LEVERAGING SIGNAL-TO-NOISE ANALYSIS TO EXPAND CLINICAL UTILITY OF PATHOGENICITY CRITERIA FOR INCIDENTAL VARIANTS IN HYPERTROPHIC CARDIOMYOPATHY-ASSOCIATED GENES

Leonie Madelaine Kurzlechner BS; Edward G. Jones MD; Amy M. Berkman MD; Hanna J. Tadros MBChB; Jill A. Rosenfeld MS; YAPING YANG PhD; Han Tunuguntla MD; Hugh D. Allen MD; Jeffrey J. Kim MD and Andrew Paul Landstrom MD, PhD, FHRS

Background: Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy and can predispose individuals to sudden death. Most HCM patients host a known pathogenic variant in a sarcomeric gene. With the increase in exome sequencing (ES) in clinical settings, incidental variants in HCM-associated genes are being identified more frequently. Diagnostic interpretation of incidental variants is crucial to enhance clinical patient management.

Objective: We sought to use amino acid-level signal-to-noise (S:N) analysis to establish pathogenic hotspots in sarcomeric locations in coding regions to rare variants (MAF < 0.0001) in gnomAD. S:N ratios were calculated at the gene- and amino acid-level to identify pathogenic hotspots. ES cohort variants were re-classified using ACMG criteria with S:N analysis as a correlate for PM1 criteria.

Methods: Incidental variants in HCM genes (MYBPC3, MYH7, MYL2, MYL3, ACTC1, TPM1, TNNT2, TNNI3, TNNC1) were obtained from a clinical ES referral database (Baylor Genetics) and compared to rare population variants (gnomAD) and variants from HCM literature cohort studies. We compared the frequency of ES and HCM variants at specific amino acid locations in coding regions to rare variants (MAF < 0.0001) in gnomAD. S:N ratios were calculated at the gene- and amino acid-level to identify pathogenic hotspots. ES cohort variants were re-classified using ACMG criteria with S:N analysis as a correlate for PM1 criteria.

Results: We identified 7,066 unrelated probands in the ES cohort, with 509 individuals hosting a rare variant in an HCM gene. Variants in sarcomeric genes, especially radical variants, were enriched in the HCM cohort compared to the ES and gnomAD cohorts (P < 0.05). In the HCM cohort, five out of nine genes carried a S:N ratio greater than 6.0, suggesting a higher relative frequency of disease-associated variants in these genes. Among ES referrals, no gene had a global S:N greater than 3.0. Within each gene, localization of variants found in the ES cohort was more similar to those found in gnomAD than those found in the HCM cohort. In MYH7, most pathogenic hotspots were in the head domain.

Conclusion: Incidental variants in HCM-associated genes were common among clinical ES referrals, though the majority were not disease-associated. Leveraging amino acid-level S:N as a clinical tool may improve the diagnostic discriminatory ability of ACMG criteria by identifying pathogenic hotspots.
Conclusion: Distinct SCN5A genetic architectures are observed for enhancer variants, which are genetic risk factors in Thai BrS cases. Coding variants of intermediate effect size and rare non-coding variants. Our data suggest that other SCN5A variant classes, including coding variants (which are relatively depleted in case cohorts). Population burden of ultra-rare and highly deleterious SCN5A variants 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 odds ratios (OR) were calculated for each bin and ancestry. Rare non-coding variants in promoter and enhancer regions of SCN5A were assessed for enrichment or depletion in BrS between populations.

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) are 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

Raquel Almeida Lopes Neves MD; Sahej Bains; Johan Martijn Bos MD, PhD; Ciorsti MacIntyre MD; John R. Giudicessi MD, PhD and Michael John Ackerman MD, PhD

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 a 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 and/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

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.