Distinct SCN5A genetic architectures are observed in Thai BrS cases. Conclusion: Enhancer variants, are genetic risk factors in Thai BrS cases. Coding variants of intermediate effect size and rare 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 analysis. SCN5A coding variants were binned by gnomAD exomes (v2.1) filtering allele frequency (FAF) and case-control analysis. 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.R965C, p.A1428S, p.V2016M) were known to affect Nav1.5 function. A rare non-coding variant in the SCN5A RE5 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-629-04

PHENOTYPES OF OVERDIAGNOSED LONG QT SYNDROME

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Background: Long QT syndrome (LQTS) is a potentially lethal, yet highly treatable, genetic heart disease that predisposes individuals to arrhythmic syncope/seizure, sudden cardiac arrest, or sudden cardiac death (SCD). Although well intended, increased physician and public awareness of LQTS-associated warning signs and an increase in ECG screening programs may contribute to an overdiagnosis of this condition. Objective: To identify the various avenues or phenotypes that can lead to an overdiagnosis of LQTS. Methods: Electronic medical records were reviewed for all patients evaluated in Mayo Clinic's Windland Smith Rice Genetic Heart Rhythm Clinic between July 2000 and March 2021 who arrived with an outside diagnosis of LQTS but were dismissed subsequently as normal. Data was abstracted for patient demographics, clinical characteristics, and cardiac and genetic test results.

Results: Overall, 291/1909 (15%) originally diagnosed LQTS patients [174 (60%) female, mean age at first Mayo evaluation 22 ± 14 years, mean QTc of 426 ± 25 ms] were dismissed as either normal (276, 95%) or having a different diagnosis altogether (15%, 5%). The main cause of LQTS misdiagnosis was misinterpretation of the QTc in 93 (32%) patients, including a borderline QT, inclusion of the U-wave in QTc calculation, or prolonged QTc associated with exercise training. This was closely followed by a prolonged QTc recorded in the emergency department following vasovagal syncope (n=89 [31%]). Furthermore, 47 patients (16%) were diagnosed because of positive family history of LQTS or SCD but dismissed as normal after the SCD was found to be unrelated to LQTS or the patient was negative for family’s LQTS-associated variant. Forty-seven (16%) patients had a variant of uncertain significance (VUS) in one of the main LQTS genes (KCNQ1, KCNH2, SCN5A), however after evaluation, the variant was demoted to likely benign or there was no LQTS phenotype in family members. Conclusion: Knowing that the four main determinants of discordance between a previously rendered diagnosis of LQTS and full diagnostic reversal/removal were misinterpretation of the QTc, vasovagal syncope, family history of LQTS, and a VUS in LQTS-causative genes, awareness and screening strategies can be fine-tuned to reduce this ongoing burden of overdiagnosed LQTS.

PO-629-05

NEONATAL PRESENTATION OF TIMOTHY SYNDROME: INITIAL REPORT ON AN INTERNATIONAL COHORT

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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.
Methods: Retrospective cohort study using data collection from Timothy Syndrome Foundation, a foundation for Timothy syndrome patients from around the world. All patients included have confirmed TS1 (CACNA1C, G406R in exon 8A).

Results: Forty-four cases of TS1 have been identified (26 male; 60%) over 28 years. Eighteen patients (41%) were born prematurely (<37 weeks gestation). Fetal bradycardia secondary to AVB presented in 17 patients (39%) and resulted in premature delivery in 12 patients (27%). From the fetal bradycardic patients, only 8 (47%) were appropriately diagnosed prenatally with AVB.

The mean gestational age for the entire cohort was 35.7 weeks (range 28 weeks - term), being 34.4 weeks in the group with fetal bradycardia compared with 37 weeks in patients without fetal bradycardia (p<0.05). A neonatal diagnosis of TS1 was made in 15 patients (34%). At birth LQT was identified in 25 patients (57%). From this group, 12 patients (48%) were diagnosed with TS1 in the neonatal period, compared with 3 patients (7%) from the group in which LQT was not identified at birth (p<0.05). Syndactyly was seen in the majority of patients (n=39, 89%). In the syndactyly group, TS1 was diagnosed neonatally in 14 cases (36%), compared with 20% in patients without syndactyly (p<0.01).

Conclusion: Extremely LQT leading to AVB and fetal bradycardia is frequent in patients with TS1. Fetal AVB is infrequently diagnosed as the cause of bradycardia in this population, which results in premature delivery with suspicion of fetal distress. Moreover, an accurate diagnosis of TS1 in the neonatal period is rare. Most patients with TS1 are diagnosed beyond the neonatal period, leaving them untreated from an arrhythmic perspective. Presentation with long QT and/or syndactyly at birth facilitates an early diagnosis.

PO-629-06

NOVEL TRANS-2,3-ENOYL-COA REDUCTASE-LIKE (TECRL) VARIANT ASSOCIATED WITH CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT) TYPE 3: FIRST TO BE REPORTED IN A CONSANGUINEOUS LEBANESE FAMILY

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Background: Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited arrhythmia characterized by polymorphic ventricular tachycardia. Recently, alterations in the trans-2,3-enoyl-CoA reductase-like (TECRL) gene have been implicated in the disease (4). To date only 16 families have been described in the literature. Reported phenotypes were notable for their clinical divergence with variable arrhythmia profile, often being highly malignant (6).

Objective: We herein report a novel mutation in the TECRL gene that was discovered in a Lebanese family of consanguineous parents.

Methods: N/A

Results: Two living siblings were affected in an autosomal recessive pattern in the context of positive family history of sudden death in the other two siblings. The late sister collapsed at the age of 16 years while climbing stairs. The youngest 5-year-old brother collapsed immediately after choking while eating. He did regain pulse after defibrillation in the hospital, but he passed away after one month. No molecular or tissue autopsy was done. A frameshift mutation (NM_001010874.4:c742_758 del) was detected on whole exome sequencing in the two living siblings (9-year-old boy and 13-year-old girl) both showing a mixed phenotype of Long QT syndrome and CPVT. This mutation creates a shift in the reading frame starting at codon Arg248. The new reading frame ends in a stop codon 8 positions downstream, leading to a loss of function in the encoded protein. Both patients were started on Nadolol, but both continued to show premature ventricular contractions (PVCs) on repeat sprint exercise stress test. Flecainide was added, which completely suppressed the exercise induced ventricular ectopy in both patients. Now ten months into the follow up, both patients remain clinically well, with no events recorded. This case presents an additional evidence in favor of the pathogenicity of the bi-allelic loss of function variants in the TECRL gene by presenting a novel mutation, and the potential requirement of dual therapy to prevent exercise induced ventricular ectopy.

Conclusion: We call for including TECRL in the NGS sudden death panels as well in the LQTS and CPVT screening panels that are commercially available worldwide.

Figure 1: Sister’s Exercise Stress test. A) Isolated PVCs during early sprint phase, then, appeared more frequently, in trigeminy, then bigeminy, followed by tri bigeminy with bidirectional PVCs, for which exercise test was immediately terminated. In recovery, Q-T prolonged to a maximum value of 500 ms. b) Flecainide T wave appearance noted, sometimes with variable T wave amplitude, and prominent u wave.

Figure 8: Extended Family Pedigree showing significant endogamy between relatives.