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REVIEW

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Historical perspective and recent progress in cardiac ion channelopathies research and clinical practice in Hong Kong

Keith Sai Kit Leung^{1,8*†} , Helen Huang^{1,9†}, Cheuk To Chung¹, Danny Radford^{1,2}, Ishan Lakhani¹, Christien Ka Hou Li¹, Tommy Wai Kei Li⁸, Simon Ranjithkumar⁸, Rajesh Rajan³, Leonardo Roever⁴, Sebastian Garcia-Zamora⁵, George Bazoukis⁶ and Tong Liu^{1,7*}

Abstract

Cardiac ion channelopathies encompass a set of inherited or acquired conditions that are due to dysfunction in ion channels or their associated proteins, typically in the presence of structurally normal hearts. They are associated with the development of ventricular arrhythmias and sudden cardiac death. The aim of this review is to provide a historical perspective and recent advances in the research of the cardiac ion channelopathies, Brugada syndrome, long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, in Hong Kong, China. In particular, recent works on the development of novel predictive models incorporating machine learning techniques to improve risk stratification are outlined. The availability of linked records of affected patients with good longitudinal data in the public sector, together with multidisciplinary collaborations, implies that ion channelopathy research efforts have advanced significantly.

Keywords Ion channelopathies, Brugada syndrome, Catecholaminergic polymorphic ventricular tachycardia, Long QT syndrome, Sudden cardiac death, Risk stratification, Machine learning

[†]Keith Sai Kit Leung and Helen Huang contributed equally to this work

*Correspondence:

Keith Sai Kit Leung
keithsaikit.leung@nhs.net
Tong Liu
liutongdoc@126.com

¹ Cardiac Electrophysiology Unit, Cardiovascular Analytics Group, Hong Kong, China

² Kent and Medway Medical School, Canterbury, Kent, UK

³ Sabah Al Ahmad Cardiac Center, Amiri Hospital, Ministry of Health, Kuwait City, Kuwait

⁴ Departamento de Pesquisa Clinica, Universidade Federal de Uberlândia, Uberlândia, MG, Brazil

⁵ Cardiac Intensive Care Unit, Department of Cardiology, Delta Clinic, Rosario, Santa Fe, Argentina

⁶ Department of Cardiology, Medical School, University of Nicosia, 2408 Nicosia, Cyprus

⁷ Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China

⁸ Faculty of Health and Life Sciences, Aston University Medical School, Birmingham, UK

⁹ Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland



Introduction

Cardiac ion channelopathies encompass a set of inherited or acquired conditions that are due to dysfunction in ion channels or their associated proteins, typically in the presence of structurally normal hearts. They are associated with the development of ventricular arrhythmias and sudden cardiac death (SCD). The aim of this review is to provide a historical perspective and recent advances in the research of the cardiac ion channelopathies, Brugada syndrome (BrS), long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), in Hong Kong, China (Fig. 1). The availability of linked records of affected patients with good longitudinal data in the public sector, together with multidisciplinary collaborations, means that ion channelopathy research efforts have advanced significantly.

Genetic testing in cardiac ion channelopathies

The diagnostic aptitude of genetic tests alone is often disputed across channelopathies in different

ethnic populations [1]. Studies have found rare non-synonymous genetic variants, i.e., <0.5% allelic frequency in genes of healthy individuals that encode for cardiac ion channels [2]. This emphasizes the necessity to interpret the pathogenicity of genetic findings and differentiate between background interference and true pathogenic mutations. It is known that the yield of genetic testing and phenotypic strength correlates strongly [3]. In this study, the yield of either “likely pathogenic” or “pathogenic” variants following either phenotype-driven genetic testing or broader gene panel genetic testing was highly dependent on whether or not a clinical genetic heart disease phenotype was identified [3]. As the yield of genetic testing is correlated strongly with phenotypic strength, it should come as little surprise that the yield of genetic testing was low (2.0%) in those deemed to have suffered an unexplained sudden cardiac arrest, for example idiopathic ventricular fibrillation. Therefore, genetic testing can be limited in diseases with variable expressivity and genetic pleiotropy. Algorithms based on the location

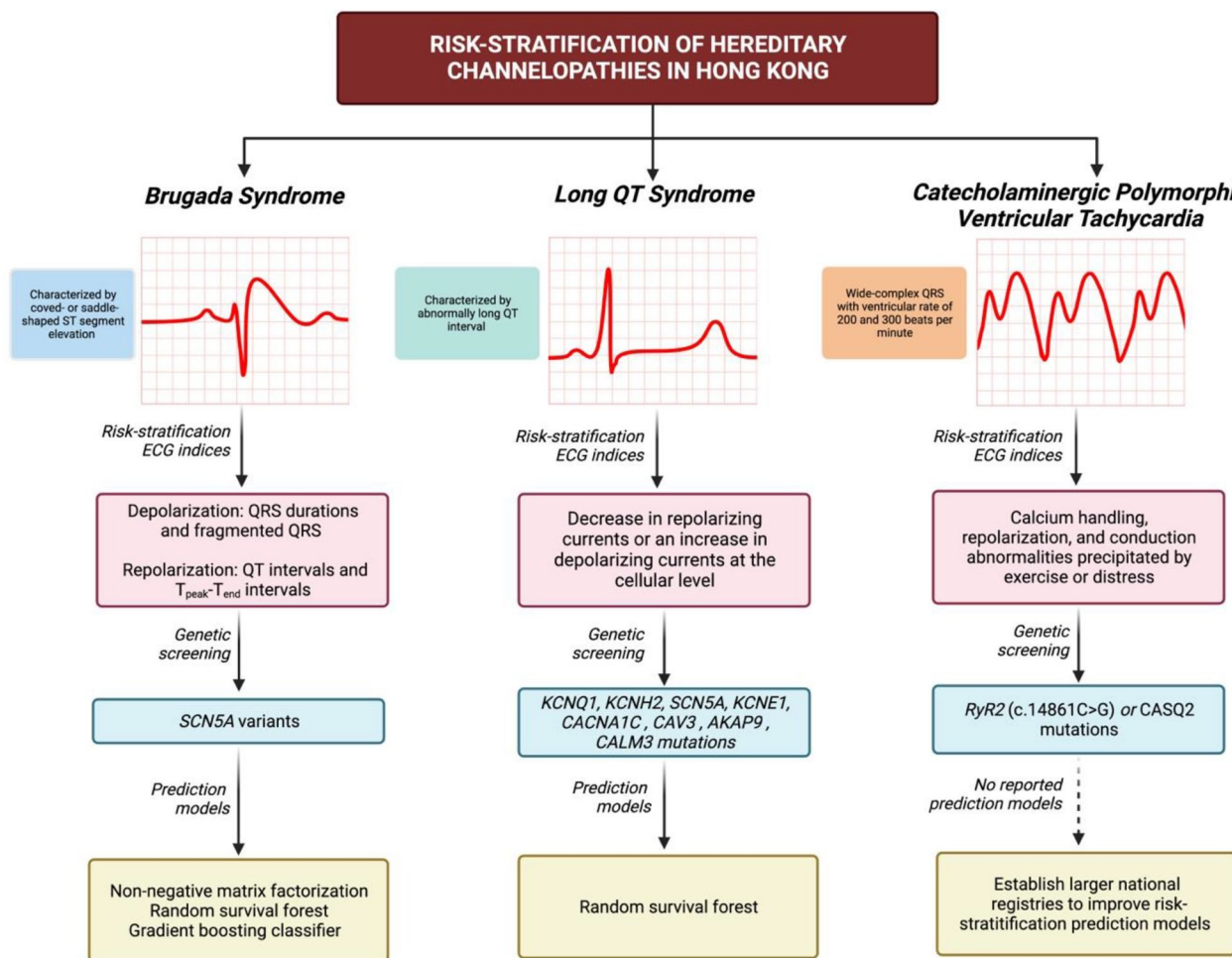


Fig. 1 Risk stratification algorithm to classify and improve prediction models for hereditary channelopathies in Hong Kong

of mutations can allow the probability of pathogenicity of each novel mutation identified within an ion channel gene to be calculated [2], and functional studies can be used to correlate with changes in ion channel electrophysiology.

In Hong Kong, genetic testing has been applied to investigate the underlying causes of sudden cardiac death, including ion channelopathies and cardiomyopathies [4]. Conventionally, Sanger’s method is utilized for genetic testing in clinical research with a cited accuracy of 99.99% and requires the use of fluorescent labels and capillary-based electrophoresis to sequence each DNA fragment at a time [5]. However, given its low throughput, the incorporation of next-generation sequencing (NGS) has become standard in genome-wide searches of possible variants implicated in sudden cardiac death (Fig. 2) [6]. NGS sequencing has the capacity to conduct massive parallel DNA sequencing through DNA fragmentation, polymerase chain reaction amplification, sequencing, variant analysis with bioinformatics, and the assembly of sequences and genome annotations. These techniques outlined in NGS can aid in the detection of

mutation-specific variants within families and could potentially detect rare mutations with phenotypic variability across different channelopathies [5]. To date, there are variations regarding the application of genetic tests for different cardiac channelopathies locally, with different research teams developing simplified diagnostic approaches to hereditary channelopathies globally [7–9]. The detection of channelopathies in Hong Kong, however, is limited by the lack of widespread genetic testing and thus disrupts the robustness of phenotype-genotype correlations. When patients present to a clinical cardiologist with a phenotype suggesting channelopathies, genetic tests must be interpreted regularly. Thereafter, clinicians are arduously tasked to match the presenting phenotypes with the presented genotypic information. Despite patients presenting with a clear clinical picture of a channelopathy, the results from genetic testing are often compared to similar variants repeatedly reported by various hospitals, and thus creates a wide discrepancy in diagnosing cardiac ion channelopathies locally [10]. As pointed out by a recent review, the eligibility criteria for genetic testing depend on regions and no uniform

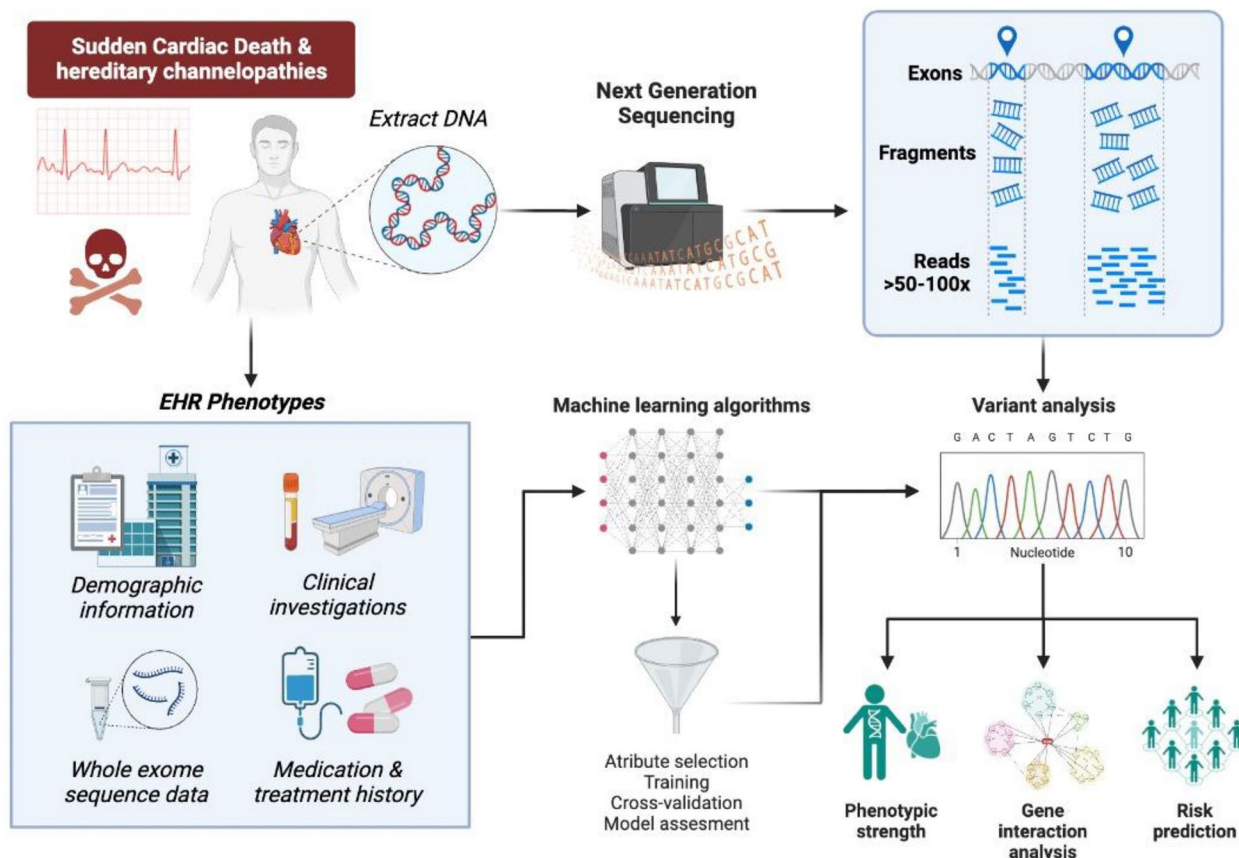


Fig. 2 The roles of next-generation sequencing and machine learning algorithms to process electronic health record phenotypes and whole exome sequencing data from patients with hereditary channelopathies

agreement exists between the guidelines published by different societies [11]. In Hong Kong, CPVT has the highest genetic testing rates for probands [12, 13], followed by LQTS [14, 15] then BrS [16]. The resulting yields are also different [17], with BrS ranked lowest, followed by CPVT and lastly LQTS with the highest value.

Brugada syndrome

Brugada syndrome (BrS) is characterized by coved- or saddle-shaped ST segment elevation in the right precordial leads [18–20]. Its diagnosis is based on electrocardiographic criteria, genetic tests, family history and clinical symptoms [21, 22]. However, risk stratification for BrS patients remains difficult [23–26], especially for those with a combination of low-risk and high-risk features [27, 28]. An understanding of the pathophysiological mechanisms underlying arrhythmogenesis from ongoing research would contribute to efforts on improving risk stratification [29–32]. From pre-clinical studies, it is recognized that abnormalities in depolarization, repolarization or combination of both are important determinants of arrhythmogenesis [33, 34].

In clinical practice, these parameters can be detected using electrocardiographic indices [35] which can be helpful for risk stratification of patients at intermediate risk of sudden cardiac fatalities [36], including those who are initially asymptomatic [27]. Depolarization indices include QRS durations and fragmented QRS reflecting conduction times and dispersion of conduction, respectively [37]. Repolarization indices such as QT intervals and $T_{\text{peak}} - T_{\text{end}}$ intervals, representing overall repolarization time and dispersion of repolarization, have demonstrated incremental values for risk prediction [38, 39]. Indices incorporating both depolarization and repolarization [40–43], as well as those reflecting dynamic changes such as restitution properties [44, 45], can further elucidate the arrhythmic risks of the patients.

In Hong Kong, the seminal works that set the scenes for studies over the next two decades arose from Dr. Ngai Shing Mok and colleagues, who provided the first descriptions of Brugada syndrome cases locally from early and late 2000's [46–53]. In 2016, detailed investigations of distinct electrocardiographic phenotypes between type 1 and non-type 1 Brugada patients started from a single tertiary center [54], which rapidly progressed to multicenter and multinational studies which were enhanced by the use of machine learning methodologies [55–57]. Thus, Brugada patients were studied based on their initial presenting features of arrhythmias, syncope or asymptomatic, with multivariable regression analyses identifying significant predictors of incident arrhythmias [56]. In efforts to improve risk stratification of Brugada syndrome in clinical practice, a territory-wide

multicenter study developed a novel risk score based on the initial presentation of ventricular tachyarrhythmias, syncope at any point, family history of SCD, spontaneous type 1 Brugada pattern, arrhythmias other than ventricular tachyarrhythmias, early repolarization pattern on peripheral leads, aVR sign, S-wave in lead I and QTc intervals ≥ 436 ms [58]. It showed good discriminative ability for predicting future arrhythmic events with an area under the curve of 0.86 for the whole cohort and 0.76 for the intermediate risk subgroup based on random survival forests and gradient boosting classifier models, which exhibited significant improvements in predicted arrhythmic events compared to traditional score. Especially for rare arrhythmic disorders such as Brugada, the development of newer machine learning techniques is a promising feat to improve the prediction of ventricular tachycardia among patients, such as with the incorporation of both nonnegative matrix factorization (NSF) and random survival forest (RSF), which has already been demonstrated to outperformed models using Cox regression, NSF or RSF alone [56]. Such improvements would also pave way to identify differences in phenotypes and cardiac outcomes between pediatric and adult patients, which could influence treatment algorithms and diagnostic aptitude [16].

Identifying BrS in clinical practice can be based on atrial electrophysiological abnormalities [59], which were subsequently related to increased risks of atrial fibrillation development [60]. Unfortunately for BrS patients, the development of tachyarrhythmias has accounted for nearly 20% of all sudden cardiac deaths in patients without structural anomalies of the heart [61]. While the incidence of sudden cardiac death among BrS patients in Hong Kong has not been previously quantified, the rate of sudden arrhythmic death is highest in the Asian population, with BrS being one of the main causes among these ethnic groups [62]. To prevent these outcomes from occurring, BrS patients are often placed with an implantable cardioverter defibrillator (ICD). However, it is important to note certain complications that may arise from ICD implantation, such as inappropriate shock delivery, malfunction of ECG leads, dislodgement of leads, and postoperative infection. In Hong Kong alone, ICD-related adverse event rates were at 22.1% among all patients but were effective at preventing SCD among deceased patients. Prevention of ventricular tachycardia was noted in 47.2% of BrS patients with ICD implantation and was noted to be similar in asymptomatic individuals [55]. Regardless, the assessment of the risks and benefits prior to ICD implantation must be improved given the likelihood of adverse events.

The incorporation of genetic information could better inform clinical decision-making algorithms given the

large phenotypic variability on initial presentation. Local teams have successfully identified six novel, pathogenic or likely pathogenic *SCN5A* variants not reported outside of the region (c.674G>A, c.2024-11 T>A, c.2042A>C, c.4279G>T, c.5689C>T, c.429del) [63]. The *SCN5A* genome encodes pore-forming alpha-subunits of cardiac sodium channels and determines the propagation of electrical currents across the heart; mutations in this gene could alter the magnitude and equilibrium of cardiac sodium currents, thus predisposing carriers to conduction disorders [64]. Specific variants of *SCN5A* vary in its pathophysiological mechanisms as described in the previously mentioned study, but it can be confirmed in previous reports that these variants are loss of function, either by disrupting acceptor splice sites (c.2024-11 T) or significant amino acid changes that alter *SCN5A* functionalities (c.2042A>C). Alternatively, a deleterious variant can cause a frameshift mutation which leads to premature truncation of *SCN5A* protein and ameliorates its functions (c.429del), or could reduce conduction velocity of cardiac action potential (c.674G>A) [63].

Serial ECG testing can be helpful as higher temporal variability in ECG markers can reflect higher arrhythmic risk [65]. The analysis of automated ECG data [66], extraction of latent features between risk variables [67] together with the application of machine learning methodologies [68] and the development of risk scores or models [21] can all improve the accuracy and precision of arrhythmic risk prediction. Overseas centers have already routinely incorporated the use of electroanatomical mapping for risk stratification which should be considered by local physicians [69, 70]. Regardless, future studies focused on transcriptional profiles of putative ion channel genes [71]; in large multicenter cohorts [57] including patients from other parts of China would allow researchers to achieve precision in determining not only the diagnosis, but also the prognosis, as well as predicting arrhythmic risks and drug responses [72].

Long QT syndrome

Long QT syndrome (LQTS) is characterized by an abnormally long QT interval on the ECG which can result from a decrease in repolarizing currents or an increase in depolarizing currents at the cellular level and can have either congenital or acquired causes [73]. For congenital LQTS, at least 17 subtypes have now been recognized. Risk stratification involves a combination of clinical and genetic findings, aided by the determination of different ECG indices [74]. While the clinical and genetic characteristics of LQTS have been extensively studied in Western populations [75, 76], characterization of ethnic groups in Asia came much later [77] and is rather limited [78–80]. In a recent retrospective study detailing

twenty-year's worth of patient information, LQTS was shown to be severely undiagnosed in Hong Kong at 1:10,000 across children compared to other Asian ethnic groups such as Japan, which potentially indicated a clinical underdiagnosis [81]. The variability of phenotypes in LQTS patients may be the culprit toward the lack of diagnostic aptitude across clinical practice in Hong Kong, which underpins a gap in the literature regarding its epidemiology. The same study described syncope and convulsions to be the main presentation in over half of LQTS participants. However, similar to BrS, participants with LQTS are predisposed to adverse cardiac events such as ventricular tachyarrhythmias. An up-to-date study of congenital LQTS across Hong Kong revealed that a significant predictor for spontaneous tachyarrhythmias after multivariate adjustment was the initial presentation with syncope, which further highlights the need to improve diagnostic aptitude across LQTS patients [15]. Across different age groups, a recent retrospective study details that adult LQTS cohorts often present with more fatal phenotypes such as tachyarrhythmias, while pediatric LQTS participants initially presented with syncope [14]. Incidentally, sudden cardiac death was more common across adult patients which contributed to higher rates of ICD implantation, while pediatric participants exhibited arrhythmic events after non-cardiac causes. Despite a better understanding of the epidemiology across Hong Kong, the incidence of ICD-related complications and sudden cardiac death attributed to LQTS in a larger cohort has not yet been achieved.

In Hong Kong, a set of genes identified in LQTS patients included *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *CACNA1C* mutations, confirming subtypes 1, 2, 3, 5 and 8, respectively. *KCNQ1* mutations encode voltage-gated potassium channels, which complex with accessory proteins to generate slow delayed calcium rectifier currents across cardiac myocytes. The gene has been strongly associated with LQTS, with over 600 *KCNQ1* mutations being identified across the genome [82]. However, the pathogenicity of these variants is widely unknown and thus requires extensive in vivo studies to document loss-of-function sites. A recent study detailing the mechanisms of *KCNQ1* dysfunction revealed that more than half loss-of-function variants destabilize the structural voltage domains of calcium channels, either due to destabilized membrane proteins or mis-trafficked proteosomes. The *KCNE1* gene co-assembles with *KCNQ1* in cardiac myocytes, but are only present in around 3% of LQTS phenotypes and rare in the general population [83]. The mechanism of action targets beta-subunits of channel proteins carrying slow delayed-rectifier potassium currents. Although *KCNE1* variants are unequivocally correlated to the functional mechanism of *KCNQ1*

mutations, the most recent study in transgenic mice with LQTS revealed that disruptions of *KCNE1* subunits accelerated the deactivation kinetics of slow- and rapid-delayed rectifier potassium currents [83]. The implications point toward a loss in voltage dependence that causes an effect on the polarized musculature of the heart. For *KCNH2* in LQTS type 2, the gene encodes the alpha-subunits of potassium channels while also exerting similar effects to rectifier potassium currents and is considered pathogenic in LQTS and BrS [84, 85]. Additionally, an overlap of genotypes for *SCN5A* and *CACNA1C* is seen across LQTS and BrS. Variants in *CACNA1C* are known to encode L-type calcium channels and are gain of function, thus causing dysfunction in calcium-handling across the cardiac myocyte. Carriers of this gene often express variable phenotypes and thus suggest that *CACNA1C* is indeed pleiotropic; for example, mutations in this genome are linked to Timothy syndrome, LQTS type 8, and Brugada syndrome across cardiac conduction disorders [86].

Additionally, monogenic variants in *CAV3* (c.277G>A), *AKAP9* (c.6065A>G) and *CALM3* (c.286G>C) were also correlated with LQTS subtypes 9, 11 and 16 and further corroborated in a recent case series which identified novel and rare genetic variants of congenital LQTS across Hong Kong [87]. Mutations in *CAV3* disrupt the function of caveolin-3, a major scaffolding protein in cardiac myocytes, and are hypothesized to induce an increase in late sodium currents [88]. Coding variants are associated with LQTS pathogenicity, although it is not confirmed whether the increase in current duration is due to molecular interactions/regulatory actions between sodium channels and caveolin-3. On the other hand, *AKAP9*, a gene that mediates the phosphorylation of *KCNQ1*-encoded potassium channels, is affected by loss-of-function variants that alter QTc duration [89]. Finally, *CALM3* encodes calmodulin proteins that are ubiquitously expressed and act as a calcium sensor and signal transducer. Although mutations in *CALM3* rarely cause LQTS based on epidemiological studies, the disruptive behavior of variants could affect several ion channels modulated by calmodulin (i.e., L-type calcium channels, sodium channels, ryanodine receptors, etc.) [90].

The identification of pathogenic mutations of LQTS could better alienate the phenotypic differences and, based on the 2022 ESC Guidelines, could be sufficient for a clinical diagnosis. However, a limitation to clinical diagnostics in Hong Kong arises from the lack of family-based genetic screening starting at adolescence and thus remains to be massively underdiagnosed. Moreover, it is not fully understood whether the identification of rare genetic mutations could improve phenotype-to-genotype correlations in LQTS for risk stratification models [15].

The limitations of clinical diagnostics directly influence cardiac outcomes in LQTS patients, which could potentially be addressed with family-based genetic screening starting at adolescence and solidifying clinical guidelines for management. The frequent usage of machine learning techniques may better achieve more accurate prediction of adverse cardiac outcomes such as ventricular arrhythmias and continue to pave advancements in clinical medicine.

Catecholaminergic polymorphic ventricular tachycardia

CPVT is usually precipitated by exercise or distress, causing bidirectional VT [91]. CPVT is often caused by mutations in either the ryanodine receptor 2 (RyR2) [92] or the calsequestrin 2 (CASQ2) genes [78, 93]. Calcium handling, repolarization, and conduction abnormalities were found to underlie ventricular arrhythmogenesis [94–96]. For Chinese CPVT patients, descriptions came from only small case series [12, 78–80] though the evidence was recently summarized by two systematic reviews [13, 97]. In Hong Kong, CPVT is the rarest cardiac ion channelopathy, with the largest cohort reporting on the findings of only 16 patients [80]. Information on the prognosis is limited [98], but in a CPVT case reported by a five-year review of autopsies [6], the patient died at 32 years old. The commonest prescribed medications were beta-blockers ($n=16$), followed by amiodarone ($n=3$) and verapamil ($n=2$) [99]. Sympathectomy ($n=8$) and ICD ($n=3$) were also performed, more commonly if patients have previously experienced adverse events. CVPT, though rare, is often very lethal and often experience SCD after emotional triggers or stressful events. ICDs are often utilized as primary and secondary prevention of recurring SCD across CVPT, which has been proven to reduce mortality [100]. Although a territory-wide incidence rate of SCD in CVPT patients has not been previously reported, one smaller study in Hong Kong reported six out of ten CVPT patients to have experienced an aborted cardiac arrest, which were potentially attributed to a delay in clinical presentation [101]. There are various pharmaceutical options that are available as the first-line management of CPVT, such as beta-blockers and anti-arrhythmics (i.e., class 1c), implicating that ICD is not commonly indicated unless maximal medical therapy was unachievable [102]. As a result, the literature lacks an accurate estimation of ICD-related complications across Hong Kong [103].

Despite the lack of phenotypic characterization across patient groups in Hong Kong, a recent CVPT study in the review identified seven of the eight gene mutation variants that have been previously reported. These included c.14848G>A [104], c.12475C>A [105], c.7420A>G [106], c.11836G>A [107], c.14159 T>C, c.10046C>T

[108, 109], and c.7202G>A [110]. Of these, one novel variant (c.14861C>G) was discovered and has not been previously reported outside of Hong Kong. These variants belong to a gene called ryanodine receptor 2 (*RyR2*), which are responsible for the release of calcium channels within the sarcoplasmic reticulum of cardiac muscle. Genetic mutations across the *RyR2* genome are the most commonly implicated in CVPT phenotypes and promote delayed depolarization due to a spontaneous release of calcium in cardiomyocytes, leading to fatal arrhythmias. (35,222,090) *In vivo* studies have strongly suggested that mutations affect accessory proteins involved in *RyR2* regulation by luminal calcium within the sarcoplasmic reticulum. Examples of accessory proteins involved include CSQ2, a major calcium buffer in the sarcoplasmic reticulum, and TRDN, a protein involved with the loss of contact across the reticulum and T-tubules of cardiomyocytes [111]. Increased *RyR2* activity are linked to disruptions in cellular processes and signaling pathways, commonly as a result of gain-of-function variants that enhance the sensitivity of its channels to luminal calcium activation [112]. However, recent literature supports the identification of mutations causing a loss-of-function phenotype in CVPT, such as E4146K and G4935R, which are thought to cause ventricular arrhythmias and sudden cardiac death by reducing the activation of cytosolic calcium across *RyR2* channels [113]. In specific to Hong Kong, the directionality of the aforementioned variants in Hong Kong are not well understood given the lack of research pertained to the specific pathogenicity of gain-of-function mutations within *RyR2*.

Limitations

Interpretation of the review should be done considering the following limitations. Firstly, as this is a narrative review, the nature of the method is subjective with regards to the decision of which studies were to be included, and the way those were then analyzed. Therefore, there exists a risk of selection bias. Moreover, there is a limitation to the sample size included in the review as it exclusively looks at the cardiac ion channelopathies in the Hong Kong population. Finally, there may be data from papers that were written in a non-English language that were not extrapolated.

Future directions

This study presents the most comprehensive review regarding the literature pertained to hereditary ion channelopathies across Hong Kong. Although a considerable amount of work has been placed on these three conditions, prevalence and genotypic data regarding short QT syndrome in Hong Kong have not yet been reported [13]. The lack of short QT cases may be attributed to

its prevalence across ancestry, which was reported to be lowest across Asian ethnic groups [114]. Regardless, future investigations should focus on uncovering associated phenotypes and variant mutations across short QT in Hong Kong to address the gap in research for the condition. Moreover, given the limitations of this study, systematic reviews and meta-analysis can be performed in future to eradicate these by including well-defined inclusion and exclusion criteria, which may allow us to better comprehend the impact of cardiac channelopathies on sudden cardiac death.

Concluding remarks

Cardiac ion channelopathies are rare but important causes of SCD. Recent studies by local teams have resulted in significant improvements on their diagnosis, risk stratification and prognosis. Future coordinated efforts to establish a multicenter international registry linking Hong Kong, other cities in China, and the other areas of the world will improve risk stratification for the betterment of patients with cardiac ion channelopathies.

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Author contributions

KSKL and HH carried out study conception, project planning, manuscript drafting, and critical review of manuscript. TL carried out study conception, project planning and critical review of manuscript. All remaining authors carried out critical review of manuscript.

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References

1. Tester DJ, Ackerman MJ. Evaluating the survivor or the relatives of those who do not survive: the role of genetic testing. *Cardiol Young*. 2017;27(S1):S19–24.
2. Kapa S, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. *Circulation*. 2009;120(18):1752–60.

3. Giudicessi JR, Ackerman MJ. Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum. *Int J Cardiol.* 2018;270:214–20.
4. Mak CM, et al. Genetic basis of channelopathies and cardiomyopathies in Hong Kong Chinese patients: a 10-year regional laboratory experience. *Hong Kong Med J.* 2018;24(4):340–9.
5. Kalayinia S, et al. Next generation sequencing applications for cardiovascular disease. *Ann Med.* 2018;50(2):91–109.
6. Mak CM, et al. Sudden arrhythmia death syndrome in young victims: a five-year retrospective review and two-year prospective molecular autopsy study by next-generation sequencing and clinical evaluation of their first-degree relatives. *Hong Kong Med J.* 2019;25(1):21–9.
7. Allegue C, et al. A new approach to long QT syndrome mutation detection by Sequenom MassARRAY system. *Electrophoresis.* 2010;31(10):1648–55.
8. Chae H, et al. Considerations when using next-generation sequencing for genetic diagnosis of long-QT syndrome in the clinical testing laboratory. *Clin Chim Acta.* 2017;464:128–35.
9. Allegue C, et al. Genetic analysis of arrhythmogenic diseases in the era of NGS: the complexity of clinical decision-making in Brugada syndrome. *PLoS ONE.* 2015;10(7):e0133037.
10. Webster G, Berul CI. An update on channelopathies: from mechanisms to management. *Circulation.* 2013;127(1):126–40.
11. Juang JJ, Horie M. Genetics of Brugada syndrome. *J Arrhythm.* 2016;32(5):418–25.
12. Tse G, et al. 104 Analysis of clinical characteristics, genetic basis, management and arrhythmic outcomes of patients with catecholaminergic polymorphic ventricular tachycardia from a Chinese city. *Heart.* 2022;108(Suppl 1):A77–8.
13. Ho Hui J, et al. Clinical characteristics, outcomes, and genetic findings of patients with catecholaminergic polymorphic ventricular tachycardia in Hong Kong: a systematic review. *Ann Clin Cardiol.* 2022;4(1):3–8.
14. Lee S, et al. Paediatric/young versus adult patients with long QT syndrome. *Open Heart.* 2021;8(2):e001671.
15. Tse G, et al. Territory-wide Chinese cohort of long QT syndrome: random survival forest and cox analyses. *Front Cardiovasc Med.* 2021;8:608592.
16. Lee S, et al. Ventricular Tachyarrhythmia risk in paediatric/young vs. adult Brugada syndrome patients: a territory-wide study. *Front Cardiovasc Med.* 2021;8:671666.
17. Modell SM, Bradley DJ, Lehmann MH. Genetic testing for long QT syndrome and the category of cardiac ion channelopathies. *PLoS Curr.* 2012;4:e4f9995f69e6c7.
18. Priori SG, et al. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation.* 2002;105(11):1342–7.
19. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J Am Coll Cardiol.* 1992;20(6):1391–6.
20. Antzelevitch C, et al. Brugada syndrome: 1992–2002: a historical perspective. *J Am Coll Cardiol.* 2003;41(10):1665–71.
21. Chung CT, et al. Predictive risk models for forecasting arrhythmic outcomes in Brugada syndrome: a focused review. *J Electrocardiol.* 2022;72:28–34.
22. Antzelevitch C, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. *Heart Rhythm.* 2016;13(10):e295–324.
23. Aziz HM, et al. Pathogenesis and management of Brugada syndrome: recent advances and protocol for umbrella reviews of meta-analyses in major arrhythmic events risk stratification. *J Clin Med.* 2022;11(7):1912.
24. Marsman EMJ, Postema PG, Remme CA. Brugada syndrome: update and future perspectives. *Heart.* 2022;108(9):668–75.
25. Beydoun N, Gharios C, Refaat MM. Toward better risk stratification of asymptomatic Brugada syndrome patients? *J Cardiovasc Electrophysiol.* 2021;32(11):3008–9.
26. Leung KSK, Radford D, Huang H, Lakhani I, Li CKH, Hothi SS, Wai AKC, Liu T, Tse G, Lee S. Risk stratification of sudden cardiac death in asymptomatic female Brugada syndrome patients: A literature review. *Ann Non-invasive Electrocardiol.* 2023 Mar;28(2):e13030. <https://doi.org/10.1111/anec.13030>. Epub 2023 Jan 11. PMID: 36628595; PMCID: PMC10023885.
27. Letsas KP, et al. Prognosis, risk stratification, and management of asymptomatic individuals with Brugada syndrome: a systematic review. *Pacing Clin Electrophysiol.* 2017;40(12):1332–45.
28. Bayoumy A, et al. Spontaneous type 1 pattern, ventricular arrhythmias and sudden cardiac death in Brugada Syndrome: an updated systematic review and meta-analysis. *J Geriatr Cardiol.* 2017;14(10):639–43.
29. Tse G, et al. Electrophysiological mechanisms of Brugada syndrome: insights from pre-clinical and clinical studies. *Front Physiol.* 2016;7:467.
30. Li KHC, et al. Brugada syndrome: a comprehensive review of pathophysiological mechanisms and risk stratification strategies. *Int J Cardiol Heart Vasc.* 2020;26: 100468.
31. Romero J, et al. Brugada Syndrome: progress in genetics, risk stratification and management. *Arrhythm Electrophysiol Rev.* 2019;8(1):19–27.
32. Brugada J, et al. Present status of Brugada syndrome: JACC state-of-the-art review. *J Am Coll Cardiol.* 2018;72(9):1046–59.
33. Tse G, et al. Determination of action potential wavelength restitution in Scn5a(+/-) mouse hearts modelling human Brugada syndrome. *J Geriatr Cardiol.* 2017;14(9):595–6.
34. Tse G, et al. Variability in local action potential durations, dispersion of repolarization and wavelength restitution in aged wild-type and Scn5a(+/-) mouse hearts modeling human Brugada syndrome. *J Geriatr Cardiol.* 2016;13(11):930–1.
35. Ragab AAY, et al. Prediction of ventricular tachyarrhythmia in Brugada syndrome by right ventricular outflow tract conduction delay signs. *J Cardiovasc Electrophysiol.* 2018;29(7):998–1003.
36. Asvestas D, et al. High risk electrocardiographic markers in Brugada syndrome. *Int J Cardiol Heart Vasc.* 2018;18:58–64.
37. Meng L, et al. Meta-analysis of fragmented QRS as an electrocardiographic predictor for arrhythmic events in patients with Brugada syndrome. *Front Physiol.* 2017;8:678.
38. Tse G, et al. Tpeak–Tend, Tpeak–Tend /QT ratio and Tpeak–Tend dispersion for risk stratification in Brugada syndrome: a systematic review and meta-analysis. *J Arrhythm.* 2018;34(6):587–97.
39. Tse G, et al. The Tpeak–Tend interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: a systematic review and meta-analysis. *Heart Rhythm.* 2017;14(8):1131–7.
40. Tse G. (Tpeak–Tend)/QRS and (Tpeak–Tend)/(QT × QRS): novel markers for predicting arrhythmic risk in the Brugada syndrome. *Eurpace.* 2017;19(4):696.
41. Tse G. Both transmural dispersion of repolarization and of refractoriness are poor predictors of arrhythmogenicity: A role for iCEB (QT/QRS)? *J Geriatr Cardiol.* 2016;13(9):813–4.
42. Tse G, Yan BP. Novel arrhythmic risk markers incorporating QRS dispersion: QRSd × (Tpeak - Tend)/QRS and QRSd × (Tpeak - Tend)/(QT × QRS). *Ann Noninvasive Electrocardiol.* 2017 Nov;22(6):e12397. <https://doi.org/10.1111/anec.12397>. Epub 2016 Aug 18. PMID: 27535213; PMCID: PMC6931740.
43. Tse G. Novel conduction-repolarization indices for the stratification of arrhythmic risk. *J Geriatr Cardiol.* 2016;13(9):811–2.
44. Tse G, et al. Correction to: restitution metrics in Brugada syndrome: a systematic review and meta-analysis. *J Interv Card Electrophysiol.* 2020;57(2):329.
45. Tse G, et al. Restitution metrics in Brugada syndrome: a systematic review and meta-analysis. *J Interv Card Electrophysiol.* 2020;57(2):319–27.
46. Mok NS, Chan NY, Chiu AC. Successful use of quinidine in treatment of electrical storm in Brugada syndrome. *Pacing Clin Electrophysiol.* 2004;27(6 Pt 1):821–3.
47. Mok NS, et al. Clinical profile and genetic basis of Brugada syndrome in the Chinese population. *Hong Kong Med J.* 2004;10(1):32–7.
48. Mok NS, et al. A newly characterized SCN5A mutation underlying Brugada syndrome unmasked by hyperthermia. *J Cardiovasc Electrophysiol.* 2003;14(4):407–11.
49. Mok NS, Chan NY, Choi YC. Late implantation of an implantable cardioverter-defibrillator in a patient with Brugada syndrome prevented sudden arrhythmic death. *Int J Cardiol.* 2003;87(2–3):269–71.
50. Mok NS, Choi YC. Brugada syndrome masquerading as acute myocardial infarction in a patient presenting with ventricular fibrillation. *Chin Med J (Engl).* 2002;115(3):458–60.

51. Mok NS, Tong CK, Yuen HC. Concomitant-acquired long QT and Brugada syndromes associated with indapamide-induced hypokalemia and hyponatremia. *Pacing Clin Electrophysiol.* 2008;31(6):772–5.
52. Mok NS, Chan NY. Supraventricular tachycardia with a baseline ECG pattern of Brugada syndrome. *Pacing Clin Electrophysiol.* 2005;28(6):602–3.
53. Mok NS, Chan NY. Brugada syndrome presenting with sustained monomorphic ventricular tachycardia. *Int J Cardiol.* 2004;97(2):307–9.
54. Tse G, et al. Higher dispersion measures of conduction and repolarization in type 1 compared to non-type 1 Brugada syndrome patients: an electrocardiographic study from a single center. *Front Cardiovasc Med.* 2018;5:132.
55. Lee S, et al. Outcomes in Brugada syndrome patients with implantable cardioverter-defibrillators: insights from the SGLT2 registry. *Front Physiol.* 2020;11:204.
56. Lee S, et al. Territory-wide cohort study of Brugada syndrome in Hong Kong: predictors of long-term outcomes using random survival forests and non-negative matrix factorisation. *Open Heart.* 2021;8(1):e001505.
57. Tse G, et al. An open invitation to join the international Brugada electrocardiographic indices registry. *Cardiovasc Innov Appl.* 2020;4(3):217–21.
58. Lee S, Zhou J, Chung CT, Lee ROY, Bazoukis G, Letsas KP, Wong WT, Wong ICK, Mok NS, Liu T, Zhang Q, Tse G. Comparing the Performance of Published Risk Scores in Brugada Syndrome: A Multi-center Cohort Study. *Curr Probl Cardiol.* 2022 Dec;47(12):101381. <https://doi.org/10.1016/j.cpcardiol.2022.101381>. Epub 2022 Sep 2. PMID: 36058344.
59. Tse G, et al. Electrocardiographic evidence of abnormal atrial phenotype in Brugada syndrome. *J Electrocardiol.* 2019;55:102–6.
60. Tse G, et al. Incidence and predictors of atrial fibrillation in a Chinese cohort of Brugada syndrome. *Int J Cardiol.* 2020;314:54–7.
61. Kabra N, et al. Sudden cardiac death in Brugada syndrome. *Cardiol Rev.* 2020;28(4):203–7.
62. Nakano Y, Shimizu W. Brugada syndrome as a major cause of sudden cardiac death in Asians. *JACC Asia.* 2022;2(4):412–21.
63. Tse G, et al. Identification of novel SCN5A single nucleotide variants in Brugada syndrome: a territory-wide study from Hong Kong. *Front Physiol.* 2020;11:574590.
64. Clerx M, et al. Predicting changes to I. *Sci Rep.* 2018;8(1):12797.
65. Lee S, et al. Temporal variability in electrocardiographic indices in subjects with Brugada patterns. *Front Physiol.* 2020;11:953.
66. Tse G, et al. Automated electrocardiogram analysis identifies novel predictors of ventricular arrhythmias in Brugada syndrome. *Front Cardiovasc Med.* 2020;7:618254.
67. Tse G, et al. Incorporating latent variables using nonnegative matrix factorization improves risk stratification in Brugada syndrome. *J Am Heart Assoc.* 2020;9(22):e012714.
68. Chung CT, et al. Machine learning techniques for arrhythmic risk stratification: a review of the literature. *Int J Arrhythmia.* 2022;23:1–13.
69. Letsas KP, et al. Right ventricular outflow tract endocardial unipolar substrate mapping: implications in risk stratification of Brugada syndrome. *Rev Cardiovasc Med.* 2022;23(2):44.
70. Letsas KP, et al. Right ventricular outflow tract electroanatomical abnormalities in asymptomatic and high-risk symptomatic patients with Brugada syndrome: Evidence for a new risk stratification tool? *J Cardiovasc Electrophysiol.* 2021;32(11):2997–3007.
71. Takla M, et al. Transcriptional profiles of genes related to electrophysiological function in Scn5a(+/-) murine hearts. *Physiol Rep.* 2021;9(19):e15043.
72. Zhang ZH, et al. Distinct features of probands with early repolarization and Brugada syndromes carrying SCN5A pathogenic variants. *J Am Coll Cardiol.* 2021;78(16):1603–17.
73. Tse G, et al. Electrophysiological mechanisms of long and short QT syndromes. *Int J Cardiol Heart Vasc.* 2017;14:8–13.
74. Tse G, et al. Meta-analysis of Tpeak–Tend and Tpeak–Tend/QT ratio for risk stratification in congenital long QT syndrome. *J Electrocardiol.* 2018;51(3):396–401.
75. Lane CM, et al. Beyond the length and look of repolarization: Defining the non-QTc electrocardiographic profiles of patients with congenital long QT syndrome. *Heart Rhythm.* 2018;15(9):1413–9.
76. Johnson JN, et al. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm.* 2008;5(5):704–9.
77. Ge HY, et al. Clinical characteristics and treatment of congenital long QT syndrome in 58 children. *Zhonghua Er Ke Za Zhi.* 2019;57(4):272–6.
78. Li Q, et al. CASQ2 variants in Chinese children with catecholaminergic polymorphic ventricular tachycardia. *Mol Genet Genomic Med.* 2019;7(11):e949.
79. Jiang H, et al. Investigation of catecholaminergic polymorphic ventricular tachycardia children in China: clinical characteristics, delay to diagnosis, and misdiagnosis. *Chin Med J (Engl).* 2018;131(23):2864–5.
80. Lee S, Zhou J, Jeevaratnam K, Lakhani I, Wong WT, Kei Wong, IC, Mak C, Mok NS, Liu T, Zhang Q, Tse G. (2021). Arrhythmic outcomes in catecholaminergic polymorphic ventricular tachycardia. <https://doi.org/10.1101/2021.01.04.21249214>
81. Kwok SY, et al. Clinical and genetic profile of congenital long QT syndrome in Hong Kong: a 20-year experience in paediatrics. *Hong Kong Med J.* 2018;24(6):561–70.
82. Huang H, et al. Mechanisms of KCNQ1 channel dysfunction in long QT syndrome involving voltage sensor domain mutations. *Sci Adv.* 2018;4(3):eaar2631.
83. Major P, et al. A novel transgenic rabbit model with reduced repolarization reserve: long QT syndrome caused by a dominant-negative mutation of the KCNE1 gene. *Br J Pharmacol.* 2016;173(12):2046–61.
84. Keller DI, et al. Characterization of novel KCNH2 mutations in type 2 long QT syndrome manifesting as seizures. *Can J Cardiol.* 2009;25(8):455–62.
85. Chen J, et al. Whole exome sequencing in Brugada and long QT syndromes revealed novel rare and potential pathogenic mutations related to the dysfunction of the cardiac sodium channel. *Orphanet J Rare Dis.* 2022;17(1):394.
86. Giudicessi JR, Ackerman MJ. Calcium revisited: new insights into the molecular basis of long-QT syndrome. *Circ Arrhythm Electrophysiol.* 2016;9(7):e002480.
87. Tse G, Lee S, Liu T, Leung KSK, Lee TTL, Wong, ICK, Mak CM, Mok NS, Jeevaratnam K, Cheng SH, & Wong, WT. (2021). Description of rare genetic variants for long QT syndrome identified from a population-based study. [Zenodo. https://doi.org/10.5281/ZENODO.5636322](https://doi.org/10.5281/ZENODO.5636322)
88. Vatta M, et al. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. *Circulation.* 2006;114(20):2104–12.
89. Huffman E, et al. New evidence to challenge Clingen’s “disputed evidence” designation for AKAP9 as a bonafide susceptibility gene for congenital long QT syndrome. *Heart Rhythm.* 2022;19(5):S161.
90. Kotta MC, et al. Calmodulinopathy: a novel, life-threatening clinical entity affecting the young. *Front Cardiovasc Med.* 2018;5:175.
91. Behere SP, Weindling SN. Catecholaminergic polymorphic ventricular tachycardia: an exciting new era. *Ann Pediatr Cardiol.* 2016;9(2):137–46.
92. Vemireddy LP, et al. A rare case of RYR2 mutation causing sudden cardiac arrest due to catecholaminergic polymorphic ventricular tachycardia. *Cureus.* 2021;13(2):e13417.
93. Ng K, et al. An international multicenter evaluation of inheritance patterns, arrhythmic risks, and underlying mechanisms of CASQ2-catecholaminergic polymorphic ventricular tachycardia. *Circulation.* 2020;142(10):932–47.
94. Ning F, et al. The RyR2-P2328S mutation downregulates Nav1.5 producing arrhythmic substrate in murine ventricles. *Pflugers Arch.* 2016;468(4):655–65.
95. Zhang Y, et al. Conduction slowing contributes to spontaneous ventricular arrhythmias in intrinsically active murine RyR2-P2328S hearts. *J Cardiovasc Electrophysiol.* 2013;24(2):210–8.
96. Saadeh K, et al. Protein expression profiles in murine ventricles modeling catecholaminergic polymorphic ventricular tachycardia: effects of genotype and sex. *Ann N Y Acad Sci.* 2020;1478(1):63–74.
97. Leung J, et al. Clinical characteristics, genetic findings and arrhythmic outcomes of patients with catecholaminergic polymorphic ventricular tachycardia from china: a systematic review. *Life (Basel).* 2022;12(8):1104.
98. Lee S, et al. Paediatric/young versus adult patients with congenital long QT syndrome or catecholaminergic polymorphic ventricular tachycardia. *Euro Heart J.* 2021;42(Supplement_1):ehab724-1870.
99. Chung CT, et al. Clinical characteristics, genetic basis and healthcare resource utilisation and costs in patients with catecholaminergic polymorphic ventricular tachycardia: a retrospective cohort study. *RCM.* 2022;23(8):276.

100. Singh M, Morin DP, Link MS. Sudden cardiac death in long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). *Prog Cardiovasc Dis*. 2019;62(3):227–34.
101. Yu TC, et al. Clinical and genetic profile of catecholaminergic polymorphic ventricular tachycardia in Hong Kong Chinese children. *Hong Kong Med J*. 2016;22(4):314–9.
102. van der Werf C, Zwinderman AH, Wilde AA. Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: state of the art and future developments. *Europace*. 2012;14(2):175–83.
103. Roston TM, Cunningham TC, Sanatani S. Advances in the diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. *Cardiol Young*. 2017;27(S1):S49–56.
104. Priori SG, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002;106(1):69–74.
105. Kawata H, et al. Catecholaminergic polymorphic ventricular tachycardia (CPVT) associated with ryanodine receptor (RyR2) gene mutations long-term prognosis after initiation of medical treatment. *Circ J*. 2016;80(9):1907–15.
106. Ozawa J, et al. Differential diagnosis between catecholaminergic polymorphic ventricular tachycardia and long QT syndrome type 1-modified schwartz score. *Circ J*. 2018;82(9):2269–76.
107. Gallegos-Cortez A, et al. Catecholaminergic polymorphic ventricular tachycardia due to de novo RyR2 mutation: recreational cycling as a trigger of lethal arrhythmias. *Arch Med Sci*. 2020;16(2):466–70.
108. Seidelmann SB, et al. Application of whole exome sequencing in the clinical diagnosis and management of inherited cardiovascular diseases in adults. *Circ Cardiovasc Genet*. 2017;10(1):e001573.
109. Christiansen SL, et al. Genetic investigation of 100 heart genes in sudden unexplained death victims in a forensic setting. *Eur J Hum Genet*. 2016;24(12):1797–802.
110. Aizawa Y, et al. A novel mutation in FKBP12.6 binding region of the human cardiac ryanodine receptor gene (R2401H) in a Japanese patient with catecholaminergic polymorphic ventricular tachycardia. *Int J Cardiol*. 2005;99(2):343–5.
111. Hamilton S, Terentyev D. RyR2 gain-of-function and not so sudden cardiac death. *Circ Res*. 2021;129(3):417–9.
112. Zhao YT, et al. Arrhythmogenesis in a catecholaminergic polymorphic ventricular tachycardia mutation that depresses ryanodine receptor function. *Proc Natl Acad Sci U S A*. 2015;112(13):E1669–77.
113. Zhong X, et al. Identification of loss-of-function RyR2 mutations associated with idiopathic ventricular fibrillation and sudden death. *Biosci Rep*. 2021;41(4):BSR20210209.
114. Funada A, et al. Assessment of QT intervals and prevalence of short QT syndrome in Japan. *Clin Cardiol*. 2008;31(6):270–4.

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