Genetic Control of Potassium Channels

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KEYWORDS

• Cardiac potassium channel • Gene • Long QT syndrome • Short QT syndrome
• Brugada syndrome • Atrial fibrillation • Ventricular fibrillation

KEY POINTS

- Approximately 80 genes in the human genome code for pore-forming subunits of potassium (K^+) channels.
- Rare variants (mutations) in K^+ channel–encoding genes may cause heritable arrhythmia syndromes.
- Not all rare variants in K^+ channel–encoding genes are necessarily disease-causing mutations.
- Common variants in K^+ channel–encoding genes are increasingly recognized as modifiers of phenotype in heritable arrhythmia syndromes and in the general population.
- Although difficult, distinguishing pathogenic variants from benign variants is of utmost importance to avoid false designations of genetic variants as disease-causing mutations.

INTRODUCTION

Cardiac K^+ channels play a pivotal role in the electrical activity of atrial and ventricular myocytes by controlling the shape and duration of the repolarization during phases 1, 2, and 3 of the action potential and by stabilizing the negative resting membrane potential during phase 4 of the action potential. In addition, K^+ channels contribute to the regulation of the heart rate by influencing the pacemaker activity in sinoatrial node (SAN) and atrioventricular node (AVN) cells. Understanding of the molecular identity of K^+ channels started in the late 1980s, when the first gene encoding a K^+ channel was identified in *Drosophila*.[1] Flies with a shaker phenotype, which involves leg shaking on exposure to ether, were found to miss a K^+ current in their leg and flight muscles. Isolation of the gene responsible for this defective K^+ current resulted in the cloning of the first K^+ channel. Next, by using the molecular cloning technique and the *shaker* gene as a homology probe, other *Drosophila* K^+ channel genes and their mammalian homologues were isolated. In addition, by using the cDNA expression method and heterologous expression systems (eg, *Xenopus* oocytes or mammalian cell lines), the products of these cloned K^+ genes were characterized and correlated with endogenous K^+ currents.[2] In this manner, numerous human K^+ channel–encoding genes have been identified. Knowledge of the genetic control of cardiac K^+ channels has greatly expanded from the early 1990s, when genetic

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linkage studies started to link rare variants (mutations) in genes encoding for cardiac K^+ channels to heritable arrhythmia syndromes.[3,4] To do this, genetic linkage studies used both positional cloning technique and candidate gene approach. The positional cloning technique links a gene to a phenotype by its approximate location on the chromosome without earlier information on the molecular basis of the disease. The candidate gene approach uses mechanistic hypotheses based on pathophysiology to associate some genes of interest to a certain phenotype. Currently, mutations in cardiac K^+ channel genes have been implicated in the etiology of various heritable arrhythmia syndromes, including long QT syndrome (LQTS), short QT syndrome (SQTS), and Brugada syndrome (BrS).[5] Experimental studies have provided further mechanistic insights into the role of these mutations by exploring their effects on expression and function of cardiac K^+ channels. Last but not least, the past decade faced trying to unravel the results of increasing numbers of large-scale genome-wide association studies (GWAS) and candidate gene studies that have discovered significant associations between common variants in cardiac K^+ channel genes and risk of sudden cardiac death and/or ECG indices of conduction and repolarization in the general population and risk of atrial fibrillation (AF).[6] This article is part of the *Cardiac Electrophysiology Clinics* issue, "Cardiac Potassium Channel Disorders." Current knowledge on the genetic control of cardiac K^+ channels in health and disease is reviewed. The molecular biology, structure, and function of K^+ channels and the clinical features of diseases linked to K^+ channel dysfunction are described in detail elsewhere in this issue (see Wu W, Sanguinetti MC: Molecular Basis of Cardiac Delayed Rectifier K+ Channel Function and Pharmacology, in this issue).

CARDIAC K^+ CHANNEL GENES IN HEALTH

A gene is a DNA fragment coding for a functional RNA or protein product. It consists of several regions of nucleotide sequences, including (1) 1 or more promoter regions that bind transcription factors and RNA polymerase to initiate transcription, (2) regulatory regions (enhancers or silencers) upstream (5'end) or downstream (3'end) of the open reading frame that can bind activator or repressor proteins to control transcription, (3) untranslated regions immediately flanking the open reading frame, which can influence mRNA translation, and (4) the open reading frame, which is the region from the start codon to the stop codon and has the potential to encode a protein (encompassing protein-coding exons and untranslated introns). Introns are removed from mRNA before translation through splicing, a process that is dictated by specific splice sites (ie, nucleotide sequences at both ends of introns). Through alternative splicing, genes are able to generate multiple mRNA variants from the same gene, thereby giving rise to diversity of the final product. This may explain why the diversity of K^+ currents in cardiac myocytes exceeds the number of K^+ channels genes identified. K^+ channel genes encode a diverse family of membrane-spanning proteins, all containing a homologous pore that selectively allows K^+ ions to flow across the cell membrane.[2] The superfamily of K^+ channels is usually classified based on the amino acid sequence of their pore-forming α-subunit. This results in 3 main families: (1) channels with 2 membrane-spanning (transmembrane) segments and a single pore, (2) channels with 6 transmembrane segments and a single pore, and (3) channels with 4 transmembrane segments and 2 pores, also called 2-pore K^+ (K_{2P}) channels.

K^+ Channels with Two Transmembrane Segments and a Single Pore

K^+ channels with 2 transmembrane segments and a single pore are also known as inwardly rectifying K^+ (K_{ir}) channels. Inward rectification refers to the functional properties of K_{ir} channel current, which involve preferential conduction of K^+ into the cell (inward) rather than out of the cell (outward). Each K_{ir} channel α-subunit contains a pore loop between its 2 transmembrane segments, a cytosolic N-terminus and a cytosolic C-terminus. **Fig. 1** shows a topological model of the α-subunit of the K_{ir} channel and the phylogenic tree of the 15 human K_{ir} channels based on the amino acid sequence of their α-subunits.[7] Subfamilies of the K_{ir} channel family in the heart include $K_{ir}2.x$, $K_{ir}3.x$, and $K_{ir}6.x$, which are responsible for the inward rectifier K^+ current (I_{K1}), the acetylcholine-activated G-protein-gated K^+ current ($I_{K,Ach}$), and the adenosine-5'-triphosphate-sensitive K^+ current ($I_{K,ATP}$), respectively (**Table 1**).[8]

Four $K_{ir}2.1$ α-subunits, encoded by *KCNJ2*, coassemble to form 1 homotetrameric I_{K1} channel.[9] Other $K_{ir}2.x$ members, including $K_{ir}2.2$, $K_{ir}2.3$, and $K_{ir}2.4$, are also expressed in the heart and may coassemble with $K_{ir}2.1$ to form heterotetrameric channels. I_{K1} conducts an inward K^+ current at membrane potentials negative to the K^+ equilibrium potential (approximately −90 mV) and a smaller but substantial outward K^+ current at potentials between −40 mV and −90 mV. These properties enable I_{K1} to maintain a negative