PO-629-07

TRIGGERED SYNCOPE AND THE RISK FOR SUBSEQUENT LIFE THREATENING EVENTS IN LONG QT SYNDROME

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Background: Syncope, associated with specific triggers, is the most powerful predictor for life-threatening events (LTE) in patients with congenital long QT syndrome (LQTS).

Objective: We aimed to evaluate the association between adrenergic/non-adrenergic syncope and the risk for subsequent LTE.

Methods: The study population comprised 3,147 genetically confirmed LQT1-LQT3 patients from the International LQTS registry. Multivariate Cox regression was used to determine the association of adrenergic (exercise, arousal, swimming, etc.) or non-adrenergic (during rest, pregnancy, medications, etc.) triggered-syncope on the risk of subsequent LTE (aborted cardiac arrest, LQTS related death, or appropriate shock) in each genotype group separately.

Results: In LQT1 patients (n=1,410) syncope occurred in 444 (31%) subjects and was triggered mostly by adrenergic triggers 55%. Syncope preceded 78% of LTEs. Syncope preceded 71% of LTEs. Non-adrenergic syncope was associated with 124% risk increase in LTE (HR 95%CI 2.2-4.11, p=0.001), whereas the risk associated with syncope events during non-adrenergic triggers was non-significant (HR 95%CI 0.25-5.7, p=0.82). In LQT2 patients (n=1,217), syncope occurred in 394 (32%) subjects and was triggered by adrenergic triggers in 28% and non-adrenergic in 45%. Syncope preceded 71% of LTEs. Non-adrenergic syncope was associated with 124% risk increase in LTE (HR 95%CI 2.2-4.11, p=0.010), whereas adrenergic was associated with a trend of 105% increase (HR 95%CI 0.97-4.34, p=0.059). In contrast, LTE was the first clinical presentation in the majority of LQT3 patients (81%). The residual rate of LTE despite beta-blocker therapy was highest in LQT1 patients with prior syncope triggered by adrenergic triggers (Figure).

Conclusion: We show for the first time that trigger-specific syncope episodes confer different risk for subsequent LTE and response to therapy by genotype.

PO-630-01

FAM13B AND RS1717131 ARE THE LIKELY GENE AND SNP RESPONSIBLE FOR THE 5Q31 ATRIAL FIBRILLATION SUSCEPTIBILITY LOCUS

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Background: Atrial fibrillation (AF) genome wide association studies (GWAS) have identified an AF susceptibility locus on chr 5q31, between the WNT8A and FAM13B genes. Our prior human left atrial appendage RNA sequencing study found that expression of FAM13B is strongly associated with the AF GWAS lead variant in this locus. However, the regulatory variant controlling FAM13B expression and the mechanism by which FAM13B impacts AF incidence are not well understood.

Objective: To identify the common genetic variant responsible for regulating FAM13B expression and to characterize FAM13B localization, activity, and its effects on cardiomyocyte gene expression in order to gain insight into the functional mechanism of the chr 5q31 AF susceptibility locus.

Methods: We conducted bioinformatic analyses, luciferase reporter gene transfections, gel mobility shift assays, and CRISPR gene editing to identify the genetic variant responsible for regulating FAM13B expression. Recombinant protein production, activity assays, and knockdown of FAM13B expression in stem cell derived cardiomyocytes (iCMs) were performed along with transcriptomic and electrophysiological analyses. GFP-tagged FAM13B was used to examine FAM13B localization in iCMs.

Results: We identified rs1717131 as the regulatory variant, in linkage disequilibrium with the lead GWAS variant, responsible for controlling FAM13B expression in the left atrium. The AF risk allele had decreased enhancer activity and bound an additional protein that may function as a transcriptional repressor. Editing the reference allele to the risk allele in iCMs resulted in decreased FAM13B expression. FAM13B knockdown in iCMs altered expression of >1000 genes and increased the late/peak inward sodium current ratio. GFP-tagged FAM13B expressed in iCMs localized to the plasma membrane and the sarcosome, near or in the Z-disc. FAM13B is a member of the Rho GTPase-activating protein (RhoGAP) gene family, but failed to demonstrate RhoGAP activity.

Conclusion: The chr 5q31 AF causal variant was identified as rs17171731, with the risk allele having less enhancer activity and leading to decreased expression of FAM13B. FAM13B resides on the plasma membrane and Z-disc and plays a role in regulation of cardiomyocyte gene expression and the late sodium current.

PO-630-02

THE EFFECT OF CHANGES IN EXTRACELLULAR CALCIUM ON THE SMALL-CONDUCTION CA2+-ACTIVATED K+ CHANNEL OF METABOLIC SYNDROME

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