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Short Communication

Diagnostic and Therapeutic Symptoms Associated with KCNJ2 Mutations

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ABOUT THE STUDY

Sudden cardiac death is brought on by ionic current anomalies linked to both hereditary and acquired arrhythmia disorders. Ionic current IK1 helps the action potential's terminal repolarization and preserves the resting membrane potential in the heart. Cardiovascular IK1 is carried by three inward rectifier channels, although Kir2.1, which is encoded by KCNJ2, carries the majority of the component. The link between KCNJ2 mutations and several hereditary arrhythmia disorders, including Andersen-Tawil Syndrome (ATS1), Short QT Syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia, highlights the significance of this protein. If IK1 is lost, action potential lengthening, Early After-Depolarization (EAD), and the lethal ventricular arrhythmia Torsade de pointes may occur as a result [1].

IK1 has also been associated in Heart Failure (HF), where it has been found to be down-regulated and to play a role in the development of acquired long QT and sudden cardiac death. The identification of the biophysical processes by which mutations in KCNJ2 influence Kir2.1 function is crucial in comprehending the aetiology of arrhythmia development associated to aberrant IK1. ATS1 is a hereditary autosomal dominant condition that affects both the cardiovascular and musculoskeletal systems. Periodic paralysis, cardiac arrhythmias, and craniofacial dysmorphic traits make up the ATS1 clinical trial [2].

A prolonged QT interval, strong U waves with a lengthy QTU, and ventricular ectopy-often seen as Premature Ventricular Contraction (PVCs), bigeminy, polymorphic VT, and less frequently, bidirectional VT-are all signs of cardiac presentations. Micrognathia, low-set ears, ocular hypertelorism, a large nasal root, clinodactyly, and syndactyly are some of the dysmorphic characteristics linked to ATS1. Because of variable phenotypic severity among gene carriers and inadequate penetrance, the diagnosis of ATS is difficult. In one research, individuals who tested positive for the gene displayed the entire clinical triad in 58% of cases, while at least 81% had two of the three classical traits, leaving 6% of people without the gene's penetrance. Expression variability may be impacted by the precise location of a disease-causing variation or hormonal modulation [3].

Deletion mutations, which can have a variety of downstream effects on the function of the Kir2.1 protein, make up the majority of KCNJ2 mutations. It has been demonstrated that ATS1 is a result of KCNJ2 mutations that disrupt PIP2 binding or an allosteric conformational change that results in decreased Kir2.1 current. Phosphatidyl Inositol 4,5-Bisphosphate (PIP2) binding is required for Kir2.1 to open. Misfolded or sequestered proteins and pore selectivity filter issues are two additional KCNJ2 mutations that cause ATS, however they account for a relatively small proportion of all disease-causing mutations. In addition to having PIP2 binding sites, the C-terminus of Kir2.1 also contains the Kir2.1 endoplasmic reticulum export sequence, which is thought to be the mechanism for Kir2.1 loss as a result of a trafficking problem [4].

The involvement of modifier genes, epigenetic factors, and channel-interacting proteins such caveolin-3 in ATS phenotype, penetrance, and arrhythmia susceptibility is also unknown. A uncommon arrhythmogenic condition called CPVT is characterised by bidirectional and polymorphic ventricular tachycardia that is dependent on the adrenergic system (PMVT). A normal resting ECG, including QTc, and an arrhythmia that may be reproduced with exercise, stress, or isoproterenol infusion are characteristics that identifies the phenotype. Patients with either cardiac ryanodine receptor (RYR2, CPVT1) or cardiac calsequestrin 2 mutations make up 50–60% of the population (CASQ2, CPVT2). The cellular calcium homeostasis is intrinsically regulated by the cardiac ryanodine receptor and calsequestrin, and arrhythmia mechanisms may be influenced by calcium overload/dysregulation, which results in delayed after-depolarization or enhanced automaticity [5].

Unusually, the ryanodine receptor is also active in pancreatic islet cells and is crucial for cell metabolism and insulin release. KCNJ2, CPVT3, ankyrinB, and triadin are some of the most recent genes to be linked to a CPVT-like phenotype. Female patients who were diagnosed with CPVT3 presented with exertion-related and emotion-related near-syncope and syncope. The individuals had normal QTc intervals and showed neither dysmorphic characteristics nor periodic paralysis. In their resting ECGs, both patients did show noticeable U waves. Following testing, salvos of polymorphic and bidirectional ventricular tachycardia were seen as exercise-induced arrhythmias.

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In heterologous cells, both V227F, Kir2.1 and R67Q-Kir2.1 showed adrenergic dependent loss of function.

CONCLUSION

A well-known regulator of inward rectifying potassium channels is Phosphatidyl Inositol 4,5-Bisphosphate (PIP2). Many Kir2.1 mutations linked to ATS1 and the R67Q-KCNJ2 mutation linked to CPVT3 exist in areas that influence how the channel interacts with PIP2. Kir2.1's inhibition by the divalent cation magnesium has been demonstrated to be amplified by an N-terminus mutation that modifies Kir2.1's sensitivity to PIP2. As a result, one theory for adrenergic regulated channel activity is that greater inhibition occurs when cellular calcium is elevated.

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