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MOLECULAR AUTOPSY FOR SUDDEN CARDIAC DEATH USING WHOLE GENOME SEQUENCING

ACC Oral Contributions
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Background: Arrhythmic sudden cardiac death (SCD) is a significant cause of mortality in industrialized countries. Clinical assessment and molecular diagnosis identifies a cause in only ~ 40% of patients. Whole genome sequencing (WGS) may identify causative genetic variants with sensitivity superior to targeted commercial sequencing approaches.

Methods: We performed WGS of genomic DNA isolated from paraffin embedded formalin fixed tissue from a previously healthy 19 year-old man who died of presumed arrhythmic SCD. We identified rare and novel variants (allele frequency < 5%) in genes known to be associated with sudden death and genes coding for ion channel, sarcomeric, costameric, sarcolemmal and Z-disc proteins. Variants of interest were confirmed with Sanger sequencing and first-degree relatives were genotyped for these variants.

Results: Toxicology screen, family history, gross autopsy, histological examination of myocardium, and commercial testing for variants associated with SCD were un-revealing. Using WGS to provide 48x coverage of 95% of genomic positions, we identified 326,000 rare/novel variants and used custom software to annotate them for cardiovascular relevance. We identified 14 rare/novel non-synonymous coding variants and two splice site variants in genes associated with cardiovascular diseases or important to cardiomyocyte function. Family genotyping revealed that two ion channel mutations assorted in a trans-acting manner with a complex inheritance pattern. The first was in exon 1 of KCNJ12, which encodes for the inward rectifying potassium channel Kir2.2 that maintains resting membrane potential and mediates late repolarization. The second was in a region of CACNA1S that encodes for a highly conserved calmodulin-binding domain of the L-type calcium channel Cav1.1, which is expressed in cardiac tissue but has unknown contribution to action potential.

Conclusions: We present the first whole genome sequence of a patient who died of SCD. Putative trans-acting mutations may comprise a new syndrome of inherited cardiac ion channelopathy associated with SCD and suggest a novel role for Cav1.1 in cardiac action potential duration.