ARRHYTHMOGENIC CHANNELOPATHIES

4286
Population based prevalence of Brugada syndrome in a young male population in southeast asia

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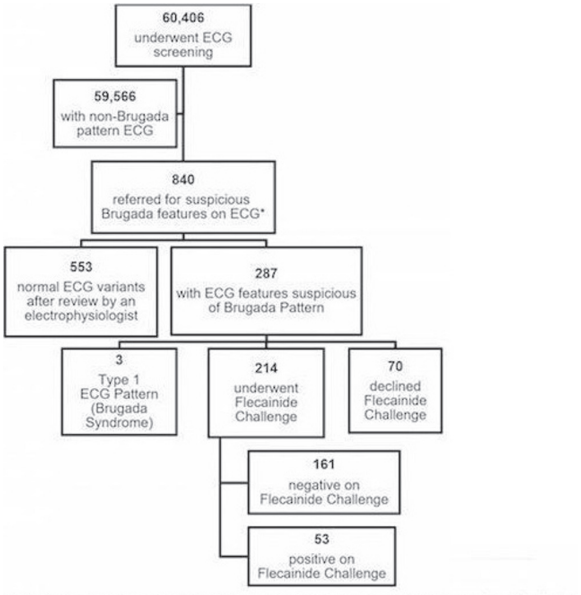
Background and introduction: Brugada syndrome has been reported to be more prevalent in Southeast Asian men compared to counterparts in Western countries, and is the most common cause of sudden cardiac death in young persons in South Asia. These conclusions were drawn mainly from autopsies and studies done in symptomatic hospital cohorts. To date, there have been no population-based studies on the prevalence of Brugada Syndrome in Southeast Asia.
Purpose: To investigate the prevalence of Brugada Syndrome in an asymptomatic young male population in a large multi-ethnic Southeast Asian cohort.
Methods: All Singaporean men undergo pre-conscription medical screening prior to enlistment for compulsory military service, where demographic, anthropometric and ECG variables were collected prospectively from January 2015 – December 2016. All individuals with ECG suspicious of Brugada pattern, as well as those with a known family history of Brugada Syndrome or sudden cardiac death were referred to a tertiary centre for clinical evaluation by certified cardiac electro-physiologists, underwent structural evaluation with a transthoracic echocardiogram and were offered Flecainide study if indicated. Subsequently, all patients diagnosed with Brugada Syndrome were followed up over a 2-year period for outcomes including sudden cardiac death and malignant tachyarrhythmias.
Results: 60,406 consecutive males (mean age 18.5±1.1 years) underwent medical screening. 840 individuals were referred for further evaluation. None had structural abnormalities on echocardiography. 287 had confirmed Brugada pattern ECG after review by an electrophysiologist. Amongst individuals with confirmed Brugada pattern ECG, 24.4% (n=70; mean age 19.2±1.7 years) declined further work-up with Flecainide challenge. 1.0% (n=3; mean age 20.4±4.0 years) had spontaneous Type 1 Brugada ECG, whilst 18.5% (n=53; mean age 18.8±1.3 years) who had ECG features consistent with Type 2/3 Brugada pattern tested positive on Flecainide. In patients with Brugada pattern ECG, QRS duration was significantly wider in Type 2/3 Brugada pattern patients who had a positive Flecainide test compare to those who had a negative Flecainide test (analysis of variance (ANOVA) p=0.038; Tukey's post hoc p=0.043). 56 individuals had a final diagnosis of Brugada syndrome, deriving a prevalence of 0.09% in our large unselected young male population. Over a 112 person-years follow-up period, there were no tachyarrhythmias or sudden cardiac deaths reported. No patients were lost to follow up.



**patients with family history of sudden cardiac death or Brugada syndrome were referred for further evaluation by an electrophysiologist, independent of their ECG findings.*

Brugada Screening Clinical Pathway

Conclusion: In a young, multi-ethnic South-east Asian male population, we found the prevalence of Brugada syndrome to be 0.09%. Long term follow-up studies will be helpful in characterizing the clinical significance and prognosis of individuals with Brugada syndrome.

4287
Systematic re-evaluation of ion channel mutations associated with Brugada syndrome

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Background: A large number of ion channel variants have been reported to underlie Brugada syndrome (BrS). However, the evidence supporting individual variants is highly heterogeneous.
Objective: We systematically re-evaluated all coding ion channel variants reported in BrS using a modified version of the ACMG-AMP guidelines
Methods: A Pubmed/Medline search was performed to identify all reported BrS ion channel variants. Standardized bioinformatic re-analysis (SIFT, PolyPhen, Mutation Taster, Mutation assessor, FATHMM, GERP, PhyloP, and SiPhy) and re-evaluation of frequency in reference databases (1000 genomes, EVS and ExAC) was performed. The ACMG-AMP guideline-based analysis was modified by stratifying evidence from INa and ICa(L) functional studies into strong (≥90% peak current reduction or ≥50% reduction with significant gating abnormalities) and moderate (50–90% peak current reduction without significant gating abnormalities).
Results: 578 unique coding ion channel variants were identified, the majority of which (79%) were SCN5A variants. 166/456 (36%) SCN5A variants were classified as pathogenic/likely pathogenic. 4/54 (7%) non-SCN5A sodium channel variants were deemed pathogenic/likely pathogenic (SCN10A n=3; SCN1B n=1). 2/39 (5%) calcium channel variants were classified as pathogenic/likely pathogenic (both CACNA1C variants). 2/13 (15%) TRPM4 variants were classified as pathogenic/likely pathogenic. None of the SCN2B, SCN3B, CACNA2D1, CACNB2, HCN4 or potassium channel variants were classified as pathogenic/likely pathogenic. Overall, 66% of reported variants were classified as variants of uncertain significance, while a further 3% were classified as benign/likely benign.
Conclusion: Based on contemporary ACMG-AMP guidelines, only a minority of ion channel variants implicated in BrS fulfil criteria for pathogenicity or likely pathogenicity.

4288
A cellular model of Brugada Syndrome with CACNB2 mutation of human-induced pluripotent stem cell-derived cardiomyocytes

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Background: Brugada syndrome (BrS) is characterized by saddle-back or coved-type ST-elevations in the electrocardiographic leads V1-V3 and these patients have a pronounced risk to develop malignant arrhythmias. Some gene mutations in the sodium channels, as well as calcium channels have been associated with BrS. However the investigation of the human cellular phenotype of BrS in presence of calcium channel mutation (beta subunit) is still lacking.
Purpose: The objective of this study was to establish a cellular model of BrS in presence of CACNB2 mutation (c.428 C>T) using human-induced pluripotent stem cell–derived cardiomyocytes (hiPSC-CMs).
Methods and results: This study recruited one patient with Brugada syndrome and recurrent sudden cardiac arrest carrying a mutation in CACNB2 as well as two healthy control subjects. We generated hiPSCs from their skin fibroblasts and differentiated hiPSCs into cardiomyocytes (hiPSC-CMs) for physiological studies and for verification of the genotype-phenotype-correlation by qPCR, Western Blot and immunostaining.
The hiPSC-CMs from the BrS patient showed a significantly reduced L-type calcium channel current (ICa-L) compared with the healthy control hiPSC-CMs. On the other hand the activation, inactivation and recovery of the ICa-L were not significantly changed. The mRNA expression and the protein expression of CACNB2 of the hiPSC-CMs from the BrS patient were significantly ($p<0.01$) decreased compared with healthy hiPSC-CMs. This together with the patch clamp data suggests that the CACNB2 gene mutation led to loss-of function L-type calcium channels in hiPSC-CMs from the patient. Although, the peak sodium current was reduced, this reduction was not significant as compared to the healthy controls. Likewise, the expression of SCN5a and CACNA1c, alpha subunit of ICaL, was not changed. Additionally all action potential characteristics were similar except the APD 50 was significantly decreased in BrS. Strikingly, arrhythmia events were more frequently triggered by 10 μM carbachol in BrS-hiPSC-CMs (54.5% in BrS versus 0% in D1 and 14% in D2; $p<0.05$), indicative of a predisposition of patient to arrhythmias.