gold standard for an epicardial VT circuit was defined by high-resolution SEEM, including circuits with 1) epicardial termination site, 2) epicardial isthmus and 3) epicardial exit.
Results: SEEM was performed in 82 VTs (44% ICM). Termination during ablation from the epicardium was present in 28%, an epicardial exit in 74%, and evidence of an epicardial isthmus in 61%. 64% of VT circuits were 3-D with circuitry on both surface; 16% had midmyocardial circuit; 15% (n= 12) were 2-D on either the endocardium (n= 4) or epicardium (n= 8); and 5% was transmurally uniform on both surfaces. Inter-observer agreement was poor for PDW, MDI and Q-inferior (Kappa 0.08, 0.179 and 0.28 respectively). ECG criteria performance is summarized in Table 1.
Conclusion: Both interobserver agreement and predictive value are poor for epicardial 12- lead ECG criteria.

Table 1. Distribution of ECG criteria's predictive performances by gold-standard Epicardial definition

ECG Criteria	Termination Epicardial surface			Epicardial exit			Evidence of Isthmus at Epicardium		
	Epi (n=23)	Non-Epi (n=59)	p. value	Epi (n=61)	Non-Epi (n=21)	p. value	Yes (n= 50)	No (n=32)	p. value
PDW ≥ 34 ms	5/23 (21.7)	18/23 (78.3)	0.287	18/23 (78.3)	5/23 (5.4)	0.793	11/23 (47.80)	12/23 (52.2)	0.098
IDT ≥ 85 ms	6/18 (33.3)	12/18 (66.7)	0.822	16/18 (88.9)	2/18 (11.1)	0.08	14/18 (77.8)	4/18 (22.2)	0.153
SRS ≥ 121 ms	3/15 (20)	12/15 (80)	0.4	13/15 (86.7)	2/15 (13.3)	0.367	11/15 (73.3)	4/15 (26.7)	0.417
MDI ≥ 0.55	20/64 (31.3)	44/64 (68.8)	0.224	4/6 (66.7)	2/6 (33.3)	0.653	3/6 (50)	3/6 (50)	0.567

Values are presented as number (%). Bold p values are statistically significant; PDW= Pseudo delta wave; IDT= Intrinsicoid deflection time; SRS= Shortest RS interval; MDI= Maximum deflection index; Q-I= Presence of Q wave in lead I; Q-Inf= Absence of Q wave in inferior leads.

ABSTRACT B-AB13:
Novel Genetic Contributors to Arrhythmias

Thursday, July 29, 2021

1:45 pm - 2:45 pm

B-AB13-01

TRANS-ANCESTRY GWAS OF 252,730 INDIVIDUALS IDENTIFIES 114 NOVEL LOCI ASSOCIATED WITH THE QT INTERVAL

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Background: The QT interval, a marker of ventricular repolarization, is a heritable, independent predictor of risk for ventricular arrhythmias and sudden cardiac death (SCD). Previous genome-wide association studies (GWAS) of the QT interval have highlighted pathways regulating cardiac ion channels, calcium signaling and myocyte internal structure. However, a large proportion of the heritability remains unexplained, suggesting additional mechanisms remain undiscovered.
Objective: To identify new candidate genes and pathways relevant to ventricular repolarization to elucidate novel mechanisms underlying arrhythmogenesis.
Methods: We performed the largest trans-ancestry QT GWAS meta-analysis to date, using 35 studies imputed with 1000G / HRC reference panels, comprising a total sample of 252,730 individuals (84% European, 7.7% Hispanic and 6.7% African ancestry/ethnicity). Candidate gene prioritisation and gene-set enrichment analyses were performed using DEPICT.
Results: We identified 176 independent loci (114 novel) associated with QT. SNP-based heritability in European ancestry UK-Biobank participants was 29.3%. The variance explained by lead and conditionally independent variants was 14.6%. Across all loci, the top 30 gene-ontology terms highlighted by DEPICT included processes involved in either muscle cell differentiation, tissue development, insulin receptor signaling or regulation of gene expression. At one locus (*CD36*), the association was driven by studies of African ancestry only. This gene encodes an immune-metabolic receptor necessary for appropriate myocardial substrate utilisation. Another novel locus (*FAM9B*) was identified in male-stratified X-chromosome analyses. Other candidate genes highlighted include cardiac Z-disk proteins (*C10orf71*), enzymes with cardioprotective roles in oxidative stress (*PON2*), cardiomyocyte glucose transporters (*GLUT4*) and regulators of cell morphology and cytoskeleton organization (*BRWD1*).
Conclusion: Our analyses highlight novel genes and pathways associated with the QT interval that may expose new mechanisms, which contribute to arrhythmogenesis and SCD and could serve as new therapeutic targets.

B-AB13-02

A NOVEL VARIANT IN MANNOSE RECEPTOR C-TYPE 2 IDENTIFIED IN INDIVIDUALS WITH FAMILIAL WOLFF-PARKINSON-WHITE SYNDROME

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Background: Wolff-Parkinson-White (WPW) syndrome is the most common arrhythmia disorder observed in patients with structurally normal hearts and affects up to 1% of the population. A common cause of supraventricular tachycardia (SVT) worldwide, WPW contributes to sudden cardiac death in otherwise healthy children and adults. The genetic basis of WPW syndrome remains to be elucidated in individuals with structurally normal hearts.
Objective: Identify a novel variant causing WPW in the structurally normal heart, leading to further insight into the molecular underpinnings of re-entry bypass tract formation.
Methods: Whole exome sequencing (WES) was performed on 2 members of a three-generation extended family in which multiple members were affected by SVT, WPW pattern, or WPW syndrome. Shared non-synonymous variants between these 2 family members were then tested in all other family members and demonstrated a variant in the Mannose Receptor C-type 2 (Mrc2) gene. In addition, 154 unrelated individuals with WPW syndrome underwent whole exome sequencing and of these 75 were trio pairs, for a total of 324 subjects. An Mrc2 E990G knock-in mouse model was generated and used for experimental analysis. Resting serial ECGs, electrophysiology studies, echocardiography and optical mapping studies were performed.
Results: WES revealed a novel monogenic heterozygous variant E990G in Mrc2 as the disease-causing candidate gene. In Mrc2 E990G knock-in mice, ECGs did not demonstrate a WPW pattern, but a significantly higher incidence of inducible supraventricular tachycardia, in both heterozygous and