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Clinical Characteristics, Genetic Findings and Arrhythmic Outcomes of Patients with Catecholaminergic Polymorphic Ventricular Tachycardia from China

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Abstract

Introduction: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare cardiac ion channelopathy. This study examined the clinical characteristics, genetic basis, and arrhythmic outcomes of CPVT patients from China.

Methods: PubMed and EMBASE were systematically searched for case reports or series reporting on CPVT patients from China until February 19th, 2022 using the keyword "Catecholaminergic Polymorphic Ventricular Tachycardia" OR "CPVT", with the location limited to "China" OR "Hong Kong" or "Macau" in EMBASE, with no language or publication type restriction. Clinical characteristics, genetic findings, and primary outcome of spontaneous ventricular tachycardia/ventricular fibrillation (VT/VF) were analyzed.

Results: A systematic search of the PubMed and Embase databases yielded 1049 and 47 articles, respectively. After the exclusion of overlapping cohorts, a total of 58 unique cases from 15 studies (median presentation age: 8 [5.0-11.8] years old) were included. All patients except for one presented at or before 19 years of age. 56 patients (96.6%) were initially symptomatic. Premature ventricular complexes (PVCs) were present in 44 of 51 patients (86.3%) and VT in 52 of 58 patients (89.7%). Genetic tests were performed on 54 patients (93.1%) with a yield of 87%. *RyR2*, *CASQ2, TERCL*, and *SCN10A* mutations were found in 35 (71.4%), 12 (24.5%), one (0.02%) patient, and one patient (0.02%) respectively. 54 patients were treated with beta-blockers, eight received flecainide, five received amiodarone, two received verapamil and one received propafenone. Sympathectomy (n=10) and implantable-cardioverter defibrillator implantation (n=8) were performed. On follow-up, 13 patients developed VT/VF.

Conclusion: This is the first systematic review of CPVT patients from China. Most patients had symptoms on initial presentation, with syncope as the presenting complaint. *RyR2* mutation accounts for more than half of the CPVT cases, followed by *CASQ2*, *TERCL* and *SCN10A* mutations.

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Introduction

Cardiac ion channelopathies increases a patient's risk of developing of spontaneous ventricular tachycardia/fibrillation (VT/VF) and sudden cardiac death (SCD) (1-6). Amongst different cardiac channelopathies, such as Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT) is a less prevalent condition in Asia (7, 8). It is typically caused by mutations in either the ryanodine receptor 2 (*RyR2*) gene (9) or the calsequestrin 2 (*CASQ2*) gene (10, 11), but mutations in other genes such as calmodulin (*CALM*) have been implicated (12-14). Patients with CPVT usually present in the first two decades of life, with symptoms manifested after exercises or when in distress, resulting in bidirectional VT (15). Globally, Western countries have mainly contributed to population-based data on CPVT. To our knowledge, the largest registry had reported 237 CPVT patients, which was created by the Pediatric and Congenital Electrophysiology Society of the United States. (16, 17). In another multi-national study, 101 CPVT patients who mainly come from France was reported (18), complementing smaller registry and case series studies by the same group (19, 20). In another study, 21 CPVT patients with CALM gene mutations were reported (12).

By contrast, limited data from Asia have been studied in comparison. Taking Japan as an example, 78 patients with CPVT were enrolled in the multi-centre registry (21). Other studies from Japan identified 30 (22) and 29 patients (23) with CPVT respectively. However, to date, no national registry has been established in China, and descriptions on CPVT patients have been limited to case reports or case series (11, 24-26). Moreover, as many of these studies were written in Chinese, researchers beyond China may have limited accessibility due to language barriers. Recently, our team conducted a situation analysis of the local CPVT burden in Hong Kong through a systematic literature search. This study, an extension of our previous work, has the aim of synthesizing evidence on the clinical characteristics, genetic basis, and arrhythmic outcomes of CPVT patients from China.

Methods

Patient Cohort and Data Collection

PubMed and Embase were systematically searched for case reports or case series that described CPVT patients from China until February 19th, 2022, which allowed a primary synthesis of cases for analysis. Keywords of the search included "Catecholaminergic Polymorphic Ventricular Tachycardia" OR "CPVT", with the country of author limited to "China" OR "Hong Kong" or "Macau" in EMBASE, with no language or publication type restriction. Diagnosis of CPVT was established based on the exercise

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treadmill test, adrenaline challenge test, or genetic testing as defined by the individual papers. Where overlapping cohorts were described, data were extracted from the publication with the largest cohort. The individual cases were analyzed according to diagnostic criteria proposed by the 2013 Heart Rhythm Society (HRS)/ European Heart Rhythm Association (EHRA) / Asia-Pacific Heart Rhythm Society (APHRS) expert consensus statement (**Supplementary Table 1**) (27). All genetic variants described in the studies were searched in the genetic database ClinVar to determine their possible pathogenicity and novelty, and VARSOME for further prediction. Mutation hotspots for RyR2 were also identified according to the criteria set by Priori and Chen (28).

Data Extraction and Statistical Analysis

The following clinical data were extracted from the published studies: 1) sex, 2) age of presentation, 3) age of diagnosis, 4) family history of SCD or CPVT, 5) initial symptoms, initial presentation with 6) syncope, 7) palpitations, 8) chest pain or 8) seizures, the presence of 10) premature ventricular complexes (PVCs) or 11) VT/VF detected on electrocardiography, Holter studies or exercise stress testing, 12) genetic testing, 13) methods of testing, 14) genetic results and 15) interpretation of the variants, 16) performance of electrophysiological study (EPS) and their respective results; 17) performance of echocardiogram and cardiac magnetic resonance imaging and results; 18) presence of bradycardic complications; 19) the presence of arrhythmias other than premature ventricular complexes (PVCs) /VT/VF, 20) prescription of pharmacological agents and 21) implantation of implantable cardioverter-defibrillator (ICD). Categorical variables were summarized as frequency (%) and continuous variables were expressed as median (Q1-Q3). All statistical analysis was performed using IBM SPSS Statistics 27.

Results

Baseline Characteristics and Predictors

A systematic search of the PubMed and Embase databases yielded 1049 and 47 articles respectively. After the exclusion of overlapping cohorts, a total of 58 unique cases from eight cities of China by 15 studies were included (11, 25, 29-41). CPVT cases were reported in the following cities: Beijing (n=22) (11, 29-31), Hong Kong (n=16) (25), Guangzhou (n=7) (32, 37), Nanjing (n=6) (33), Shanghai (n=4) (34, 35, 38, 40), Chengdu (n=1) (36), Shenzhen (n=1) (39) and Xi'an (n=1) (41). Their clinical characteristics and test results are shown in **Table 1**. 21 patients fulfilled at least two criteria and 41 patients fulfilled one criterion of the 2013 HRS/EHRA/APHRS expert consensus statement

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(**Supplementary Table 1**). 22 (37.9%) patients were female and all patients were of Han Chinese origin. All patients except for one presented at or before 19 years of age. The median age of presentation and diagnosis were 8.0 (5.0-11.8) and 10.1 (8.3-13.0) years old respectively, with a median delay of 16 (3.0-46.8) months. 56 patients (96.6%) were initially symptomatic. PVCs were present in 44 out of 51 patients and VT was present in 52 out of 58 patients. An abnormal echocardiogram was found in four patients. Duan *et al.* reported a patient with mild mitral and tricuspid regurgitation with a subsequent finding of a mildly dilated left ventricle on follow-up (36). Ge *et al.* reported a patient with a mildly dilated left ventricle (29). Lin *et al.* reported a patient with a thinner apical myocardium of the left ventricle (37). Abnormality on echocardiogram was also found in a patient conducted by Lee *et al.* but findings were not reported in the study (25). Genetic tests were performed on 54 patients (93.1%) with a yield of 87%. *RyR2*, *CASQ2, TERCL*, and *SCN10A* mutations were found in 35 (71.4%), 12 (24.5%), one (0.02%) patient, and one patient (0.02%) respectively (**Table 2**).

Pharmacological and non-pharmacological treatments for this cohort are summarized in **Table 3**. 54 patients were treated with β-blocker, eight patients received flecainide, five patients received amiodarone, two received verapamil and two received propafenone. Sympathectomy (n=10) and ICD implantation (n=8) were performed. On follow-up, 13 patients developed incident VT/VF.

Discussion

To the best of our knowledge, the present study is the first systematic review of published cases of CPVT patients from China. The main findings are that: 1) RyR2 mutations account for over half of the CPVT cases, 2) 24 *RyR2* variants, eight *CASQ2* variants, two *TERCL* variants and one *SCN10A* variant were described, 3) β-blocker are used in 93.1% of the cases, followed less frequently by flecainide, amiodarone, verapamil and propafenone, and 4) 17.2% patients underwent cardiac sympathectomy and 13.8% received ICDs.

SCD is an important clinical problem globally, with congenital and acquired causes (42-45). Regarding the phenotype of congenital cardiac ion channelopathies, CPVT is characterized by exercise-induced bidirectional VT. Significant delays from the date of initial presentation to the date of diagnosis of around six months have been reported in international registry studies on North American and European patients (17, 46). By contrast, the epidemiology and characteristics of studies in Asia are limited. In China, cases of CPVT have been limited to small case reports or case series.

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The incidence of adverse outcomes in CPVT patients has been examined in multiple studies, which have focused on syncopal events and SCD (18, 19, 47, 48). Existing evidence suggests that subjects who are initially symptomatic, who constituted the majority of the cohort represented in this systematic review, as well as those who are younger at diagnosis with no administration of β-blocker therapy, have a significantly higher susceptibility to cardiac events, including syncope, aborted cardiac arrest, and/or SCD (18). Regarding electrocardiographic parameters, their effectiveness in risk prediction for VT/VF in patients with CPVT remains uncertain due to a relative shortage of literature assessing such aspects. For assessing SCD as an outcome, although some studies have demonstrated significant differences in QRS durations of the recorded PVCs between patients who remained alive and those who suffered SCD during follow-up, whereas most of the other ECG variables, such as heart rate and QTc interval, failed to demonstrate any notable variations with time (18).

Regarding the genetic basis, this study identified 24 *RyR2* variants. Of these, 13 have been reported outside China: c.490C>T (49), c.2410C>T (RCV000639160.2), c.6886G>A (RCV000465586.1), c.7202G>A (50), c.7258A>G (51), c.7420A>G (52), c.10046C>T (53, 54), c.11836G>A (55, 56), c.12272C>T (RCV00182811.1), c.12475C>A (57), c.13933T>C (58), c.14159T>C (RCV000182842.2), c.14848G>A (56). Since *RyR2* variants have been reported in previous animal studies to be associated with a disruption in calcium homeostasis and a reduction in conduction velocity, functional studies should also be conducted to identify how such variants could lead to the generation of electrophysiological substrates (59-61).*CASQ2*, in comparison, accounts for a fewer proportion of CPVT cases. In our study, 8 variants were reported. Three have been reported from publications arising from outside China: c.97C>T (63), c.98G>A (64), and c.748C>T (RCV000694480.2), with five novel mutations. The two *TERCL* variants as well as one *SCN10A* variant reported in our study are also novel mutations. Finally, *CALM2* has also been implicated in CPVT but our study did not identify mutations in this gene.

Strengths and limitations

The major strengths of the present study include a comprehensive extraction and integration of data which allows easier interpretation by researchers beyond China and comprehensive analysis of clinical characteristics, genetic basis, and arrhythmic outcomes of CPVT patients from China. This study also forms a basis for further studies in comparing CPVT between China and other Asian or non-Asian populations. However, the major limitation is that data were extracted from case reports or case series. Without a national registry, cases reported may not include all the domains that were assessed in this

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current study, therefore the data may not reflect the actual picture of CPVT patients from China, especially regarding arrhythmic events on follow-up.

Conclusion

This is the first systemic review of CPVT patients from China. Most patients had symptoms on initial presentation, with syncope as the presenting complaint. RyR2 mutation accounts for more than half of the CPVT cases, followed by CASQ2, TERCL and SCN10A mutations.

Authors' Contributions: Sharen Lee, Justin Leung, and Gary Tse: study conception, data acquisition, database building, statistical analysis, manuscript drafting, manuscript revision

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Data Availability Statement: The data described in this study are available from the published studies.

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Table 1. Baseline clinical and demographic characteristics of CPVT patients from China.

Parameter	Median (Q1-Q3) / frequency (%)
Female	22 (37.9)
Presentation Age (years)	8.0 (5.0-11.8)
Diagnosis Age (years)	10.1 (8.3-13.0)
Presentation to Diagnosis (months)	16 (3.0-46.8)
Family History of CPVT/SCD	14 (24.1)
Initially symptomatic	56 (96.6)
Initial syncope	54 (93.1)
Initial VT/VF/SCD	15 (25.9)
Initial palpitations	12 (20.7)
Initial chest pain	7 (12.1)
Initial seizure	17 (29.3)
PVC	44 (75.9)
VT/VF	52 (89.7)
VT/VF post-presentation	13 (22.4)
Echocardiogram	43 (74.1)
Abnormal echocardiogram	4 (9.3)
Cardiac MRI performed	5 (8.6)
Abnormal cardiac MRI	0 (0)
Genetic Test	54 (93.1)
Positive Genetic Test	47 (87)
Adrenaline Challenge	9 (15.5)
Positive Adrenaline Challenge	9 (100)
Exercise Tolerance Test	46 (79.3)
Positive Exercise Tolerance Test	44 (97.8)
EPS	3 (5.2)
Positive EPS	3 (100)
Holter Study	43 (74.1)
Arrhythmia in Holter Study	34 (81)

CPVT: catecholaminergic polymorphic ventricular tachycardia; SCD: sudden cardiac death; VT: ventricular tachycardia; VF: ventricular fibrillation; PVC: premature ventricular complex; MRI: magnetic resonance imaging; EPS: electrophysiological study

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Table 2. Genetic test results.

Gene	Mutation	Region in Genome	Coding Effect	Mutation type	Mutation Hotspots for RyR2	Pathogenicity	Prediction	Reported Mutation outside China	Reference
RyR2	c.229C>T	Exon 3	P77S	Substitution	Domain I	VUS	VUS	Novel mutation	Ge 2017
RyR2	c.490C>T	Exon 8	P164S	Substitution	Domain I	VUS	Likely Pathogenic	No: (49)	Lin 2018
RyR2	c.494C>A	Exon 8	A165D	Substitution	Domain I	VUS	Pathogenic	Novel mutation	Xiong 2018
RyR2	c.1639A>C	Exon 17	N547H	Substitution	Non-hotspot	VUS	VUS	Novel mutation	Ge 2017
RyR2	c.2410C>T	Exon 22	L804F	Substitution	Non-hotspot	Likely benign	Benign	RCV000639160.2	Ge 2017
RyR2	c.5564C>A	Exon 37	A1855D	Substitution	Non-hotspot	VUS	VUS	Novel mutation	Zhang 2019
RyR2	c.6577G>T	Exon 43	V2193L	Substitution	Non-hotspot	VUS	VUS	Novel mutation	She 2020
RyR2	c.6886G>A	Exon 45	E2296K	Substitution	Domain II	VUS	VUS	RCV000465586.1	Hou 2019
RyR2	c.7202G>A	Exon 47	R2401H	Substitution	Domain II	Likely Pathogenic	Pathogenic	No: (50)	Lee 2021
RyR2	c.7258A>G	Exon 48	R2420G	Substitution	Domain II	VUS	VUS	No: (51)	Ge 2017
RyR2	c.7420A>G	Exon 49	R2474G	Substitution	Domain II	VUS	Likely Pathogenic	No: (52)	Lee 2021
RyR2	c.7580T>G	Exon 50	L2527W	Substitution	Domain II	VUS	VUS	Novel mutation	Duan 2018
RyR2	c.10046C>T	Exon 69	S3349L	Substitution	Non-hotspot	VUS	VUS	No: (53, 54)	Lee 2021
RyR2	c.11836G>A	Exon 88	G3946S	Substitution	Domain III	Pathogenic	Pathogenic	No: (55, 56)	Ge 2017, Lee 2021
RyR2	c.12014A>T	Exon 90	E4005V	Substitution	Domain III	VUS	VUS	Novel mutation	Yang 2021
RyR2	c.12272C>T	Exon 90	A4091V	Substitution	Domain III	VUS	VUS	RCV00182811.1	Yang 2021
RyR2	c.12475C>A	Exon 90	Q4159K	Substitution	Domain III	VUS	Likely Pathogenic	No: (57)	Lee 2021
RyR2	c.13933T>C	Exon 96	W4645R	Substitution	Domain IV	VUS	VUS	No: (58)	Ge 2017
RyR2	c.14159T>C	Exon 99	L4720P	Substitution	Domain IV	VUS	VUS	RCV000182842.2	Lee 2021
RyR2	c.14570T>G	Exon 101	I4857S	Substitution	Domain IV	VUS	VUS	Novel mutation	Ge 2017
RyR2	c.14593C>A	Exon 102	L4865I	Substitution	Domain IV	VUS	VUS	Novel mutation	Ge 2017
RyR2	c.14834A>G	Exon 105	Q4945R	Substitution	Domain IV	Likely benign	VUS	Novel mutation	Ge 2017
RyR2	c.14848G>A	Exon 105	E4950K	Substitution	Domain IV	VUS	Likely Pathogenic	No: (56)	Lee 2021
RyR2	c.14861C>G	Exon 105	A4954G	Substitution	Domain IV	VUS	VUS	Novel mutation	Lee 2021
CASQ2	c.97C>T	Exon 1	R33X	Substitution	Not applicable	Likely Pathogenic	Pathogenic	No: (63)	Gao 2018, Li Q 2019
CASQ2	c.98G>A	Exon 1	R33Q	Substitution	Not applicable	VUS	VUS	No: (64)	Li Q 2019
CASQ2	c.244C>T	Exon 1	Q82X	Substitution	Not applicable	VUS	Pathogenic	Novel mutation	Ge 2017
CASQ2	c.532+1G>A	IVS		Splice site mutation	Not applicable	VUS	Pathogenic	Novel mutation	Li Q 2019
CASQ2	c.748C>T	Exon 7	R250C	Substitution	Not applicable	VUS	VUS	RCV000694480.2	Gao 2018, Li Q 2019
CASQ2	c.838+1G>A	IVS		Splice site mutation	Not applicable	VUS	Pathogenic	Novel mutation	Li Q 2019
CASQ2	c.1074_1075delinsC	Exon 11	E359Rfs*12	Deletion and insertion	Not applicable	VUS	Pathogenic	Novel mutation	Li Q 2019
CASQ2	c.1175_1178delACAG	Exon 11	D392Vfs*84	Deletion	Not applicable	VUS	Pathogenic	Novel mutation	Li Q 2019
TECRL	c.587C>T	Exon 6	R196Q	Substitution	Not applicable	VUS	VUS	Novel mutation	Xie 2019
TECRL	c.918+3T > G	IVS		Splice site mutation	Not applicable	VUS	VUS	Novel mutation	Xie 2019
SCN10A	c.4086G>C	Exon 22	Q1362H	Substitution	Not applicable	VUS	VUS	Novel mutation	Zhang 2019

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Table 3. Management for CPVT patients in China.

Treatment	Frequency (%)
β-blocker	54 (93.1)
Verapamil	2 (3.4)
Amiodarone	5 (8.6)
Flecainide	8 (13.8)
Propafenone	2 (3.4)
Sympathectomy	10 (17.2)
ICD implantation	8 (13.8)