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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

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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

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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

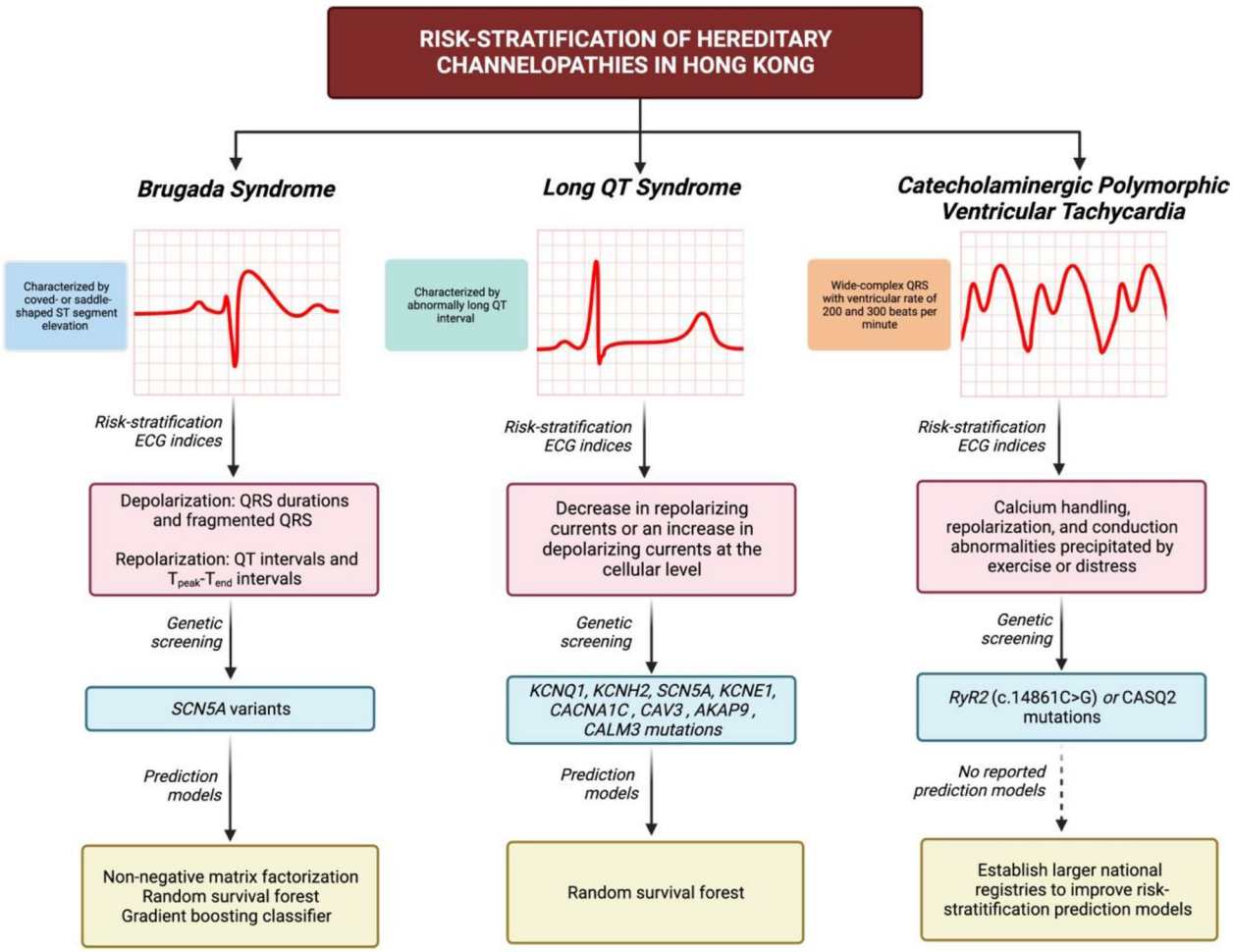

Fig. 1 Risk stratification algorithm to classify and improve prediction models for hereditary channelopathies in Hong Kong

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

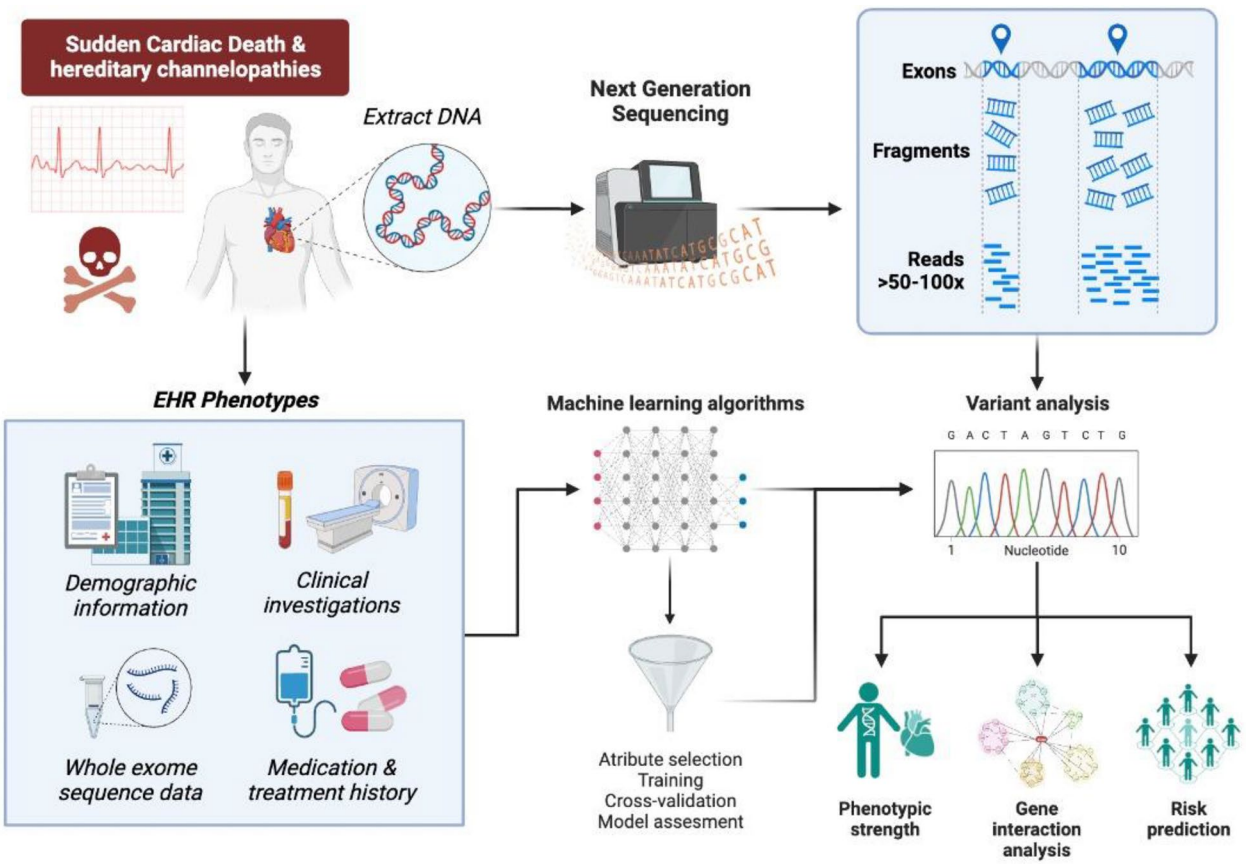

Fig. 2 The roles of next-generation sequencing and machine learning algorithms to process electronic health record phenotypes and whole exome sequencing data from patients with hereditary channelopathies

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 $T_{peak} - T_{end}$ 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 $\geq$ 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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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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