Introduction: Brugada syndrome (BrS) is an important heritable arrhythmic syndrome in which the commonest causative gene identified is SCN5A. However, the inheritance pattern of SCN5A is complex and distinguishing benign from pathogenic SCN5A variant alleles is not straightforward. To aid understanding of this problem, we report SCN5A rare variant prevalence in subjects with suspected BrS undergoing intravenous flecainide drug challenge (FC).

Methods: This study was carried out at the national cardiovascular disease center of Singapore. Singapore is a multi-ethnic society which has a conscript military. Military pre-enlistees underwent screening with a targeted history, physical examination and 12-lead electrocardiogram. Subjects with a type 2 or 3 BrS ECG pattern were referred to electrophysiologists who evaluated and offered intravenous flecainide drug (FC) challenge as necessary (2mg/kg over 10 minutes) together with SCN5A sequencing via targeted panel next generation sequencing coupled with confirmatory Sanger sequencing. Rare variants were then identified by comparison of the minor allele frequency (MAF) derived from a reference database (the gnomAD EAS dataset which includes ~9K East Asians).

Result: 125 men with a mean age of 18 years agreed to both FC and SCN5A sequencing. 61 were FC positive, while 64 were FC negative. All 125 underwent SCN5A sequencing, and a total of 12 rare variants were identified at a MAF cut-off of 0.0006 – R225Q, A226V, G292S, R376C, R568C, A665T, S705F, R1027Q, Q1153H, E1225K, T1645M, S1776N. A226V, which has MAF (EAS) of 0.0013, was added to this list, as we have previously reported functional and pedigree studies confirming its pathogenicity. With this data, we performed an association study comparing rare variant alleles in the suspected BrS cohort versus those of gnomAD EAS (Table). This showed marked enrichment of SCN5A rare variants (OR=2.3, p=0.02). Further enrichment is shown in the FC positive subgroup (OR=3.9, p=0.0004), but no enrichment is evident in the FC negative subgroup (p=NS). The positive and negative predictive values, and sensitivity and specificity of a SCN5A rare variant to predict a positive FC was estimated as 83%, 55%, 16% and 97% respectively.

Conclusion: We show that SCN5A rare variants are insensitive (16%) but specific (97%) for the prediction of drug-inducible BrS. This observation is consistent with an oligogenic model of BrS causation, where rare variants alone might be insufficient to lead to expression of the BrS phenotype but in conjunction with flecainide, leads to expression of the characteristic BrS ECG type 1 pattern. We
believe this observation has implications for variant interpretation in BrS, which currently remains challenging. Larger cohorts will be necessary to confirm these observations. An important limitation of this study is that all subjects were male.