LQT1

LQT1 is a subtype of Long QT Syndrome (LQTS), a genetic disorder that affects the heart's electrical system, leading to an increased risk of arrhythmias, or irregular heartbeats. LQT1 is specifically caused by mutations in the KCNQ1 gene, which encodes a protein that is crucial for the proper function of potassium ion channels in the heart.

Key Points about LQT1: Genetic Cause:

LQT1 is caused by mutations in the KCNQ1 gene. This gene encodes the alpha subunit of the potassium channel that forms the slow delayed rectifier current (IKs) in cardiac cells. These potassium channels are responsible for repolarizing the heart muscle after each heartbeat. Mutations in KCNQ1 reduce the function of these channels, leading to prolonged repolarization. Electrocardiogram (ECG) Findings:

In individuals with LQT1, the QT interval on an ECG is prolonged, which means that the heart takes longer than usual to recharge between beats. This prolonged QT interval can lead to a potentially life-threatening arrhythmia called Torsades de Pointes, which can degenerate into ventricular fibrillation and cause sudden cardiac arrest. Symptoms and Triggers:

Symptoms of LQT1 can include fainting (syncope), seizures, and in severe cases, sudden cardiac death. Triggers for arrhythmias in LQT1 patients are often related to physical exertion, especially swimming or other forms of exercise, and emotional stress. Because LQT1 is often triggered by exercise, patients are typically advised to avoid strenuous physical activities that could induce arrhythmias.

Management and Treatment:

Beta-blockers: These medications are the first line of treatment for LQT1. They work by reducing the heart rate and decreasing the risk of arrhythmias. Lifestyle modifications: Patients are often advised to avoid strenuous exercise and to manage stress carefully. Implantable Cardioverter-Defibrillator (ICD): In severe cases or in those with a history of life-threatening arrhythmias, an ICD may be implanted to automatically correct dangerous heart rhythms. Genetic counseling: Since LQT1 is inherited in an autosomal dominant manner, family members of affected individuals are often advised to undergo genetic testing and receive counseling. Prognosis:

With appropriate treatment and lifestyle modifications, many individuals with LQT1 can lead normal lives. However, the condition requires careful management to prevent arrhythmias and other complications. Summary: LQT1 is a subtype of Long QT Syndrome caused by mutations in the KCNQ1 gene, leading to prolonged repolarization in the heart. This can cause life-threatening arrhythmias, particularly during exercise or stress. Management typically involves beta-blockers, lifestyle modifications, and in some cases, an ICD. Early diagnosis and appropriate treatment are key to preventing serious outcomes.

The KCNQ1+KCNE1 (IKs) potassium channel plays a crucial role in cardiac adaptation to stress, in which β-adrenergic stimulation phosphorylates the IKs channel through the cyclic adenosine monophosphate (cAMP)/PKA (protein kinase A) pathway. Phosphorylation increases the channel current and accelerates repolarization to adapt to an increased heart rate. Variants in KCNQ1 can cause long-QT syndrome type 1 (LQT1), and those with defective cAMP effects predispose patients to the highest risk of cardiac arrest and sudden death. However, the molecular connection between IKs channel phosphorylation and channel function and why high-risk LQT1 mutations lose cAMP sensitivity remains unclear.

Regular patch clamp and voltage clamp fluorometry techniques were utilized to record pore opening and voltage sensor movement of wild-type and mutant KCNQ1/IKs channels. The clinical phenotypic penetrance of each LQT1 mutation was analyzed as a metric for assessing their clinical risk. The patient-specific-induced pluripotent stem-cell model was used to test mechanistic findings in physiological conditions.

By systematically elucidating mechanisms of a series of LQT1 variants that lack cAMP sensitivity, we identified molecular determinants of IKs channel regulation by phosphorylation. These key residues are distributed across the N-terminus of KCNQ1 extending to the central pore region of IKs. We refer to this pattern as the IKs channel PKA phosphorylation axis. Next, by examining LQT1 variants from clinical databases containing 10 579 LQT1 carriers, we found that the distribution of the most high-penetrance LQT1 variants extends across the IKs channel PKA phosphorylation axis, demonstrating its clinical relevance. Furthermore, we found that a small molecule, ML277, which binds at the center of the phosphorylation axis, rescues the defective cAMP effects of multiple high-risk LQT1 variants. This finding was tested in high-risk patient-specific induced pluripotent stem cell-derived cardiomyocytes, where ML277 remarkably alleviates the beating abnormalities.

The findings not only elucidate the molecular mechanism of Protein Kinase A (PKA)-dependent IKs channel phosphorylation but also provide an effective antiarrhythmic strategy for patients with high-risk LQT1 variants [1)]

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Zhong L, Yan Z, Jiang D, Weng KC, Ouyang Y, Zhang H, Lin X, Xiao C, Yang H, Yao J, Kang X, Wang C, Huang C, Shen B, Chung SK, Jiang ZH, Zhu W, Neher E, Silva JR, Hou P. Targeting the IKs Channel PKA Phosphorylation Axis to Restore Its Function in High-Risk LQT1 Variants. Circ Res. 2024 Aug 21. doi: 10.1161/CIRCRESAHA.124.325009. Epub ahead of print. PMID: 39166328.