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Clinical profile and genetic basis of Brugada syndrome in the Chinese population

Brugada綜合症華裔患者的臨床特點及患病的遺傳基礎

Objective. To study the clinical profile and genetic basis of Brugada syndrome in Chinese patients.
Design. Prospective observational study.
Setting. Seven regional public hospitals, Hong Kong.
Main outcome measures. The clinical and follow-up data of 50 patients (47 men, 3 women; mean age, 53 years) were collected, and genetic data of 36 probands and eight family members of three genotyped probands were analysed.
Results. Eight patients survived sudden cardiac death (group A), 12 had syncope of unknown origin but no sudden death (group B), and 30 were asymptomatic before recognition of Brugada syndrome (group C). Programmed electrical stimulation induced sustained ventricular arrhythmias in 88% (7/8), 82% (9/11), and 27% (3/11) of patients in group A, group B, and group C, respectively. New arrhythmic events occurred in 50% (4/8) of patients in group A and 17% (2/12) of patients in group B after a mean follow-up period of 30 (standard deviation, 13) months and 25 (7) months, respectively. All group C patients remained asymptomatic during a mean follow-up period of 25 (standard deviation, 11) months. Five of 36 probands and three of eight family members who underwent genetic testing were found to have a mutation in their *SCN5A* gene.
Conclusions. Chinese patients with Brugada syndrome who are symptomatic have a high likelihood of arrhythmia recurrence, whereas asymptomatic patients enjoy a good short-term prognosis. The prevalence of *SCN5A* mutation among probands is 14%. Thus, Chinese patients with Brugada syndrome share with their western counterparts similar clinical and genetic heterogeneity.

目的：研究 Brugada 綜合症華裔患者的臨床特點，以及患病的遺傳基礎。
設計：預期觀察研究。
安排：七所分區公立醫院，香港。
主要結果測量：本研究合共收集了 50 名患者的臨床數據和隨訪資料；男性佔 47 位，其餘 3 人為女性；患者平均年齡為 53 歲。本研究並分析了 36 名先證者，及 3 名遺傳型先證者的 8 位家庭成員的基因數據。
結果：A組共8名患者，曾經出現心臟性猝死而獲救生存；B組共12名患者，曾有成因不明的暈厥，但無出現心臟性猝死；C組共30位患者，在確定患上Brugada綜合症前並無任何病徵。三組患者接受電刺激測試而出現持續性心律失常的比例分別為：A 組 88% (7/8)、B 組 82% (9/11)、及 C 組 27% (3/11)。至於出現心律失常新症的比例，A 組在平均 30(標準差：13)個月的隨訪期後為 50% (4/8)，B 組在平均 25(標準差：7)個月的隨訪期後為17% (2/12)，C 組在平均25(標準差：11)個月的隨訪期後並無患者出現任何症狀。接受基因測試的 36 名先證者和 8 名家庭成員中，發現有 5 名先證者和 3 名家庭成員的 *SCN5A* 基因出現突變。
結論：Brugada 綜合症華裔患者中，有症狀的病人，其心律失常復發的機會相當高；無症狀的病人的短期預後則良好。先證者發生 *SCN5A* 基因突變的比率為 14%。由此證明，Brugada綜合症華裔患者的臨床表現多樣性及遺傳異質性和西方同類型病患者相似。

Key words:
Arrhythmia;
Chinese;
Death, sudden, cardiac;
Genetics;
Recurrence

關鍵詞：
心律失常；
華裔；
死亡，突然的，心臟性；
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Introduction

In 1992, Brugada[1] first described a specific form of idiopathic sudden death, which is now known as the Brugada syndrome. The hallmark of the syndrome is

the characteristic coved-type, and less commonly saddleback–type, ST-segment elevation in leads V_1 to V_3 on an electrocardiogram (ECG) recorded during sinus rhythm (Fig 1). Patients with this syndrome have no structural heart disease and yet are prone to develop syncope or sudden cardiac death (SCD) due to ventricular tachyarrhythmias. The characteristic ECG pattern frequently shows intermittent changes over time, which may give rise to diagnostic difficulties. To date, implantation of an implantable cardioverter-defibrillator (ICD) remains the only established therapy that can prevent SCD in patients with Brugada syndrome; antiarrhythmic drugs have no proven prognostic benefits.[2]

In the past decade, a large body of medical literature has shed light on the pathophysiology and epidemiology of Brugada syndrome. It is now known that the syndrome is an inheritable arrhythmogenic disorder with an autosomal dominant pattern of transmission, and genetic data have linked the syndrome to mutations in the cardiac sodium channel gene *SCN5A* in chromosome 3.[3,4] Epidemiological data suggest that Brugada syndrome is ubiquitous but more prevalent in some Asian countries[5]; however, it has only been rarely reported in Chinese patients.[6-12] The clinical profile and genetic basis of Brugada syndrome in the Chinese population is largely unknown. In Hong Kong, the first cases in Chinese patients were described in April 1999.[7,8] In September 1999, on behalf of the Hong Kong Interhospital Network of Pacing and Cardiac Electrophysiology (HK-IN-PACE)—a collaboration of seven regional public hospitals—we initiated a Brugada syndrome registry to identify individuals in the local Chinese population who have Brugada syndrome, and to study the clinical characteristics and genetic basis of this syndrome among these affected individuals.

Materials and methods

Study population and clinical evaluation

The study population consisted of 50 Chinese patients identified in seven regional hospitals between September 1999 and April 2002, who demonstrated ST-segment elevation of more than 2 mm in the right precordial leads (V_1-V_3) with or without right bundle branch block on ECG, either spontaneously or during an intravenous flecainide challenge test (FCT) [Fig 1]. Study participants gave informed consent for clinical and genetic evaluation. In all participants, the presence of structural heart disease was excluded by echocardiography (n=50), coronary angiography (n=24), magnetic resonance imaging (n=5), and endomyocardial biopsy (n=1).

Demographic, clinical, and prospective follow-up data were obtained during patients' hospital visits and telephone interviews, and were entered into a dedicated database of the HK-IN-PACE Brugada Registry. Patients were categorised into three groups: survival from prior SCD, syncope of unknown origin, or lack of symptoms prior to recognition of Brugada syndrome. In this study, SCD was defined as sudden and unexpected death occurring within 1 hour from

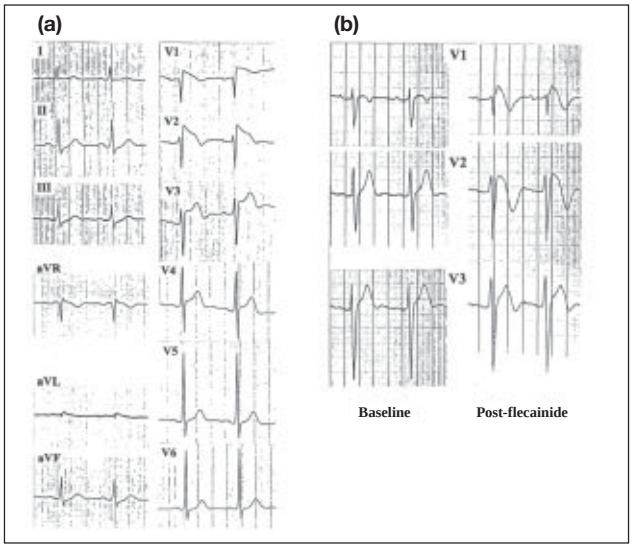

Fig 1. Electrocardiograms (ECGs) showing (a) spontaneous coved-type ST-segment elevation in leads V_1-V_3 with a right bundle branch block pattern (Brugada ECG pattern) in a patient with Brugada syndrome who presented with sudden cardiac death; (b) Brugada ECG pattern unmasked by intravenous flecainide in a family member of a proband with Brugada syndrome

the onset of symptoms. Syncope of unknown origin was defined as syncope without any identifiable cause. An arrhythmic event was defined as a documented episode of syncopal ventricular arrhythmia or sudden death, or as an appropriate shock discharged by an ICD. Patients were treated on the basis of clinical judgement of their referring cardiologists; FCT and electrophysiology study using programmed electrical stimulation (PES) were optional. For FCT, flecainide (2 mg/kg) was administered intravenously as a bolus over 10 minutes under continuous cardiac monitoring in a coronary care unit. A positive test result was defined as a 2-mm rise in ST segment in leads V_1 to V_3. As for PES for the induction of sustained ventricular arrhythmias, the stimulation protocol for symptomatic patients included a maximum of three ventricular extrastimuli at two basic pacing cycle lengths delivered at two sites down to a minimum coupling interval of 200 ms. For asymptomatic patients, PES was limited to a maximum of two ventricular extrastimuli.

Genetic analysis

Genetic analysis for 36 probands and eight family members of three genotyped probands was performed at the Molecular Cardiology Laboratories of the Maugeri Foundation in Pavia, Italy. DNA was extracted from peripheral blood lymphocytes by following standard procedures. Intronic primer pairs for the amplification of the entire open reading frame of the *SCN5A* gene were used. Single-strand conformational polymorphism analysis, with or without denaturing high-performance liquid chromatography analysis, was performed on amplified genomic DNA. Abnormal patterns were directly sequenced or subcloned and sequenced on both strands with an automated DNA analyser (ABI Prism 310; Perkin Elmer, Wellesley, US). A

Table. Demographic and clinical profiles of 50 Chinese patients with Brugada syndrome

Characteristic/clinical presentation	Previous sudden cardiac death (Group A)	Syncope (Group B)	Asymptomatic (Group C)	P value
No.	8	12	30	–
Male/female	8/0	12/0	27/3	0.35
Mean age (standard deviation) [years]	41 (12)	56 (9)	55 (16)	0.03
Family history of sudden cardiac death	1	1	5	0.23
ST-segment elevation				
Coved type	6	11	26	0.57
Saddle-back type	2	1	4	
Programmed electrical stimulation				
Inducible VT/VF*				
Yes/No (%)	7/1 (88%)	9/2 (82%)	3/8 (27%)	NA†
No. of extrastimuli (1/2/3)	0/5/2	1/2/6	1/2/not tested	
Treatment				
ICD‡	3	4	1	–
Drugs	1	1	2	–
ICD+drugs	1	1	0	–

* VT/VF ventricular tachycardia/ventricular fibrillation
† NA not applicable (different protocols were used)
‡ ICD implantable cardioverter-defibrillator

panel of 400 healthy white individuals (800 alleles) and 100 healthy Chinese individuals (200 alleles) was used as controls.

Statistical analysis

Data are presented as mean (standard deviation [SD]). The Chi squared test was used to compare categorical variables and analysis of variance was used to compare continuous variables among the different groups. A value of $P<0.05$ was considered statistically significant. Event-free analysis was estimated by the Kaplan-Meier method and the results were compared by means of the log-rank test. In the estimation of event rates during follow-up, 95% confidence intervals (CIs) were calculated using the Fleiss exact formula.

Results

Demographic and clinical characteristics

Among the 50 patients with Brugada syndrome, there were 46 probands and four affected family members. Eight patients had survived SCD (group A), 12 had syncope of unknown origin but no sudden death (group B), and 30 had been asymptomatic before diagnosis (group C). Their demographic and clinical characteristics are shown in the Table. The results showed a male preponderance for Brugada syndrome. Patients who survived SCD were significantly younger than patients in the other two groups (P=0.03). A family history of SCD was uncommon (14%) in our cohort. The majority of the patients showed the coved-type rather than saddle-back–type ST-segment elevation on ECG, either spontaneously or after flecainide challenge. Among the 20 symptomatic patients, only four from group A and five from group B received ICD implants. The remaining symptomatic patients either refused any form of treatment or preferred empirical pharmacological treatment despite the lack of documented benefit. New arrhythmic events occurred in four patients in group A (event rate 50%; 95% CI, 16%-84%) and in two patients in group B (event rate 17%; 95% CI, 2%-48%) during a mean follow-up period of 30 (SD, 13) months and 25 (7) months, respectively. Among patients with new arrhythmic events, one from group B who refused ICD implantation died of SCD, whereas the remaining five patients had a total of 33 arrhythmic events that were successfully defibrillated by ICD during the follow-up period and remained alive at the last follow-up (Fig 2). All group C patients remained asymptomatic (event rate 0%; 95% CI,

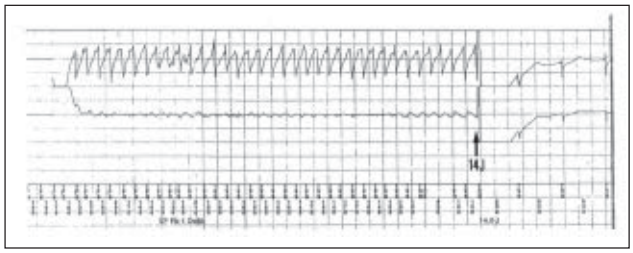

Fig 2. Stored intracardiac electrocardiogram in an implantable cardioverter-defibrillator (ICD) implanted in a patient with Brugada syndrome showing an episode of ventricular fibrillation, which was successfully defibrillated within 6 seconds of its onset by an electric shock of 14 J (arrow) delivered by the ICD

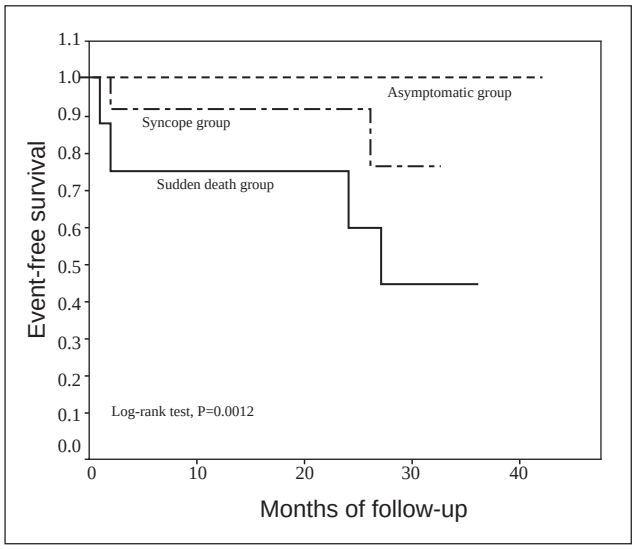

Fig 3. Kaplan-Meier analysis of event-free survival during prospective follow-up of 50 symptomatic and asymptomatic Chinese patients with Brugada syndrome

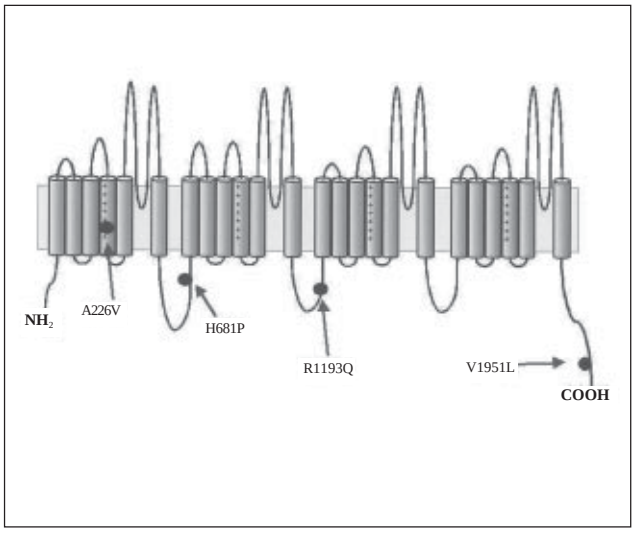

Fig 4. Mutations identified in Chinese patients with Brugada syndrome in the present study depicted on the predicted topology of the SCN5A protein

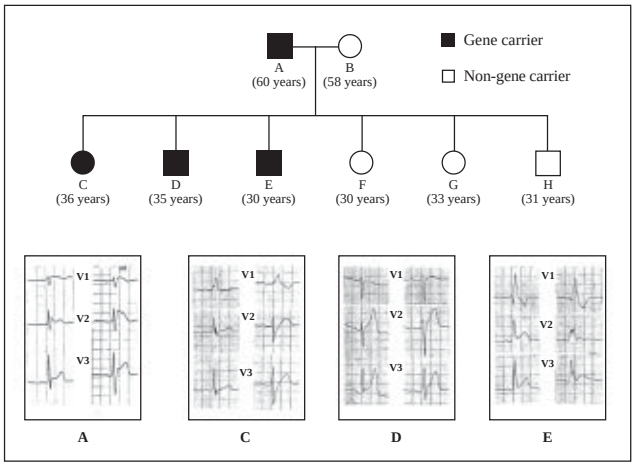

Fig 5. A case of Brugada syndrome with an autosomal dominant mode of inheritance and variable penetrance
Top: Pedigree of a proband with *SCN5A*-A226V mutation. Square indicates male; circle indicates female; ages in brackets.
Bottom: Electrocardiogram (V_1-V_3) of the proband (A) and his three children who carry the same mutation (C-E) at baseline (left tracing) and after intravenous flecainide challenge (right tracing). Note that only the proband demonstrates the Brugada electrocardiogram phenotype

0%-12%) over a mean follow-up period of 25 (SD, 11) months (Fig 3). The positive and negative predictive values of inducible ventricular arrhythmia during PES for future arrhythmic events were 38% and 100%, respectively, among symptomatic patients and 0% and 100%, respectively, among asymptomatic patients.

Genetic analysis

Four different amino acid substitutions (A226V, H681P, V1951L, R1193Q) in the open reading frame of the *SCN5A* gene (Fig 4) were identified in five (14%) of 36 probands (two symptomatic and three asymptomatic). None of the 500 controls (1000 chromosomes) carried the same DNA alterations. In a genetic evaluation of family members of the proband with the A226V mutation, three of his six asymptomatic children were found to carry the same *SCN5A* mutation; yet, only the proband showed a Brugada ECG phenotype (Fig 5). All these newly identified missense mutations involved highly conserved residues important for sodium channel function. However, to exclude the presence of rare polymorphism, we undertook functional characterisation. The available data for H681P confirm the loss of sodium current, which is compatible with a Brugada syndrome phenotype.[11]

Discussion

In the past decade, Brugada syndrome has emerged as an increasingly important cause of SCD affecting both adult and paediatric patients without structural heart disease.[13,14] Brugada syndrome may be diagnosed when the characteristic ECG pattern is recognised and when structural heart diseases or other causes of a similar ECG pattern are ruled out.[15] However, dynamic changes or even transient normalisation of the ST segment may obscure the correct diagnosis. Flecainide—a strong sodium channel blocker—has been used successfully in FCT to unmask the syndrome in affected patients who had normal or borderline baseline ECGs.[16] In 18 of the 50 patients enrolled in this study, the typical Brugada ECG pattern and the diagnosis of Brugada syndrome were uncovered by FCT. Although this test is useful, it is not without risk.[17] It should only be performed in the appropriate setting (eg a coronary care unit), where close cardiac and haemodynamic monitoring, as well as emergency resuscitation facilities, are available. Local experience with FCT showed that three of 26 patients who underwent FCT developed unifocal premature ventricular complexes, but none had sustained ventricular arrhythmias during or after the test.[18]

Few studies in the medical literature have reported the clinical profile or genetic basis of this syndrome among patients of different ethnic origins.[12,14,19-21] To date, this is the first prospective clinical and genetic evaluation of Brugada syndrome in a large cohort of Chinese patients.

Brugada syndrome is not rare in the Chinese population

Since Brugada syndrome was first described in the medical literature in 1992,[1] it has been found in most parts of the world. In Asia, it is a prevalent disease in Japan and Thailand.[20,21] However, it has been described rarely in Chinese patients, even though the Chinese population accounts for one fifth of the global population. Teo et al[6] reported the first three Chinese patients with Brugada syndrome in 1998. This report was followed by a few isolated case reports and a small series on Brugada syndrome in Chinese.[7-12] In Hong Kong, which has a population of 7 million, of which 95% are Chinese, Brugada syndrome was virtually unknown before 1999. In this study, 50 Chinese patients with Brugada syndrome were identified in seven local regional public hospitals within just 2.5 years of enrollment. Considering these seven regional hospitals serve

a total Chinese adult population of 2.5 million, the prevalence of Brugada syndrome is estimated to be no less than 2 per 100 000 adult Chinese population. This finding suggests that Brugada syndrome among the Chinese population is not as rare as previously thought, and is underreported. Notably, in one patient who presented with recurrent syncope in the 1980s and ventricular fibrillation in 1989, the Brugada ECG pattern was not recognised until 1999 when Brugada syndrome was retrospectively diagnosed as the cause of his ventricular fibrillation.[9] The significant number of patients with Brugada syndrome found during the study period most likely reflects an improvement in the diagnosis of the syndrome within the local medical community.

Arrhythmic events during follow-up

Akin to the worldwide experience that symptomatic patients with Brugada syndrome have a poor prognosis without treatment,[14,19-21] symptomatic Chinese patients with Brugada syndrome in our series had a high likelihood of arrhythmia recurrence within 3 years of diagnosis. One half of survivors of SCD and 17% of those who had syncope had new arrhythmic events over a mean follow-up period of 30 and 25 months, respectively. Furthermore, one patient who had recurrent syncope and inducible ventricular arrhythmia on PES refused ICD implantation and died of SCD subsequently. All 33 recurrent new arrhythmic events occurring in five symptomatic patients were documented to be polymorphic ventricular tachycardia or ventricular fibrillation and were successfully defibrillated by ICD. In one patient, a SCD survivor, ventricular fibrillation did not recur until 12 years after his index cardiac arrest.[22] These observations are consistent with findings that ICD is effective in preventing SCD in Brugada syndrome, and support the current practice that patients with Brugada syndrome who have survived SCD or have had syncope of unknown origin should receive ICD implants for maximal protection.[23,24] The possibility of late arrhythmia recurrence implies that lifelong ICD protection in these high-risk patients is warranted.

In contrast to the poor prognosis we found in symptomatic Chinese patients with Brugada syndrome, our data suggest that asymptomatic Chinese patients who demonstrate the Brugada ECG pattern enjoy a benign short-term prognosis (no arrhythmic event in 25 months) irrespective of the results of PES. In the literature, data on the prognosis of asymptomatic patients with Brugada syndrome are mixed. Although Brugada et al[14] reported that asymptomatic patients have 8% chance of developing arrhythmic events over 27 months of follow-up and deserve more aggressive treatment if they are inducible into ventricular arrhythmia in PES, our findings are more in agreement with the data from Priori et al[19] and Atarashi et al,[20] and lend support to a more conservative approach in managing asymptomatic cases unless clinical arrhythmia is documented.

The role of PES in predicting arrhythmia recurrence in Brugada syndrome has been a subject of controversy in the past few years. Whereas Brugada et al[25] concluded that having inducible ventricular arrhythmia on PES is a good clinical predictor for future arrhythmic events, their results were not reproduced by other groups.[4,26] It is noteworthy that the inducibility of ventricular arrhythmias during PES is largely dependent on the aggressiveness of the stimulation protocol. In our study, although the results of PES are not directly comparable between symptomatic and asymptomatic groups because different stimulation protocols were used, the low positive predictive values but very high negative predictive values in both groups suggest that inducibility of ventricular arrhythmias in PES have limited power in predicting future arrhythmic events; non-inducibility is quite reassuring. However, a word of caution must be noted. As the predictive values of PES vary when new arrhythmic events occur in more patients as the follow-up period lengthens, it might be premature to draw any solid conclusion at this juncture on the predictive values of PES when patients were followed up for only 2 to 3 years.

Genetic heterogeneity of Brugada syndrome among Chinese patients

Mutation of the sodium channel gene *SCN5A* in chromosome 3 has been implicated as the underlying cause of Brugada syndrome.[3,4] Genetic analysis to look for *SCN5A* mutations as a diagnostic test for Brugada syndrome is limited by its low sensitivity. Such a genetic defect was found in only 14% of Chinese probands in this study. This figure is similar to 15% (8 of 52 probands) reported by Priori et al[19] and suggests that genes other than *SCN5A* are implicated in the Brugada syndrome (ie genetic heterogeneity). Recent studies have shown that *SCN5A* mutation is not specific for Brugada syndrome: it may also be found in patients with the LQT3 subtype of congenital long QT syndrome[27] and with progressive cardiac conduction disease.[28] Syndromes with overlapping phenotypes due to a single *SCN5A* mutation have also been reported.[29] While it is as yet unknown whether the presence of a *SCN5A* mutation might have any prognostic significance, and what the functional consequences of such genetic abnormalities are, it is interesting to note that none of the SCD survivors in this study carried an *SCN5A* mutation, and only one of the five mutation carriers had an arrhythmic event during follow-up. Brugada syndrome has been described as an inheritable disease with an autosomal dominant mode of inheritance and a variable penetrance.[30] This observation is supported by our findings in a genotyped family in which three of the six (50%) asymptomatic children of a symptomatic proband who carried the *SCN5A*-A226V mutation carried the same mutation, but none of them exhibited the Brugada ECG pattern at baseline or after flecainide challenge (Fig 5). Functional characterisation of this *SCN5A* mutant in the future may help to clarify this intriguing differential phenotype-genotype correlation within the same family.

Conclusions

The HK-IN-PACE Brugada Registry has provided data on the clinical profile and genetic basis of Brugada syndrome

in a large cohort of Chinese patients. The results illustrate that Brugada syndrome is not rare among the local Chinese population. Its rarity in the past was largely because of its underdiagnosis. Brugada syndrome should therefore be considered as a differential diagnosis in healthy Chinese adults who present with syncope or cardiac arrest, particularly when patients have a family history of SCD. Chinese patients with Brugada syndrome who have survived SCD or who have a history of syncope have a high chance of arrhythmia recurrence, whereas asymptomatic patients enjoy a good short-term prognosis. We found four missense mutations in five of the 36 probands. The prevalence of *SCN5A* mutation is thus 14% among local Chinese patients with Brugada syndrome. Ongoing functional characterisation of these four mutations will help to clarify their roles in the pathogenesis of Brugada syndrome. Finally, Chinese patients with Brugada syndrome share with their western counterparts similar clinical and genetic heterogeneity. Findings of this study lend support to the current belief that Brugada syndrome is a ubiquitous disease and that ST-segment elevation in leads V_1 to V_3 with or without right bundle branch block in the absence of structural heart disease is an ECG marker for SCD, irrespective of the ethnic origin of the affected patients.

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