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.

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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_001010874.4c742_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.