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Manuscript 1506

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REVIEW ARTICLE

Precision Medicine for Cardiac Ion Channelopathies in Hong Kong: From Case Reports to Identification of Novel Genetic Variants and Development of Risk Prediction Tools Using Population-based Datasets

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Abstract

Congenital cardiac ion channelopathies refer to a set of inherited conditions characterized by abnormalities in the structure and/or function of ion channels, their associated proteins or other signalling components, predisposing affected individuals to life-threatening ventricular tachyarrhythmias and therefore sudden cardiac death. This is a literature review focusing on the progress of clinical research on congenital cardiac ion channelopathies in Hong Kong, from case reports in the 1990s to population-based studies in the 2020s. Locally, patients with Brugada syndrome, long QT syndrome and catecholaminergic polymorphic ventricular tachycardia have been studied. Leveraging the power of linked electronic health records data in the public sector, the epidemiology, clinical characteristics, genetics, genotype–phenotype relationship and predictive factors of arrhythmic events have received attention. Future efforts should focus on multidisciplinary collaborations between clinicians, scientists and data scientists the use of genomic data combined with clinical data for personalised risk prediction. With the Government's drive for innovations and recent announcement of the Strategic Development of Genomic Medicine in Hong Kong, future efforts should be focused on the development of a national registry linking the databases and standardizing the data fields and reporting in different centres in Hong Kong, other cities in the Greater Bay Area and the wider mainland. Eventually the goal is to incorporate the vast amount of genomic information with clinical details to achieve personalised risk prediction through multidisciplinary collaborations.

Keywords: Ion channelopathies, Brugada syndrome, Long QT syndrome, Catecholaminergic polymorphic ventricular tachycardia, Sudden cardiac death, Genetics

Introduction

Congenital cardiac ion channelopathies refer to a set of inherited conditions characterized by abnormalities in the structure and/or function of ion channels, their associated proteins or other signalling components, in turn leading to abnormalities in

depolarization, repolarization and/or calcium handling and predisposing affected individuals to life-threatening ventricular tachyarrhythmias and therefore sudden cardiac death. This is a literature review focusing on the progress of clinical research on congenital cardiac ion channelopathies in Hong Kong, from case reports in the 1990s to population-

Received 19 December 2022; revised 19 March 2023; accepted 23 March 2023.
Available online 5 May 2023

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based studies in the 2020s. Locally, the epidemiology, clinical characteristics, genetics, genotype–phenotype relationship and predictive factors of arrhythmic events of Brugada syndrome (BrS), long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) have been studied. Recent studies have included population-based studies, leveraging the power of linked data from electronic health records (EHRs) in the public sector to facilitate the development of predictive models and economic analysis of healthcare resource utilisation and costs.

Brugada syndrome

BrS is characterized by coved- (type 1) or saddle-shaped (type 2) ST segment elevation in the right precordial leads in the absence of overt structural abnormalities [1–3]. Its diagnosis is established based on clinical, electrocardiographic and genetic findings [4,5]. Currently, its management is difficult and complex because of uncertainties in risk prediction for adverse arrhythmic events [6–8], which is more marked for asymptomatic patients with low-risk features [9,10]. Better understanding of the electrophysiological mechanisms can lead to more accurate risk prediction [11–14]. Defects in depolarization and/or repolarization can increase the propensity for developing ventricular arrhythmic events [15,16]. These can be detected non-invasively by electrocardiography [17]. Different types of ECG markers can be used for risk prediction and they can be broadly divided into depolarization or repolarization markers [18]. Examples of depolarization markers are QRS durations and fragmented QRS, which reflect conduction speed and dispersion of conduction, respectively [19]. Repolarization indices such as QT intervals and $T_{\text{peak}}-T_{\text{end}}$ intervals reflect the duration of total ventricular repolarization and dispersion of ventricular repolarization, respectively [20,21]. Indices reflecting dynamic changes in conduction or repolarization such as action potential or conduction velocity restitution [22,23], as well as those including features of both depolarization and repolarization defects [24–27], can further improve risk prediction.

The first cases of BrS in Hong Kong were reported in the 2000s [28–35]. Additional rare cases and single-centre studies subsequently emerged in 2016 [36,37], gradually expanding to multi-centre and then territory-wide studies [38–40]. The latter have enabled the identification of significant predictors for future arrhythmic events, where risk prediction was improved by combining both non-negative matrix factorization (NSF) and random survival

forest (RSF) [39]. Our team recently evaluated the performance of published risk scores using local Hong Kong data [5,41–45], and developed our own risk scores that are specific for the Chinese population [46]. We found that the score developed by Sieira et al. showed the best performance with an area under the curve (AUC) of 0.806 (95% CI: 0.747–0.865) using receiver operating characteristic (ROC) analysis. Using the parameters and original weighting of the score by Sieira et al., we then included additional variables that were found to be significant predictors on univariable Cox regression, which were arrhythmias other than ventricular tachyarrhythmias, early repolarization pattern in the peripheral leads, aVR sign, S-wave in lead I, $QTc \geq 436$ ms. Our score showed the best performance with an AUC of 0.86. Furthermore, we developed seven additional models using machine learning (random survival forest, Ada boost classifier, Gaussian naïve Bayes, light gradient boosting machine, RSF, gradient boosting classifier and decision tree classifier). Of these, RSF and gradient boosting classifier models showed improvements compared to the score-based models [46].

Our other contributions include i) comparing the clinical characteristics and outcomes between BrS patients presenting at paediatric/young (≤ 25 years old) and adult ages (> 25 years old) [47], ii) identification of atrial electrophysiological abnormalities [48], iii) predictions of incident atrial fibrillation using P-wave parameters [49], iv) identification of novel pathogenic or likely pathogenic *SCN5A* variants not reported outside of Hong Kong region (c.674G > A, c.2024–11T > A, c.2042A > C, c.4279G > T, c.5689C > T, c.429del) [50], v) linking increased visit-to-visit temporal variability in repolarization indices from serial ECGs to higher likelihood of arrhythmic events [51], vi) the use of automated ECG analysis from raw XML data [52] and vii) extraction of latent features between risk factors [53] for risk prediction. Further details can be found from our reviews on the different machine learning methodologies [54] and different predictive risk models in BrS [4]. Possibilities for future works in BrS locally are i) application of electroanatomical mapping as already performed in overseas centres [55,56], ii) the integration of Hong Kong datasets with other cities in the Greater Bay Area and wider China in large multi-centre cohorts which is led by our team in collaboration with leading researchers in mainland China [40], and iii) clarifying genotype–phenotype relationships. This will achieve the goal of personalised care for accurate individualised risk prediction [57,58].

Long QT syndrome

Long QT syndrome (LQTS) is defined as an abnormally long QT interval on the ECG, which is due to reduced repolarizing currents or increased depolarizing currents [59]. Congenital LQTS now has 17 subtypes identified. Whilst the clinical and genetic characteristics of LQTS have been extensively studied in Western populations [60,61], the study of congenital LQTS in Chinese subjects followed later in large case series [62]. Clinical assessment and evaluation of ECG including ECG indices can aid risk stratification [63]. The contributions from our Hong Kong team include i) leading the first population-based study of congenital LQTS patients, where we applied RSF to enhance risk prediction of arrhythmic events [64], ii) comparing the clinical characteristics and outcomes between congenital LQTS patients presenting at paediatric/young (≤ 25 years old) and adult ages (> 25 years old) [65], iii) identification of novel pathogenic or likely pathogenic variants not reported outside of Hong Kong region (KCNQ1, KCNH2, SCN5A, CACNA1C, CAV3 and AKAP9 mutations corresponding to LQTS subtypes 1, 2, 3, 8, 9 and 11) [64], and iv) identification of possible pathogenic variants in genes not classified in the LQTS 1 to 17 subtypes [66,67].

Catecholaminergic polymorphic ventricular tachycardia

CPVT is characterized by bidirectional VT and is usually revealed during exercise or moments of increased distress [68]. CPVT is most frequently caused by mutations in genes encoding for the ryanodine receptor 2 (RyR2) [69] or calsequestrin 2 (CASQ2) [70,71]. Calcium handling abnormalities, which in turn can lead to abnormal repolarization, and/or conduction, explain the increased propensity to ventricular arrhythmias [72–74]. For Chinese CPVT patients, descriptions came from only small case series [71,75]. Our contributions include i) the detailed characterization and descriptions and outcomes and identification of a novel genetic variant not reported outside (c.14861C > G) Hong Kong [76–79] and ii) the healthcare resource utilization of CPVT patients in the public sector [80]. Recently, our team has critically analysed and combined all of the published evidence on Chinese patients with CPVT in a systematic review and meta-analysis [81]. Future coordinated efforts to establish a national registry linking Hong Kong, other cities in the Greater Bay Area, and the wider mainland China will improve risk stratification for the betterment of CPVT patients from China.

Comparisons of genetic testing, healthcare resource utilization and costs between BrS, LQTS and CPVT in Hong Kong

There is shift from a deterministic to probabilistic view on the results of genetic testing [82]. Up to 4% of individuals from a Caucasian background and 8% of individuals from non-Caucasian backgrounds carry rare ($< 0.5\%$ allelic frequency) non-synonymous variants in genes that encode for cardiac ion channels [83]. Thus, distinguishing between background noise and pathogenic mutations is needed, and the pathogenicity must be interpreted. The yield of genetic testing generally increases with stronger phenotypes [84]. By contrast, the yield is lower in idiopathic cases. To determine whether novel mutants identified are pathogenic, functional and computational studies can be performed [83].

In Hong Kong, genetic testing has been used to identify mutations in patients who presented with sudden cardiac death or their family members as part of cascade screening [85]. More recent studies have applied next generation sequencing to achieve genome-wide searches of possible variants [86]. A review of the published studies reveals variations in clinical practice regarding the use of genetic tests for different cardiac ion channelopathies in Hong Kong and other territories [87]. This can be explained by different levels of expertise in hospitals and the availability of budgets for genetic testing, to which a lack of agreement between the guidelines published by different societies also contribute [88]. In BrS, combining the published studies, the rate of genetic testing is 59.4% with an overall yield of 26.3%. Some centres achieved a testing rate of 100%, which reflects the expertise available and possibly a research-driven culture to advance clinical knowledge. Similarly, most large cohort studies on LQTS reported testing rates at, or close to, 100% with yields of 98–100% [60,89]. Regarding CPVT, a large international cohort has reported a testing rate of 81% with a yield of 49% [90]. Future systematic reviews and meta-analyses are needed to evaluate the variations in clinical practice for genetic testing in LQTS and CPVT carefully and comprehensively. Locally in Hong Kong, the highest rate of genetic testing is seen in CPVT (88%) [77,78], followed by LQTS (39%) [64,65] and BrS (10%) [47] (Table 1). The yields are different [91], with the highest yield found in LQTS (81%), followed by CPVT (57%) and BrS (34%). The novel genetic variants identified by local teams are shown in Table 2.

Table 1. Number of cases, genetic testing, yield of testing, and number of novel mutations identified for patients with Brugada syndrome (BrS), long QT syndrome (LQTS) or catecholaminergic polymorphic ventricular tachycardia (CPVT) from Hong Kong, China.

Disease	Number of Cases identified between 2000 and 2020 ^a	Genetic Testing Performed ^b	Yield ^c	Novel Mutations Identified ^d
BrS	550	55/550 (10%)	19/55 (34%)	6
LQTS	134	52/134 (39%)	42/52 (81%)	15
CPVT	16	14/16 (88%)	8/14 (57%)	1

^a Electronic health records were searched using International Classification of Diseases (ICD)-9 coding. Some cases were likely missed due to under-coding and inaccurate coding.

^b Variation in practice between different hospitals.

^c Methods of genetic testing changed over time.

^d Not all novel mutations identified have pathogenicity confirmed.

Table 2. Novel genetic variants identified in Hong Kong for Brugada syndrome (BrS), long QT syndrome (LQTS) or catecholaminergic polymorphic ventricular tachycardia (CPVT).

Disease	Gene and Mutation	Region in Genome	Coding Effect	Mutation type	Location in Protein Subunit	
BrS [50]	SCN5A, c.429del	Exon 4	p.Asn144Thrfs*57	Deletion	DI-S1 (truncation)	
	SCN5A, c.674G > A	Exon 6	p.Arg225Gln	Missense	DI-S4	
	SCN5A, c.2024–11T > A	Exon 14	Acceptor splice site abolition and creation of cryptic splice site	Missense	DI-DII	
	SCN5A, c.2042A > C	Exon 14	p.His681Pro	Missense	DI-DII	
	SCN5A, c.4279G > T	Exon 24	p.Ala1427Ser	Missense	DIII-S5/S6	
	SCN5A, c.5689C > T	Exon 28	p.Arg1897Cys	Missense	C-terminus	
	LQTS [64,67]	KCNQ1, c.31G > A	Exon 1	p.Glu11Lys	Missense	N-terminus
		KCNQ1, c.782A > G	Exon 6	p.Glu261Gly	Missense/splicing	S4/S5
		KCNQ1, c.1018T > C	Exon 7	p.Phe340Leu	Missense	S5-pore-S6
		KCNQ1, c.1032G > A	Intron 7	p.Ala344=	Synonymous/splicing	S5-pore-S6
KCNQ1, c.1831G > A		Exon 16	p.Asp611Asn	Missense	C-terminus	
KCNH2, c.211G > T		Exon 2	p.Gly71Trp	Missense	N-terminus	
KCNH2, c.1738G > A		Exon 7	p.Asp580Ala	Missense	S5-pore-S6	
KCNH2, c.2233_2365del133		Exon 9		Deletion	C-terminus	
SCN5A, c.1201T > C		Exon 10	p.Ser401Pro	Missense	DI-S6	
ANK2, c.1627G > A		Exon 15	p.Val 543Met	Missense	Membrane-binding domain	
LQTS [64,67]	CACNA1C, c.1186G > C	Exon 8	p.Val396Leu	Missense	DI-S6	
	CACNA1C, c.2188T > A	Exon 15	p. Cys730Ser	Missense	DII-S6	
	CACNA1C, c.2276C > T	Exon 16	p.Ala759Val	Missense	DII-S6	
	CAV3, c.277G > A	Exon 2	p.Ala92Thr	Missense	Membrane-spanning domain	
CPVT [76,78]	AKAP9, c.6065A > G	Exon 29	p.Gln2022Arg	Missense	Coiled coil domain	
	RyR2, c.14861C > G	Exon 105	p.Ala4954Gly	Missense	Cytoplasmic domain	

Through the linkage of EHRs in the territory, attendances data were recently analysed by our team, enabling the quantification of patient-level and population-level healthcare resource

utilisation and the attendance costs of congenital cardiac ion channelopathies. Published costs for BrS [92], LQTS [93] and CPVT [80] are summarized (Table 3).

Table 3. Healthcare resource utilisation and costs for patients with Brugada syndrome (BrS), long QT syndrome (LQTS) or catecholaminergic polymorphic ventricular tachycardia (CPVT) from Hong Kong, China. Median values for individual patient-level costs in US Dollars are provided.

Disease	Accident and Emergency Costs	Accident and Emergency Annualized Costs	Inpatient Costs	Inpatient Annualized Costs	Specialist Outpatient Costs	Specialist Outpatient Annualized Costs
BrS [92]	949 (474–1818)	110 (52–224)	58724 (16279–247625)	6812 (1982–32414)	5353 (2524–11089)	557 (326–1001)
LQTS [93]	790 (316–1739)	69 (30–183)	101579 (23599–590953)	10270 (2248–64006)	6118 (3212–13613)	675 (393–1329)
CPVT [80]	711 (395–1146)	66 (40–95)	151754 (37679–496022)	10521 (5240–66887)	10554 (6615–14110)	747 (546–1105)

Concluding remarks

Cardiac ion channelopathies are rare but important causes of SCD in Hong Kong. The most prevalent condition is BrS, followed by LQTS and CPVT. Local teams have conducted a number of studies defining the epidemiology and investigating the clinical characteristics, predictive factors of arrhythmic events and forecasting prognosis enhanced by machine learning models. With the Government's drive for innovations and recent announcement of the Strategic Development of Genomic Medicine in Hong Kong, future efforts should be focused on the development of a national registry linking the databases and standardizing the data fields and reporting in different centres in Hong Kong, other cities in the Greater Bay Area and the wider mainland China. Eventually the goal is to incorporate the vast amount of genomic information with clinical details to achieve personalised risk prediction through multidisciplinary collaborations.

Acknowledgements

This article is based partly on the lecture by GT entitled Genetic Basis of Inherited Cardiac Ion Channelopathies, as part of the Central Commissioned Training Programme 2021/22 Genetics and Genomics in Medicine – Common Diseases (Cardiac Genetics & Genomics) organised by NSM.

Funding

None reported.

Conflict of interest

None.

Ethical information

Not applicable.

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