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Heterogeneity of Clinical Syndromes Related to Loss of Function Mutations in *KCNJ2*

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Commentary

Ionic current abnormalities related to both inherited and acquired arrhythmia syndromes cause sudden cardiac death [1,2]. In the heart, ionic current I_{K1} maintains the resting membrane potential and augments terminal repolarization of the action potential [3]. Three inward rectifier channels contribute to cardiac I_{K1}, but the dominant component is carried by Kir2.1, encoded by *KCNJ2*. The importance of this protein is emphasized by the association *KCNJ2* mutations and various inherited arrhythmia syndromes, such as Andersen-Tawil Syndrome (ATS1), Short QT Syndrome 3, and Catecholaminergic Polymorphic Ventricular Tachycardia 3 [4-6]. The loss of I_{K1} may lead to arrhythmias by action potential prolongation and subsequent development of early after-depolarization (EAD) and the fatal ventricular arrhythmia Torsade de pointes. Importantly, I_{K1} has also been shown to be down regulated in heart failure (HF) and contributes to the acquired long QT and sudden cardiac death in this disease [7,8]. Critical to understanding the pathogenesis of arrhythmia development related to abnormal I_{K1} is the determination of the biophysical mechanisms by which mutations in *KCNJ2* affect Kir2.1 function. Here we review the known and hypothesized mechanisms of Kir2.1 channel dysfunction as it relates to varied clinical syndromes.

ATS1 is an autosomal dominant inherited disease that has a multisystem phenotype spanning the musculoskeletal and cardiac systems [9]. The clinical triad of ATS1 consists of periodic paralysis, ventricular arrhythmias and craniofacial dysmorphic features. Cardiac presentations on ECG reveal prolongation of the QT interval, prominent U waves with a long QTU, and ventricular ectopy frequently in the form of PVCs, bigeminy, polymorphic VT, and less commonly, bidirectional VT [10]. Dysmorphic features associated with ATS1 include micrognathia, low-set ears, ocular hypertelorism, broad nasal root, clinodactyly and syndactyly [9,10]. The diagnosis of ATS is challenging due to incomplete penetrance and varying phenotype severity amongst gene carriers. In one study, gene positive individuals, 58% expressed the whole clinical triad while at least 81% had two of the three classical characteristics, leaving 6% of individuals showing no penetrance of the gene [11]. The specific location of a disease causing variant or hormonal regulation may affect expression variability [12,13].

Predominantly mutations in *KCNJ2* are missense or deletion mutations with a variety of downstream affect on Kir2.1 protein function. Phosphatidylinositol 4,5-bisphosphate (PIP2) binding is necessary for Kir2.1 to open [14], and ATS1 has been shown to be a result of *KCNJ2* mutations that affect PIP2 binding or an allosteric conformational change leading to decreased Kir2.1 current [15]. Other ATS causing *KCNJ2* mutations include disturbances in the pore selectivity filter and misfolded or sequestered proteins, but these make up the minority of disease causing mutations [15,16]. The C-terminus of Kir2.1, in addition to PIP2 binding sites, is home to the Kir2.1 endoplasmic reticulum export sequence and is implicated as mechanism for Kir2.1 loss due to trafficking defect [12]. Additionally, channel interacting proteins, such as caveolin-3, modifier genes, and epigenetic factors may play a role in ATS phenotype, penetrance and arrhythmia susceptibility [17-19], but are not well understood.

CPVT is a rare arrhythmogenic disorder characterized by adrenergic dependent bidirectional and polymorphic ventricular tachycardia (PMVT). Defining features of the phenotype include a normal resting ECG, including QTc, and an arrhythmia reproducible with exercise, stress or isoproterenol infusion. Approximately 50-60% of patients harbor mutations in either the cardiac ryanodine receptor (RYR2, CPVT1) or cardiac calsequestrin 2 (CASQ2, CPVT2) [6,20,21]. The cardiac ryanodine receptor and calsequestrin are intrinsic to cellular calcium homeostasis, and arrhythmia mechanisms may be related to calcium overload/dysregulation and production of delayed after-depolarization [22] or increased automaticity [23]. Interestingly, the ryanodine receptor is also active in pancreatic islet cells and plays a significant role in insulin secretion and cell metabolism [24]. More recently other genes have been associated with a CPVT-like phenotype such as *KCNJ2*, designated CPVT3, ankyrinB and triadin [6,25-27].

To date, two *KCNJ2* mutations associated with CPVT3 have been characterized, V227F and R67Q, by our group [28,29]. The patients identified with CPVT3 were female and presented with exertion/emotion related near-syncope and syncope. The patients demonstrated neither dysmorphic features nor periodic paralysis and had normal QTc intervals. Both patients did have prominent U waves on resting ECG. Subsequent testing demonstrated exercise-induced arrhythmias that included salvos of polymorphic and bidirectional ventricular tachycardia. Both V227F-Kir2.1 and R67Q-Kir2.1 demonstrated adrenergic dependent loss of function in heterologous cells [28,29].

There is debate as to whether the KCNJ2-related arrhythmia syndromes classified here as ATS1 and CPVT3 are: (1) two distinct entities with different outcomes and with different underlying molecular and cellular mechanisms, are (2) the same clinical syndrome with variability in presentation as CPVT phenocopies, or (3) if the arrhythmia syndromes associated with *KCNJ2* mutations have been unintentionally misclassified for the lack of a better definition for these syndromes. It is clear that there has been considerable overlap between mutations that have been associated with ATS1 and CPVT3 [11,29]. However, supporting two clinical entities includes both the distinct clinical presentation and cellular physiology. As described above, exercise is not a constant trigger for the arrhythmias associated with the clinical phenotype of ATS1, and in some instances, exercise suppresses these arrhythmias [11,13]. In contrast, the arrhythmias in patients characterized as having CPVT3 mutations were precipitated by exercise or stress. Additionally, in terms of functional characterization, most Kir2.1 mutations associated with ATS1 exhibit dominant-negative Kir2.1 current when co-expressed with WT-Kir2.1 while the Kir2.1 mutations associated with CPVT3 displayed markedly decreased outward Kir2.1 current only after adrenergic stimulation.

The mechanisms underlying the functional differences observed with these mutations are not clear at this time; however, they are an area of active research for our laboratory and others. Phosphatidylinositol 4,5-bisphosphate (PIP2) is a well-established regulator of inward rectifying potassium channels [14]. Many of the Kir2.1 mutations associated with ATS1 and the R67Q-KCNJ2 mutation associated CPVT3 occur in regions that affect the interaction of the channel with PIP2 [30]. An N-terminus mutation that alters Kir2.1 sensitivity to PIP2 has been shown to exaggerate the inhibition of Kir2.1 by a divalent cation, magnesium [31]. Therefore, one hypothesis for adrenergic modulated channel function may be enhanced inhibition in the presence of increased cellular calcium [29].

Important questions remain in the phenotype-genotype correlation for clinical syndromes related to *KCNJ2* mutations. Careful clinical phenotyping as well as functional studies, which focus on the underlying arrhythmia mechanisms, will allow greater clarity for these syndromes. Such an understanding is crucial in providing clinical care and applying concepts of precision medicine for the care of these patients.

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