

Catecholaminergic polymorphic ventricular tachycardia, type 3: An autosomal recessive inherited cardiac arrhythmia caused by novel mutation in the TECRL gene

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Introduction: Primary cardiac arrhythmias could be one of the important causes of sudden cardiac deaths (SCD) in children and adolescents. Mutations in cardiac channel and their ancillary protein encoding genes have frequently been described in primary cardiac arrhythmias. Of them, KCNQ1, KCNH2, SCN5A, RYR2, CASQ2, CALM1-2 are the important ones. The aim is to present a new type of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and elucidate its genetic etiology.

Methods: Two families described in this study originated from Sudan. The parents in both families are first-degree cousins. Seven of their 13 children presented with exertion-induced arrhythmias or SCD. Five children died following the arrhythmic event. In the surviving two children, an Implantable Converter Defibrillator (ICD) was implanted in one child while the other suffered severe brain damage. Whole exome sequencing was performed to explore the genetic defect. Patient-specific stem cell induced-cardiomyocytes (hiPSC-CM) were made to evaluate the functional phenotype.

Results: ECG showed polymorphic ventricular fibrillation and torsade de pointes. ECG at rest showed borderline prolonged QTc interval of 450 ms. ICD interrogation of one surviving child revealed an episode of ventricular tachycardia. All affected children were homozygous for a splice donor site mutation, c.331+1G>A in the TECRL (also annotated SRD5A2L2) gene on chromosome 4. iPSC derived cardiomyocytes demonstrated elevated diastolic Ca²⁺ concentration, action potential prolongation and adrenergic induced triggered activity. Antiarrhythmic medication flecainide significantly reduced the triggered activity.

Conclusion: CPVT type 3 is a novel malignant form of cardiac arrhythmia, caused by homozygous mutation in the TECRL gene. These findings have implications for diagnosis and treatment of inherited cardiac arrhythmias.