in Rajshahi, was found to be heterozygous for the genetic defect (mutation), which made him a carrier, but not a CPVT3 patient, as this is a recessive disease. It was concluded that his excessive sweating was due to panic and anxiety emanating from the sudden deaths of his three siblings. Earlier prescribed medication "propranolol" was withdrawn and he was reassured that he would not suffer from this malignant form of arrhythmia. He had two living sisters, one was found heterozygous for the pathogenic variant of the gene and the second one was completely normal (figure 1, III:5 and III:6). Some immediate family members (II:1 and II:2) went through genetic investigations, where we did not find any new members with bi-allelic pathogenic variants, which reassured them that they were not at risk to suffer from sudden syncopal events. Those who had no genetic defect or were heterozygous carriers (II:1 and II:2), were also reassured about any unlikely occurrence of syncope linked to the faulty gene that led to sudden deaths of three siblings. This was the history of the first familial Catecholaminergic Polymorphic Ventricular Tachycardia, type 3 patients in Bangladesh, which was later included in an international, multi-centre retrospective review.[3]

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac rhythm disorder. It is a rare disease with an estimated prevalence of 1:10,000.[4] CPVT was first described as a new clinical entity in a series of four patients by Coumel et al (1978).[5] This first study later expanded with the inclusion of twenty one patients, patients were followed up for 7-yrs, which led to the identification of key features of CPVT.[6] Four distinguishing features that characterizes CPVT and differentiates it from other inherited forms of arrhythmias are: 1) normal resting electrocardiogram (ECG) with a normal QT prolongation; 2) exercise- or emotion-induced severe ventricular tachycardia; 3) a typical pattern of bi-directional ventricular tachycardia; and 4) a structurally normal heart.[6] Marked bradycardia was also observed in CPVT patients.[6] Familial history of syncope or sudden death was reported in 30% of CPVT patients.[6] The mean age at which the first syncope occurred was 7.8±4 yrs. (range 3 to 16 yrs.).[6] In general, CPVT has a highly malignant course, with an estimated mortality rate of 31% by 16 to 48 yrs., if untreated.[7] The disease locus was mapped to chromosome 1q42-q43; subsequently, mutations in Ryanodine receptor 2 (*RYR2*) gene was identified causal to the disease.[7, 8-11] This autosomal dominant form of CPVT was later annotated as CPVT type 1 or CPVT1. Presently, CPVT could be classified as three major categories, CPVT1, CPVT2 and CPVT3; they differ in their inheritance pattern (autosomal dominant and recessive) and also in their causal genetic etiologies.[1-3, 8-12] CPVT1 is the most common within all CPVTs, and heterozygous (single gene defect) mutations in *RYR2* gene are found in almost 50% of CPVT patients.[13] CPVT2 is predominantly a recessive form of CPVT, first elucidated in a Bedouin family, where nine children (age, 7± 4 yrs.) from seven related families died suddenly, and twelve other children suffered from recurrent syncope and seizures starting at the age of 6±3 yrs.[12] Both homozygous and compound heterozygous mutations in Calsequestrin 2 (encoded by *CASQ2* gene) have been reported in CPVT2 patients.[12,14,15] CASQ2 mutations could be found in 2-5% of CPVT patients.[14,16] Autosomal recessive CPVT2 usually have an early age of onset (mean ± SD = 7±4 yrs.), with a penetrance of 97% - 100% by age 10 yrs., and a high mortality rate if left untreated.[12,17] Resting bradycardia was also observed in these patients.[12] A recent study reevaluated the

inheritance pattern of CASQ2 pathogenic variants and its carriers and elucidated that CPVT2 is not always a recessive disease; occasionally, it could also be an autosomal dominant disease, which depends on the pathogenic strength of the CASQ2 mutation.[17] Pathogenic mutations, mainly *de novo*, in Calmodulin 1, 2 and 3 genes, initially have been described in patients with CPVT.[18,19] But with the accumulation of clinical data, it was revealed that mutations in these three calmodulin encoding genes are mostly causal to severe QT prolongation in childhood with features of CPVT in some patients.[20,21]

Going back to the cause of the sudden cardiac deaths in three children from Ishwardi, who died due to CPVT3, a recessive inherited arrhythmia disorder.[1] CPVT3 was first described by us in 2007 in children from a consanguineous family originated from the Nile delta region of Sudan.[1] Children between 4 yrs. and 12 yrs. had syncopal events during physical activities.[1] ECG revealed polymorphic ventricular tachycardia along with mild QTc prolongation in some cases.[1-3] This third form of CPVT has initially been linked to chromosome-7, where linkage study was done with only two affected person, and analysis was also misled by the phenotype of a sibling who was considered non-diseased but later exhibited the clinical phenotype.[1,2] A few yrs. after the first publication and following the birth of two children who developed CPVT3, linkage analysis was re-performed and the genetic locus was reallocated to chromosome 4.[1,2] Exome sequencing was conducted and we identified the pathogenic variant, c.331+1G>A, homozygously in the *TECRL* (Trans-2-Enoyl-CoA Reductase Like) gene in all affected individuals in the family.[2] Arrhythmias in CPVT3 patients are highly malignant and characterized by exercise-induced polymorphic ventricular tachycardia; minor QT-prolongation might be seen in some patients.[1,2] Severe as well as early age onset cardiac arrhythmias were observed in patients with truncating mutations, large deletions, while compared to the patients with missense mutations.[2,3] We have conducted an international multicenter study with genetically confirmed CPVT3 patients, where it was found that c.331+1G>A is the most common *TECRL* pathogenic mutation.[3] c.331+1G>A mutation in *TECRL* gene has also been found in our patients from Ishwardi (figure 1 and 2), which was exactly the same mutation found earlier in the Sudanese family.[2,3] Question might naturally arise, whether this mutation (c.331+1G>A, *TECRL*) (Fig 2) arose from a common source in both families i.e. do the Sudanese and Ishwardi family have a common ancestor long way back ? Or is it just a hot-spot location for mutation that we see for Arg420Trp (RYR2) mutation in CPVT1.[16] This question remains to be solved by further future genetic studies. Present evidence shows that pathogenic mutations in *TECRL* gene are very likely responsible for d" 5% of all CPVT patients.[22]

Increased Ca^{2+} leakage from the cardiomyocyte sarcoplasmic reticulum during diastole leads to delayed after depolarization in cardiomyocytes, which is considered to be the cause of arrhythmia in patients with mutations in *RYR2* or *CASQ2* genes i.e., in CPVT1 and CPVT2 patients.[23] We have also observed increased Ca^{2+} leakage during diastole in stem cell generated cardiomyocytes from our CPVT3 patients.[2] What is the reason of this diastolic Ca^{2+} leakage due to mutation in *TECRL* gene? Whether mutation in *TECRL* exhibits impaired synthesis of fatty acids in the heart, which is the main source of energy in the heart i.e. cardiac ATP generation, remains a matter of investigation. Another hypothesis could be that *TECRL* is involved in the electron transport chain pathway in the heart during ATP generation, abrogation of which leads to cardiac rhythm dysfunction in the heart.

In conclusion, it is imperative that genetics led precision medicine imparts an integral part in familial arrhythmia diagnosis and treatment. I have drawn an example from CPVT3 patients from Ishwardi, in whom genetic investigation led to diagnostic confirmation. In addition, genetic screening leads to identify the patients in the family who are still free from any symptoms, but could suddenly express fulminant cardiac arrhythmia or even sudden cardiac death; identifying such patients are crucial in order to save their lives. This allows the cardiologists timely intervention in preventing

patients' malignant arrhythmias by offering proper treatment (β-blocker, flecainide, left cardiac sympathetic denervation, implantation of intra-cardiac defibrillator, *etc.*). Concurrently, when the genetic pathology causal to CPVT3 is detected in a family, we could conduct targeted genetic analysis for the known pathogenic mutation in the family members and relatives. This allows detection of the heterozygous carriers as well as family members who are completely normal. Carriers and non-carriers equally could be reassured that they would not develop the disease, which would relieve them from a big psychological agony. This type of targeted genetic analysis is not very expensive, often costs less than 10,000 taka, but this is necessary to be done with proper genetic counselling by a cardiac geneticist. In rare scenarios, when both parents are carriers for the disease, prenatal genetic testing utilizing the chorionic villus or amniotic fluid could also be offered.

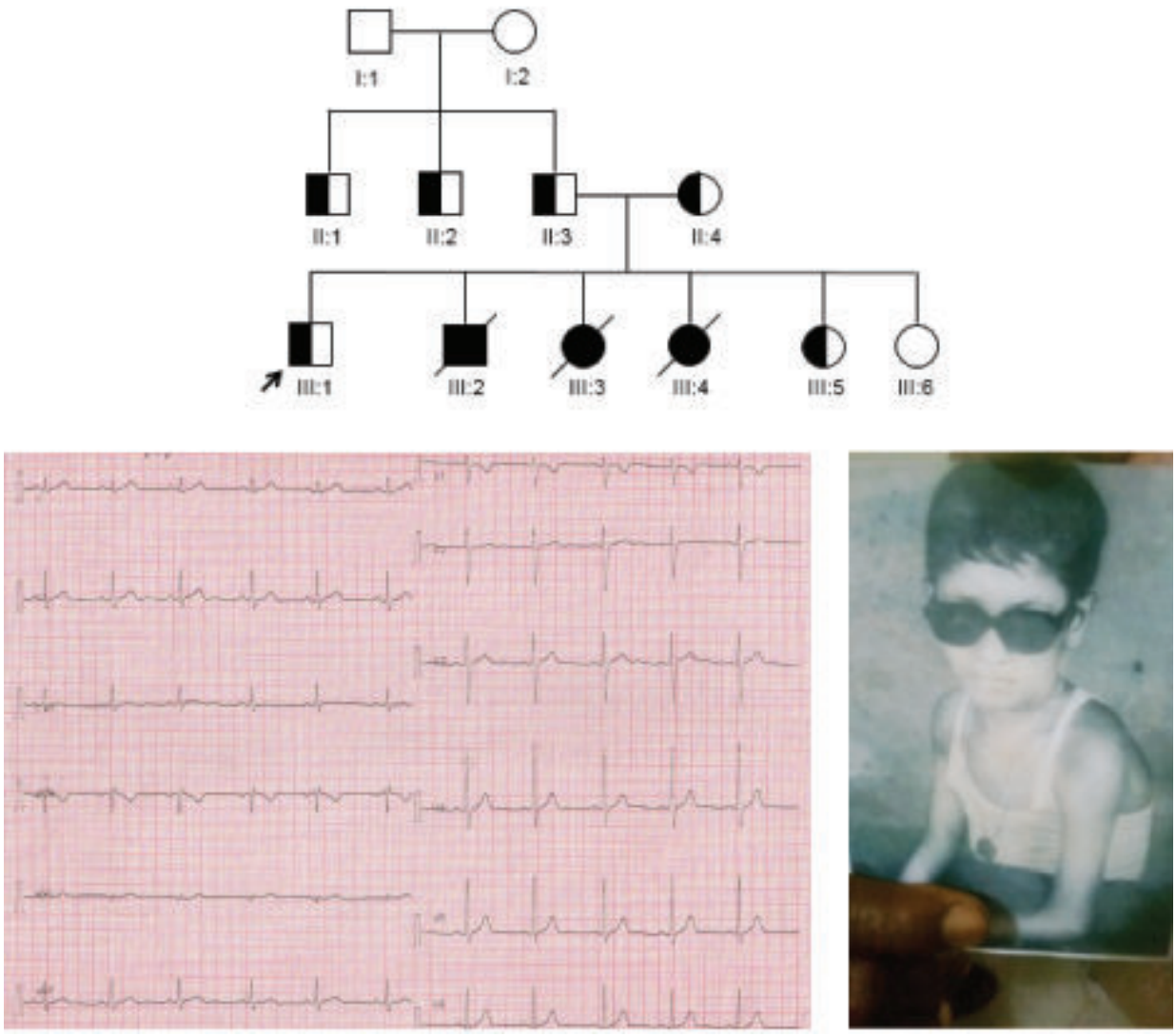

Fig.-1: *Above: Pedigree drawing of the family from Ishwardi with autosomal recessive CPVT3. Proband is shown with an arrow. Non-filled circles and squares are non-carriers for the mutation (except the grand parents of the proband, who were not tested). Affected individuals are shown as filled circles (female) and squares (male). Half-filled squares and circles are individuals who are carriers for a heterozygote mutation. Deceased individuals are indicated by slashes.*

Below: *12-lead ECG of the 14-year-old boy (III:1) who is heterozygous carrier for the c.331+1G>A mutation in TECRL gene.*

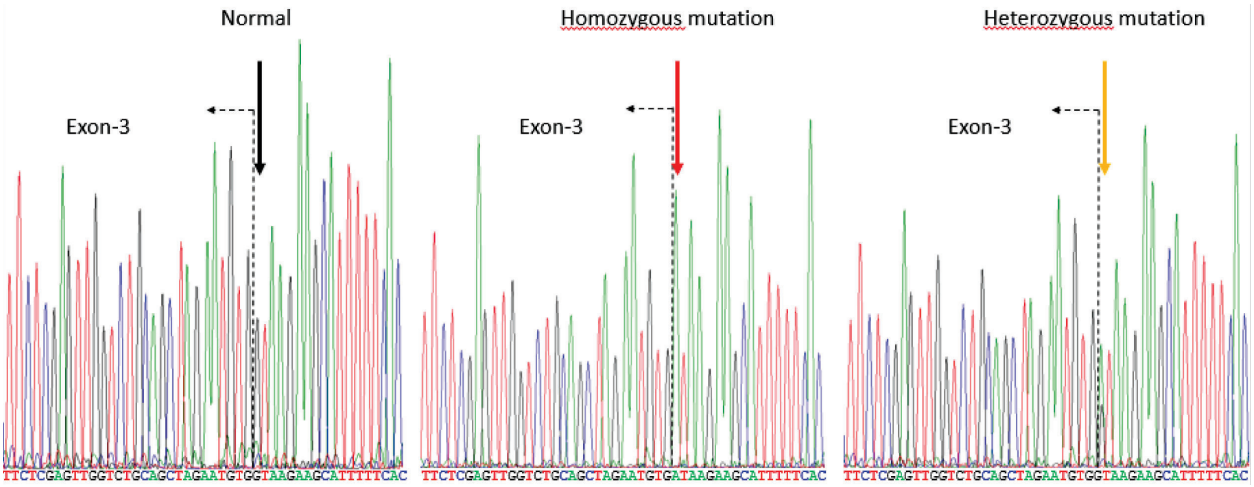

Fig.-2: *Splice site mutation, c.331+1G>A in the TECRL gene was found. Homozygous mutation is shown with a red arrow. Heterozygous mutation is shown with a yellow arrow. A normal TECRL gene is shown with black arrow. Exon-intron boundary is shown by a dotted line with arrow pointing toward exon-3.*

Note: If you have patients with familial cardiac arrhythmias, you could contact me by e-mail: Z.A.Bhuiyan@chuv.ch. Please provide me the family pedigrees, detailed clinical history and ECG from at least two patients.

References:

1. Bhuiyan ZA, Hamdan MA, Shamsi ET, et al. A novel early onset lethal form of catecholaminergic polymorphic ventricular tachycardia maps to chromosome 7p14-p22. *J Cardiovasc Electrophysiol* 2007; 18: 1060-1066.
2. Devalla HD, Gélinas R, Aburawi EH, et al. TECRL, a new life-threatening inherited arrhythmia gene associated with overlapping clinical features of both LQTS and CPVT. *EMBO Mol Med* 2016; 8: 1390-1408.
3. Webster G, Aburawi EH, Chaix MA, et al. Life-threatening arrhythmias with autosomal recessive TECRL variants. *Europace* 2020: euaa376. doi: 10.1093/europace/euaa376.
4. Lieve KV, van der Werf C, Wilde AA. Catecholaminergic Polymorphic Ventricular Tachycardia. *Circ J* 2016; 80: 1285-1291.
5. Coumel P, Fidelle J, Lucet V, Attuel P, Bouvrain Y. Catecholaminergic-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. *Brit Heart J* 1978; 40 (suppl.): 28-37.
6. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children: a 7-year follow-up of 21 patients. Circulation. 1995; 91: 1512-1519, 1995.
7. Swan H, Piippo K, Viitasalo M, et al. Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. *J Am Coll Cardiol* 1999; 34: 2035-2042.
8. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001; 103: 196-200.
9. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002; 106: 69-74.
10. Postma AV, Denjoy I, Kamblock J, et al. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *J Med Genet* 2005; 42: 863-870.
11. Bhuiyan ZA, van den Berg MP, van Tintelen JP, et al. Expanding spectrum of human RYR2-related disease: new electrocardiographic, structural, and genetic features. Circulation 2007; 116: 1569-1576.
12. Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet* 2001; 69: 1378-1384.
13. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. 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. *J Am Coll Cardiol* 2009; 54: 2065-2074.
14. Postma AV, Denjoy I, Hoorntje TM, et al. Absence of calsequestrin 2 causes severe forms of

catecholaminergic polymorphic ventricular tachycardia. *Circ Res* 2002; 91: e21-6.

15. Li Q, Guo R, Gao L, et al. CASQ2 variants in Chinese children with catecholaminergic polymorphic ventricular tachycardia. *Mol Genet Genomic Med* 2019; 7: e949.
16. Roston TM, Yuchi Z, Kannankeril PJ, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. *Europace* 2018; 20: 541-547.
17. Ng K, Titus EW, Lieve KV, et al. An International Multi-Center Evaluation of Inheritance Patterns, Arrhythmic Risks, and Underlying Mechanisms of CASQ2-Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation* 2020; 142:932–947.
18. Nyegaard M, Overgaard MT, Søndergaard MT, et al. Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. *Am J Hum Genet* 2012; 91: 703-712.
19. Makita N, Yagihara N, Crotti L, et al. Novel calmodulin mutations associated with congenital arrhythmia susceptibility. *Circ Cardiovasc Genet* 2014; 7: 466-474.
20. Crotti L, Spazzolini C, Tester DJ, et al. Calmodulin mutations and life-threatening cardiac arrhythmias: insights from the International Calmodulinopathy Registry. *Eur Heart J* 2019; 40: 2964-2975.
21. Adler A, Novelli V, Amin AS, et al. An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome. *Circulation* 2020; 141: 418-428.
22. Moscu-Gregor A, Marschall C, Müntjes C, et al. Novel variants in TECRL cause recessive inherited CPVT type 3 with severe and variable clinical symptoms. *J Cardiovasc Electrophysiol* 2020; 31:1527-1535.
23. Faggioni M, Kryshtal DO, Knollmann BC. Calsequestrin Mutations and Catecholaminergic Polymorphic Ventricular Tachycardia. *Pediatr Cardiol* 2012; 33: 959–967.