Short QT Syndrome or Andersen Syndrome
Yin and Yang of Kir2.1 Channel Dysfunction
Eric Schulze-Bahr

In 1994, the complete human cDNA of an inwardly rectifying K+ channel gene, KCNJ2 or Kir2.1, was isolated. Kir2.1 channels are important regulators of resting membrane potential of the cardiac (and also skeletal) muscle and cellular excitability,1 since they cause an outflow of K+ in the hyperpolarized membrane state during the terminal phase of cardiac action potential repolarization. The cDNA encodes a small protein of 427 amino acids with 2 putative transmembrane domains (M1, M2) and a pore region (H5) and regulates the inward rectifier K+ current I_K1. Northern blot analysis demonstrated a 5.5-kb transcript with high levels in the heart, brain, placenta, lung, and skeletal muscle and lower levels in the kidney; in the heart, Kir2.1 channels are abundant in the atria, ventricle (with a high I_K1 conductance) and Purkinje fibers, but less frequent in nodal cells. On current knowledge, 4 subunits form a functional (ie, tetrameric) channel, but they also may co-assemble with other subunits of the Kir2.x family as heteromultimers2 which indicates functional complexity and diversity.

In 2001, Plaster et al performed a genome-wide linkage analysis to identify the disease locus for Andersen (also Andersen–Tawil) syndrome.3 This rare syndrome can be found as a sporadic or autosomal dominant genetic trait and is characterized by a skeletal muscle phenotype (potassium-sensitive periodic paralysis caused by abnormal muscle relaxation, and histologically tubular aggregates), a cardiac phenotype (borderline or mildly prolonged QT interval, adrenergically mediated multifocal ventricular ectopy or tachycardia) and a distinct developmental dysmorphology that may include short stature, scoliosis, clinodactyly, hypertelorism (wide-set eyes), low-set small ears, micrognathia, and a broad forehead.3 Widespread phenotypic variability of KCNJ2 mutation carriers was noted.3,4 Because significant genetic linkage of the disease locus for Andersen syndrome was found on the long arm of chromosome 17 (lod score, 3.23 and 0) and overlapped the KCNJ2 gene locus (region 17q23.1–q24.2), KCNJ2 was investigated for disease gene mutations and, finally, turned out to be altered in more than 50% of patients with Andersen syndrome.3 To date, allelic heterogeneity is indicated by the presence of more than 20 different missense mutations for Andersen syndrome (Figure 1)3,4–7 that have been identified in the heterozygous state. Heterologous expression of mutant Kir2.1 channel subunits revealed a loss of channel function and a dominant-negative effect of mutant subunits on wild-type protein with a large reduction of I_K1 current3,4 or abnormal binding of phosphatidylinositol-4,5-bisphosphate (PIP2) at the cytoplasmic C-terminus (amino acid residues 175 to 206, 207 to 246, 324 to 365) of Kir2.1 subunits that is required for regular Kir2.1 channel activity.

Taken together, KCNJ2 mutations that cause a reduction of the I_K1 current decelerate cellular action potential repolarization, prolong the action potential duration, and by depolarizing and destabilizing the resting membrane potential are likely to induce ventricular arrhythmias1 or cause myotonic skeletal muscle contractions. Moreover, the dysmorphic phenotypic spectrum of Andersen syndrome patients suggests that Kir2.1 dysfunction and I_K1 reduction play an unexpected, but important role in developmental signaling in nonexcitable tissues.3,5

In this issue of Circulation Research, Priori et al extended the phenotypic spectrum of KCNJ2 mutations through the identification of a particular missense mutation (D172N; the phenotypic spectrum of Andersen syndrome patients suggests that Kir2.1 dysfunction and I_K1 reduction play an unexpected, but important role in developmental signaling in nonexcitable tissues.3,5

Because D172N is located at an evolutionary conserved amino acid domain of the Kir2.1 protein, because of its absence in the general population and a physiologically relevant effect on I_K1 current even by equimolar co-expression with wild-type protein (reflecting the heterozygous state of the mutation carriers), the results favor a causal relationship with the N172 allele with SQTS rather than an arbitrary finding. As previously shown, experiments using in vivo gene transfer of myocytes overexpressing Kir2.1 showed a significantly shorter action potential duration by acceleration of terminal repolarization and abbreviated QTc intervals (guinea pigs).1 In contrast to the loss of Kir2.1 channel function that tends to prolong the action potential1 and prolong the QT interval, no other phenotypic features, particularly a skeletal or dysmorphic bone phenotype, have been associated with the N172-related gain of Kir2.1 channel function. Interestingly, the shortened repolarization led to an asymmetric T-wave...
with an exceedingly rapid terminal phase that is unusual and probably an electrocardiographic sign of N172 allele carriers. Taken together, these findings indicate a novel subform of SQTS (SQT-3) that is in line with very recent reports that a gain of \( I_{Kr} \) or \( I_{Ks} \) channel function through mutations in \( KCNH2 \) (SQT-1)\(^{10}\) or \( KCNQ1 \) (SQT-2)\(^{11}\) cause a short repolarization syndrome. SQTS now appears that it may turn out to be genetically heterogeneous as its clinical and genetic counterpart, the long-QT syndrome. Both syndromes reflect the close, but opposite relationship of potassium channel dysfunction in the setting of normal repolarization.

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References


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