Background: Brugada syndrome (BrS) is a cardiac arrhythmia disorder that can cause sudden death in young adults. Genetic variation in the Nav1.5 cardiac sodium channel encoding SCN5A gene is robustly associated with BrS, across both rare coding and common non-coding variants. Despite a markedly higher prevalence of BrS, the diagnostic yield from SCN5A genetic testing in east and southeast Asia has been reported to be much lower than other regions.

Objective: To compare the contribution of different classes of SCN5A variants (by variant type and rarity) to BrS between northwest European and Thai populations in order to investigate the apparent paradox between high disease prevalence and low diagnostic yield in southeast Asia.

Methods: Genome sequencing data from European (412 cases, 769 controls) and Thai (202 cases, 410 controls) samples was analysed. SCN5A coding variants were binned by gnomAD exomes (v2.1) filtering allele frequency (FAF) and case-control analysed. SCN5A coding variants were binned by gnomAD exomes (v2.1) filtering allele frequency (FAF) and case-control analysed. Rare non-coding variants in promoter and enhancer regions of SCN5A and SCN10A were assessed for enrichment or depletion in BrS between BrS cohorts.

Results: Ultra-rare (FAF<0.00001) SCN5A coding variants are more prevalent and enriched in European (22.6% of cases, OR = 22.1, 11.4-43.0) compared to Thai (5.9% of cases, OR = 4.3, 1.6-11.5) BrS patients. In contrast, low frequency variants (FAF 0.00005-0.001) that are expected to have intermediate effect sizes are uniquely enriched in Thai samples, occurring in 9.9% of patients. 3/6 of these variants (p.R696C, p.A1428S, p.V2016M) are known to affect Nav1.5 function. A rare non-coding variant in the SCN5A RES enhancer region (GRCh37:3-38621871-A-C), affecting a base conserved across species, was highly and uniquely enriched in Thai BrS cases (4.5% vs 0.2%, OR = 19.1, p = 3e-04).

Conclusion: Distinct SCN5A genetic architectures are observed in European and southeast Asian BrS patients. The increased prevalence of BrS in southeast Asia is not due to an increased population burden of ultra-rare and highly deleterious SCN5A coding variants (which are relatively depleted in case cohorts). Our data suggest that other SCN5A variant classes, including coding variants of intermediate effect size and rare non-coding enhancer variants, are genetic risk factors in Thai BrS cases.

**PO-629-05**

**NEONATAL PRESENTATION OF TIMOTHY SYNDROME-INITIAL REPORT ON AN INTERNATIONAL COHORT**

Alexandra Matthews MBChB; M. Cecilia Gonzalez Corcia PhD, CEPS-P and Katherine W. Timothy BS

Background: Timothy syndrome is a rare multisystem disorder. It is generally caused by a de novo mutation in exon 8A (type 1) and exon 8 (type 2) of the CACNA1C gene. Most common clinical features in type 1 Timothy syndrome (TS1) include long QT (LQT), syndactyly and congenital heart defects. Neonatal TS1 may present as LQT causing 2:1 atrioventricular block (AVB) and fetal bradycardia.

Objective: Report on the neonatal cardiac findings of the largest international cohort of Timothy syndrome and identify markers of perinatal risk.