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Genetic Discovery of K_{ATP} Channels in Cardiovascular Diseases

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Abstract

The adenosine triphosphate (ATP)-sensitive K+ (K_{ATP}) channels are hetero-octameric protein complexes comprising four pore-forming subunit Kir6.x subunits and four regulatory subunit sulfonylurea receptor SURx subunits. They are prominent in myocytes, pancreatic β cells and neurons, and link cellular metabolism with membrane excitability. Using genetically modified animals and genomic analysis in patients, recent studies have implicated certain K_{ATP} channel subtypes in physiological and pathological processes in a variety of cardiovascular diseases. In this review, we focus on the causal relationship between K_{ATP} channel activity and pathophysiology in the cardiovascular system, particularly from the perspective of genetic changes in human and animal models.

Journal Subject Terms

Animal Models of Human Disease; Basic Science Research; Clinical Studies; Ion Channels/ Membrane Transport; Pathophysiology

Keywords

KATP; candidate genes; Kir6.1; arrhythmia; heart failure; ABCC9; ABCC8; KCNJ8; KCNJ9; Kir6.2; SUR1; SUR2A; SUR2B; Cantu syndrome

Introduction

It has been over 30 years since Noma first discovered adenosine triphosphate-sensitive potassium channels in cardiac muscle in 1983[1]. They were subsequently found in skeletal myocytes[2], pancreatic β cells[3], vascular smooth muscle[4], vascular endothelium[5] and the central nervous system[6]. Although they may be the most densely expressed potassium channels in the heart[7], K_{ATP} channels are closed under normal condition and play little or no role in cell excitability. However, when exposed to a severe metabolic stress, such as anoxia,

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metabolic inhibition, or ischemia, these channels can open and the consequent decrease in excitability and contractility is thought to be cardioprotective because of preservation of ATP[8]. In addition to preservation of ATP, K_{ATP} activation-dependent shortening of the action potential, as well as reduction of Ca^{2+} entry and inhibition of contractility, may in turn lead to arrhythmias and cardiac insufficiency[9]. If fully activated, K_{ATP} channel density in the heart can result in complete cessation of cardiac electrical activity and contractile failure[7, 8]. Therefore, the K_{ATP} channel may represent a 'double-edged sword' in regulating cardiac excitability. In vascular smooth muscle and endothelium, activation of K_{ATP} channels will lead to membrane hyperpolarization, resulting in decreased Ca^{2+} current and vasodilation[10]. Conversely, inhibition of K_{ATP} channels will cause membrane depolarization, increase in Ca^{2+} current and vasoconstriction[10]. Hence, K_{ATP} channels can also play a key role in regulating vessel tone and blood flow. Here, we give an overview of recent advances in understanding of the molecular structure and physiological function of K_{ATP} channel in heart and blood vessels, with specific focus on the relationship between genetic changes in K_{ATP} channels and cardiovascular function.

Molecular structure, distribution and regulation of K_{ATP}

K_{ATP} channels are hetero-octamers composed of four pore-forming inward rectifier Kir6.X (Kir6.1 and Kir6.2, encoded by *KCNJ8* and *KCNJ11* respectively) subunits, each coupled with a regulatory subunit sulfonylurea receptor SURX (SUR1 or SUR2, encoded by SUR1 and SUR2 respectively, Figure 1A)[11–13] . The SUR genes are large, each containing ~40 exons, and there are two recognized major spliced variants of SUR2, SUR2A and SUR2B, which result from alternative splicing of the terminal exon in *ABCC9*[14, 15]. SUR2A and B consequently differ in the last 42 amino acids of the C terminus, resulting in distinct physiological and pharmacological properties. The obligate octameric arrangement may result from co-regulation of expression of Kir6 and SUR subunits: *ABCC8* and *KCNJ11* are immediately adjacent to each other on human chromosome 11p15.1[13], whereas *ABCC9* and *KCNJ8* are immediately adjacent to one another on human chromosome 12p12.1(Figure 1B)[13, 14].

Kir6.X subunits are typical Kir channel subunits, consisting of two transmembrane M1 and M2 helices connected by a pore-forming loop with a glycine-phenylalanine-glycine signature motif for K^+ selectivity, and cytoplasmic N- and C-termini[16]. SUR subunits are members of the ABC protein superfamily, and consist of two six-helix transmembrane domains (TMD1 and TMD2), and an additional unique five-helix TMD0 at the N-terminus of SUR subunit joined to TMD1 by a cytoplasmic linker (L0) that provides a physical link between SUR function and Kir6 subunit gating and trafficking[17]. As in all ABC proteins, each of TMD1 and TMD2 are linked at the C-terminal ends to cytoplasmic nucleotide binding domains (NBD1 and NBD2, respectively)[18]. The structure and the sequence of NBDs are highly conserved. Both contain a conserved Walker A (WA) motif and a Walker B (WB) motif. These motifs contain Mg^{2+}-adenosine nucleotide binding sites. At least NBD2 catalyzes ATP hydrolysis and is critical for Mg-nucleotide regulation of ABC protein functional activity (Figure 1C)[19, 20].

K_{ATP} channels are expressed in various tissues, but the constitution differs significantly between and within different tissues. The current consensus is that K_{ATP} channels consist primarily of Kir6.2 and SUR2A in both normal human atrial and ventricular myocyte cells, although all four subunits are detected[21]. Under different physiological or pathological conditions, the K_{ATP} channel subunit constitution may change or there may be plasticity of SUR subunits which can lead to different subunits being functional in different conditions[21]. In mice, it is clear that SUR1 and Kir6.2 are the primary subunits in atrial K_{ATP} while SUR2 and Kir6.2 are the main subunits in the ventricle[22, 23]. K_{ATP} channels have also been identified throughout the cardiac pacemaker/conduction system, including the sino-atrial (SA) node[24], atrio-ventricular (AV) node[25] and Purkinje fibers[26], and several studies have indicated Kir6.1, Kir6.2 and SUR2B are necessary for functional K_{ATP} in these tissues[23, 25–28]. Vascular smooth muscle K_{ATP} channels are primarily formed by Kir6.1 and SUR2B, whereas vascular endothelial K_{ATP} channel is suggested to be composed of Kir6.1, Kir6.2 and SUR2B[29, 30].

In addition to the cell membrane, K_{ATP} channels have been reported to be present in mitochondria, and to be involved in regulation of oxidative phosphorylation, and protection from ischemia-reperfusion injury[31–34]. Recent studies have suggested that this proposed mitoK_{ATP} may contain Kir1.1 and/or SUR2A-55[35–38], but direct evidence is lacking, and even the constitution of any mitoK_{ATP} remains unclear.

K_{ATP} channel regulation is complex, and involves metabolites, hormones and neurotransmitters as well as transcriptional mechanisms[39]. A hallmark feature of K_{ATP} channels is their sensitivity to metabolic changes in nucleotide levels. Micromolar ATP inhibits channels by direct interaction with Kir6 subunits, and since the cellular ATP concentration is relatively high (i.e. millimolar) in physiological conditions, ATP inhibition is usually sufficient to maintain channels in predominantly closed states (Figure 1D)[40] . However, ATP inhibition is overridden by MgATP and MgADP interacting with SUR subunit NBFs[7], and ATP sensitivity is reduced by membrane phosphoinositides, such as phosphatidylinositol-4,5-bisphosphate (PIP2), long-chain acyl-CoA esters (LC-CoAs), and metabolic derivatives of free fatty acids[41]. Both PIP_2 and LC-CoAs act on Kir6.2 to antagonize ATP inhibition and increase channel open probability[42]. In addition, other metabolic factors including PH, nitric oxide (NO), eicosanoids, hydrogen sulfide (H_2S) as well as hormones and neurotransmitters, can also affect K_{ATP} channel activity[39, 43, 44].

K_{ATP} channels are uniquely endowed with sensitivity to a large number of pharmacological agents that interact with the SUR subunits. Multiple K_{ATP} channel openers (KCOs) (e.g., nicorandil, cromakalim, pinacidil and diazoxide) act on SURx subunits to activate the channel[18]. SUR1-containing channels can be strongly activated by diazoxide, but not by pinacidil or cromakalim[23, 45, 46], whereas channels containing SUR2A respond potently to both pinacidil and cromakalim, but weakly to diazoxide[46–48]. Channels containing SUR2B are sensitive to diazoxide and cromakalim, as well as to pinacidil[47–49]. Because nucleotide binding and hydrolysis at NBDs are important for the binding and action of these KCOs, the different sensitivities of SUR1 and SUR2 subtypes to these KCOs may partially result from differences in nucleotide sensitivity[45, 49–51]. Pinacidil and cromakalim effectively act to decrease sensitivity to inhibitory ATP, leading to increased channel opening at a given level

of cytosolic ATP, whereas diazoxide needs the presence of intracellular ADP for channel activity[49]. All SUR isoforms can be inhibited by sulfonylureas such as tolbutamide and glibenclamide, which are commonly used as K_{ATP} channel inhibitors[52]. SUR1-containing channels are more sensitive to sulfonylureas than SUR2-containing channels[53–55], and are widely used to treat diabetes, where they act to trigger insulin secretion via interactions with SUR1-dependent K_{ATP} channels in pancreatic β-cells[18].

K_{ATP} channels and cardiovascular diseases

There is now a significant literature reporting association of K_{ATP} gene mutations and variants with cardiovascular pathologies (Table 1). As discussed below, the evidence in support of causal association is weak in many cases, but some clear causal links have now been established.

Kir6.2

Kir6.2 is the primary pore-forming subunit of K_{ATP} channels in both cardiac myocytes and pancreatic β-cells[91]. Over 50 human mutations in *KCNJ11*–encoded Kir6.2 have been reported, and gain- and loss-of-function of Kir6.2 are were well known to cause neonatal diabetes and congenital hyperinsulinism, respectively[92]. In addition, the common Kir6.2 variant, E23K (encoded by c.67G>A, rs5219) in *KCNJ11*, has been well characterized as a type 2 diabetes-associated risk factor. It has also been reported to be overrepresented in human congestive heart failure[60], and associated with adverse subclinical myocardial remodeling among subjects with hypertension in a cross-sectional community-based cohort study, as well as abnormal cardiopulmonary stress test results in heart failure patients, and also occurrence of ventricular arrhythmias (VAs) in dilated cardiomyopathy patients[60, 61, 63]. Other studies have also indicated an association of E23K, A190A (c.570C>T, rs5218) and I337V(c.1009G>A) variants in the *KCNJ11* gene to hypertension susceptibility, especially in the Asian population[56–59, 62]. In one animal study, it was suggested that the E23K variant increases susceptibility to ventricular arrhythmia in response to ischemia in rats[93]. However, another study that aimed to evaluate the clinical impact of single-nucleotide polymorphisms in *KCNJ11* found the SNPs - rs5215_GG, rs5218_CT, and rs5219_AA for *KCNJ11* – did not affect susceptibility to ischemic heart disease (IHD) or coronary microvascular dysfunction[94]. More recently, the I337V and E23K variants were reported to be associated with left ventricular mass and left ventricular end-diastolic volume in heart failure patients[64], but direct causation remains unconfirmed.

Animal models with transgenic expression of ATP-insensitive Kir6.2 subunits are strikingly insensitive to any potential overactivity[95]. Genetic ablation of the Kir6.2 subunit in mice ($Kir6.2^{-/-}$) results in poor cardiac functional recovery after exercise[96] or IR injury[97], but does not alter cardiac function under basal aerobic conditions[98]. However, another study showed increased basal AMPK activity, fatty acid oxidation, and glycogen storage, as well as decreased glycolysis and reduced mitochondrial density in $Kir6.2^{-/-}$ hearts. This suggests that K_{ATP} channels may somehow regulate cardiac metabolism[99]. Further studies might consider whether genetic variations in *KCNJ11* may help to provide biomarkers of relevance to various cardiac problems.

Kir6.1

Kir6.1 is the main channel forming subunit of K_{ATP} channels in smooth muscle. Disruption of *KCNJ8* in mouse has been reported to cause ST segment elevation followed by atrioventricular block and early sudden cardiac death (SCD) because of coronary spasm[100]. Other studies do not report sudden death, but both Kir6.1$^{-/-}$ and mice with specific deletion Kir6.1 in smooth muscle do show elevated blood pressure[101, 102]. Two *KCNJ8* mutations, an in-frame deletion (p.E332del, c.del995–997 GAA) and a missense mutation (p.V346I, c. 1036 G>A), both localized to the Kir6.1 C-terminus, were identified in sudden infant death syndrome (SIDS) patients, and demonstrated to be LOF mutations[67].

Conversely, transgenic expression of gain-of-function Kir6.1 subunits in smooth muscle leads to hypotension[102], consistent with a major role in BP control. Kir6.1 may also be expressed in the cardiac conduction system[27]. Transgenic mice expressing Kir6.1 subunits in cardiomyocytes revealed AV nodal conduction abnormalities and junctional rhythm[103], and a recent study reported that mice with Kir6.1 specifically knocked out of conducting tissues display decreased heart rate and sinus arrest[104]. Several mutations in Kir6.1 subunits have been reported in human patients with rhythm disturbances. A missense variant in exon 3 (p. S422L, c.1265C>T) of the *KCNJ8* gene was first reported in a patient with recurrent ventricular fibrillation secondary to early repolarization syndrome[68]. Subsequent studies indicated a higher K_{ATP} current in cells heterologously expressing Kir6.1/S422L+SUR2A channel in whole-cell patch-clamp studies, as well as reduced ATP sensitivity in inside-out patch clamp experiments[69–71]. However, causal association to the J-wave syndrome has been questioned by additional studies that (1) revealed the S422L variant to be a common occurrence in Ashkenazim[105], (2) reported no effect on K_{ATP} channel activity or ATP-sensitivity[66], and (3) show lack of any effects on the ECG of mice transgenically expressing the S422L variant in cardiac myocytes[106]. Most significantly, two novel *KCNJ8* mutations have now been identified in patients with Cantu syndrome (see SUR2, below). A Cantu syndrome patient with the V65M (c. 193 G>A) variant in *KCNJ8* had striking vascular abnormalities, including a dilated aortic root, very dilated and tortuous cerebral arteries and veins[65], but no evidence of J-wave syndrome. Another Cantu patient with a missense mutation encoding Kir6.1[p.C176S, c.526 T>A], exhibited all clinical features of Cantu syndrome including cardiomegaly. Both of these two mutations were confirmed as gain of function mutations[66, 107]. ‘Cantu mice’, in which the Kir6.1[V65M] mutation was introduced to the endogenous gene locus using CRISPR/Cas9, also displayed the same phenotypes as Cantu patients, including dilated vessels, low blood pressure and cardiac hypertrophy[108]. These results, together with the findings of SUR2 association with Cantu syndrome (below) definitively tie this channel to a defined cardiovascular pathology.

SUR1

SUR1 is the predominant regulatory subunit of K_{ATP} channels in pancreatic β-cells as well as in mouse atria. Gain- and loss-of-function mutations in *ABCC8* cause neonatal diabetes and congenital hyperinsulinism, respectively[92]. Recently several clinical studies have reported *ABCC8* mutations to also be associated with cardiovascular diseases, including coronary heart disease, pulmonary arterial hypertension and atrial fibrillation[72–74]. The

SUR1 (p. A1369S, c.4105G>T) missense variant, an inherited haplotype with the Kir6.2[E23K] variant (above), which is strongly associated with risk of type 2 diabetes, has been reported to be favorable for body fat distribution and reduced risk of coronary heart disease, based on analysis of data from the UK Biobank[74]. More recently, Bohnen et al[72] reported twelve SUR1 coding variants (p.R958H, p.N72D, p.E186D, p.A240T, p.E791Q, c.T2694+2G, p.G111R, p.L135V, p.D813N, p.D1472N, p.T229I, p.R1314H) in a cohort study of pulmonary arterial hypertension. Patch-clamp analysis of recombinant channels revealed these to be consistently loss of function mutations, which could be pharmacologically rescued by the SUR1 activator diazoxide. Some of these variants have previously also been reported in association with hyperinsulinism, a disease that is definitively causally associated with loss of SUR1 or Kir6.2-dependent channel activity[18]. The N72D, L135V, D813N, R1314H variants were also associated with congenital heart disease, large atrial septal defect, first-degree heart block, atrial flutter and ventricular septal defect, respectively[72]. Coincidentally, a separate study reported the same SUR1 R1314H mutation in a cohort study of atrial fibrillation at almost the same time[73], suggesting that SUR1 loss of function may also be related to atrial fibrillation. Given that K_{ATP} channels in both human heart and blood vessels are predominantly composed of SUR2, but not SUR1, the question then arises as to how these SUR1 variants are associated with cardiovascular diseases? Potentially, the precise subunit composition in any given cell type may, as suggested above, be more subtly variable, or more labile, than is currently perceived, making it critical to focus on precise subunit distributions. No basal cardiovascular problems have been reported to date in animal models with SUR1 deletion or mutation, although SUR1 knockout ($SUR1^{-/-}$) mice exhibited reduced infarct size and preservation of left ventricular function in myocardial ischemia/reperfusion injury[109]. These results are not trivially consistent with the findings in Kir6.2 knockout ($Kir6.2^{-/-}$) mice, which showed enhanced ischemic damage function in myocardial ischemia/reperfusion injury[97, 110], which may imply that these cardiovascular outcomes may be dependent on SUR1 function in other tissues, emphasizing the need for investigation of cell- and tissue-specific elimination or expression of SUR1 subunits before and after ischemic events.

On the other hand, overexpression of SUR1 subunits in mouse heart does not result in overt cardiac phenotypes other than PR prolongation, unless Kir6.2 subunits are also overexpressed[111]. It should be noted that several SUR1 splice variants are expressed in the heart, but their contributions to cardiovascular function have not been explored[112–114]. A recent study described the presence of SUR1 in both atrial and ventricle, but although SUR1-containing K_{ATP} channels constitutively reach the cell surface in atrial myocytes, they are normally stalled in the Golgi of ventricular myocytes, until deployed to the cell surface under sustained β-adrenergic stimulation[115]. Such findings lend further support for the need to carefully define K_{ATP} channel subunit composition in specific cardiovascular cell types under different physiological and pathological conditions.

SUR2

SUR2 is the major regulatory sulfonylurea receptor of K_{ATP} channel in both hearts and vessels. There have been many isolated reports of mutations associated with human cardiovascular pathology. A heterozygous frameshift SUR2A mutation L1524fs(c.4570–

4572 delta InsAAAT) and heterozygous missense SUR2A mutation A1513T(c.4537G>A) were identified in two patients in a cohort of 323 individuals with idiopathic dilated cardiomyopathy. Both individuals had severely dilated hearts with compromised contractile function and rhythm disturbances. Both mutations are located in exon 38 of *ABCC9*, which encodes the C-terminal domain of SUR2A and both were reported to reduce ATP hydrolytic activity, thus leading to loss-of-K_{ATP} channel function, and enhanced susceptibility to dilated cardiomyopathy[89]. Another *ABCC9* missense mutation (c.4640C>T), also resulting in a coding mutation (T1547I) in the C-terminal domain of SUR2A, was shown to result in attenuated channel activation by MgADP and associated with predisposition to adrenergic AF originating from the vein of Marshall[90]. In addition, a missense mutation (p.Met1198Ile, c.3594G>A) in *ABCC9* was detected in one Left Ventricular Non-Compaction Cardiomyopathy (LVNC) patient[85]. In a cohort study of 144 victims of sudden unexplained nocturnal death syndrome (SUNDS), a SUNDS victim with AF hosted a rare *ABCC9* variant(p.Arg1197Cys, c.3589C>T)[84]. The functional characteristics of these two mutations have not been determined.

$SUR2^{-/-}$ mice exhibited similar phenotypes to Kir6.1 $^{-/-}$ mice, including repeated episodes of coronary artery vasospasm, elevated resting blood pressures and sudden death[116]. It was initially assumed that the presence of vasospasm and hypertension in $SUR2^{-/-}$ mice arose from the critical role of K_{ATP} channels in VSM cell function. However, subsequent studies provided conflicting results. In one[117], SUR2 overexpression specifically in vascular smooth muscle cells, failed to rescue the SUR2 null phenotype, suggesting that spontaneous coronary vasospasm and sudden death in SUR2 null mice arose from a coronary artery vascular smooth muscle– extrinsic process. In another, overexpression of SUR2A generated a cardiac phenotype resistant to ischemia[118]. However, it was found that SUR2 null mice were also resistant to acute cardiovascular stress and exhibited reduced infarct size and improved cardiac function[119]. Clearly, further studies are required to fully explain SUR2 loss-of-function phenotypes.

The above mutations were all putative loss-of-function mutations, but a potential gain-of-function *ABCC9* missense mutation, Val734Ile(c.2200G>A) in exon 17 which encodes a 13 amino acids peptide located in the first nucleotide binding fold (NBD1) of SUR2 was detected in one precocious myocardial infarction (MI) patient, with which the individuals have a 6.40-fold risk of suffering MI before the age of 60 years as compared to healthy controls[77]. This mutation was also identified in a further eleven patients diagnosed with acute myocardial infarction (AMI)[78]. In this study, the sensitivity to MgATP was assessed in cell lines expressing Kir6.2 and either SUR2x or SUR2x-V734I. It was found that mutant Kir6.2/SUR2B channels, but not Kir6.2/SUR2A or Kir6.1/SUR2B channels, had reduced sensitivity to MgATP inhibition, suggestive of K_{ATP} overactivity in the endothelial cell subunit combination. In addition, the V734I variant was reported as a gain-of-function mutation in four early repolarization syndrome (ERS) patients with bradycardia[79] and in a patient with a permanent pacemaker who presented with isolated cardiac conduction disease[80], perhaps consistent with K_{ATP} channels playing a unique role in pacemaker and conduction system cells.

In many of the above cases, phenotypes are subtle, or associations of specific phenotypes with the *ABCC9* gene have not been replicated. However, this is not the case for Cantu syndrome, a multi-organ disease characterized by congenital hypertrichosis, distinctive facial features, osteochondrodysplasia and cardiac defects including cardiomegaly and dilated vessels. Cantu syndrome, was first reported in 1982 by Cantu[120], and since the first genetic association of Cantu syndrome with *ABCC9* in 2012[75, 76], more than 15 mutation sites in the gene have been reported from more than 100 patients[75, 76, 81–83, 86–88, 121, 122]. All identified mutations lead to GOF in K_{ATP} channel activity in recombinant cell experiments[66, 107, 123]. The mechanisms underlying these GOF mutations include decreased ATP inhibition and enhanced MgADP activation[107, 123]. A clear picture has emerged for mice carrying Cantu Syndrome SUR2 gain-of-function mutations introduced to the endogenous locus by CRISPR/Cas9 mutagenesis[108]. As with 'V69M Cantu mice' (above), introduction of the A478V mutation into the equivalent mouse SUR2 locus using CRISPR/Cas9, SUR2[A478V], results SUR2[A478V] 'Cantu mice' that display the same phenotypes as Cantu patients, including dilated vessels, low blood pressure and cardiac hypertrophy[108108], definitively tying Kir6.1/SUR2-dependent K_{ATP} channels to a defined cardiovascular pathology. These 'Cantu mice' now make available appropriate models for mechanism study and treatment exploration in Cantu syndrome.

Summary

Over the last 30 years, much effort has been expended to investigate the role of K_{ATP} channels in cardiovascular tissues. Multiple lines of evidence, from detection of K_{ATP} channel variants in patients, and from animal models, indicate that the K_{ATP} channel is causally involved in cardiovascular pathologies, although a note of caution should be sounded regarding the relevance of all reported associations, and to caution against over-interpretation of human variants. The NIH Clinical Genome Resource Consortium (https://www.clinicalgenome.org/curation-activities/gene-disease-validity/educational-and-training-materials/standard-operating-procedures/) has developed specific guidelines for variant interpretation which currently conservatively only considers *ABCC8* to be associated with hyperinsulinism, and *ABCC9* to be associated with Cantu Syndrome. However, the evidence that *ABCC8* is also associated with neonatal diabetes is very strong, and it is to be expected that additional associations will gradually be validated. In addition, the possibility that interaction of certain variants with other (seemingly benign) variants in other genes may contribute to disease progression, should be borne in mind. Even for variants within K_{ATP} channel genes, additional complexities may arise from the potentially complex subunit make-up of what should be considered a family of ion channels[124], leading to distinct K_{ATP} channel properties and regulatory features in different organs and tissues, as well as potentially in subcellular organelles.

Although there is a rich available pharmacology of K_{ATP} channels, drug therapy as well as gene therapy for K_{ATP} channel mutant diseases remains unexplored. In future, animal models carrying different mutations identified in patients, as well as cell- and tissue-specific expression of K_{ATP} channel subunits, and isogenic human induced pluripotent stem cells should provide powerful tools with which to recapitulate and seek explanations for

phenotypes observed in patients, and thereby advance our understanding of pathogenesis as well as pharmacotherapy for such diseases.

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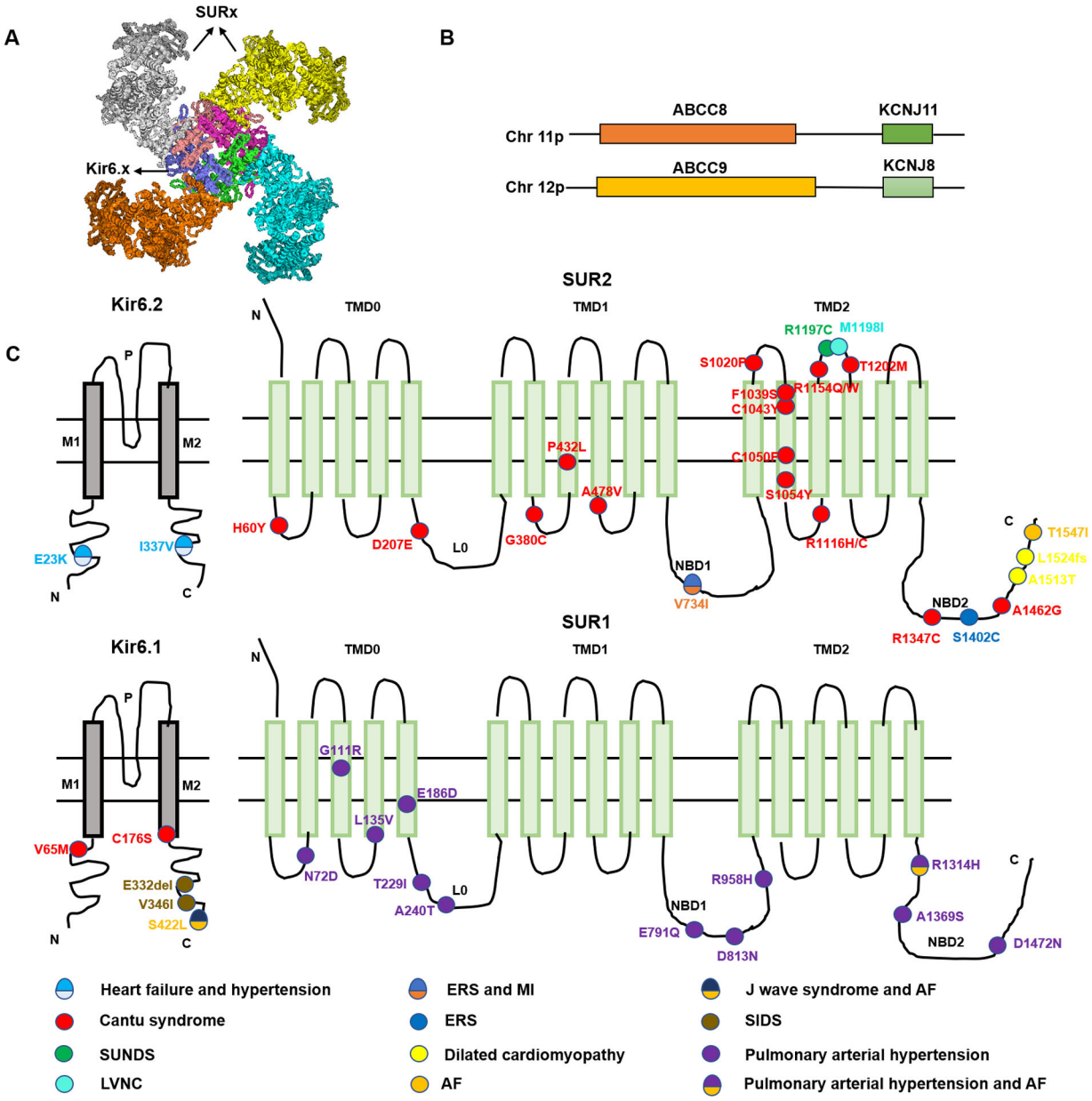

Figure 1:

K_{ATP} channel structure and K_{ATP} channel mutations associated with cardiovascular diseases. (A) K_{ATP} channels are octameric complexes of four Kir6 subunits and four SUR subunits. (B) Human SUR and Kir6 gene structures. *ABCC8* and *KCNJ11* are next to each other and located on human chromosome 11p15.1, *ABCC9* and *KCNJ8* are also adjacent to each other, located on human chromosome 12p12.1. (C) K_{ATP} channel subunit mutations associated with cardiovascular pathologies. P - p-helix, M1, M2 - transmembrane helices , TMD - transmembrane domain, L0 - intracellular linker domain, NBD1 - first nucleotide binding domain, NBD2 - second nucleotide binding domain.

Table 1

: Cardiovascular pathologies associated with K_{ATP} channel variants

Gene	Nucleotide change	Protein change	Mutation feature	Clinical Condition	References
KCNJ11	**c.67 G>A**	**E23K**	**GOF**	**Heart failure, hypertension, ventricular arrhythmias**	56–63
	c.570 C>T	A190A	GOF	Hypertension	56, 58, 59
	c.1009 G>A	I337V	GOF	Heart failure, hypertension	56, 64
KCNJ8	**c.193 G>A**	**V65M**	**GOF**	**Cantu syndrome**	65
	c.526 T>A	**C176S**	**GOF**	**Cantu syndrome**	66
	c.del995–997 GAA	**E332del**	**LOF**	**sudden infant death syndrome**	67
	c.1036 G>A	**V346I**	**LOF**	**sudden infant death syndrome**	67
	c.1265C>T	*S422L*	*GOF*	*J wave syndrome, atrial fibrillation*	68–71
ABCC8	**c.A214G**	**N72D**	**LOF**	**Pulmonary arterial hypertension, Atrial septal defect**	72
	c.G331A	**G111R**	**LOF**	**Pulmonary arterial hypertension**	72
	c.C403G	**L135V**	**LOF**	**Pulmonary arterial hypertension, Heart block**	72
	c.G558T	**E186D**	**LOF**	**Pulmonary arterial hypertension**	72
	c.C686T	**T229I**	**LOF**	**Pulmonary arterial hypertension**	72
	c.G718A	**A240T**	**LOF**	**Pulmonary arterial hypertension**	72
	c.G2371C	**E791Q**	**LOF**	**Pulmonary arterial hypertension**	72
	c.G2437A	**E813N**	**LOF**	**Pulmonary arterial hypertension, Atrial fibrillation**	72
	c.G2873A	**R958H**	**LOF**	**Pulmonary arterial hypertension**	72
	c.G3941A	**R1314H**	**LOF**	**Pulmonary arterial hypertension,** Ventricular septal defect, Atrial fibrillation	72, 73
	c.4105G>T	A1369S	LOF	Reduced risk of coronary heart disease	74
	c.G4414A	**D1472N**	**LOF**	**Pulmonary arterial hypertension**	72
ABCC9	**c.178C>T**	**H60Y**	**GOF**	**Cantu syndrome**	75
	c.621C>A	**D207E**	**GOF**	**Cantu syndrome**	75
	c.1138G>T	**G380C**	**GOF**	**Cantu syndrome**	75
	c.1295C>T	**P432L**	**GOF**	**Cantu syndrome**	75
	c.1433C>T	**A478V**	**GOF**	**Cantu syndrome**	76
	c.2200G>A	**V734I**	**GOF**	**myocardial infarction, Bradycardia, ICCD early repolarization syndrome,**	77–80
	c.3058T>C	**S1020P**	**GOF**	**Cantu syndrome**	75
	c.3116T>C	**F1039S**	**GOF**	**Cantu syndrome**	75
	c.3128G>A	**C1043Y**	**GOF**	**Cantu syndrome**	76
		C1050F	**GOF**	**Cantu syndrome**	81
	c.3161C>A	**S1054Y**	**GOF**	**Cantu syndrome**	75
	c.3347G>A	**R1116H**	**GOF**	**Cantu syndrome**	75

Gene	Nucleotide change	Protein change	Mutation feature	Clinical Condition	References
	c.3346C>T	**R1116C**	**GOF**	**Cantu syndrome**	75
	c.3460C>T	**R1154W**	**GOF**	**Cantu syndrome**	75, 76, 82, 83
	c.3461G>A	**R1154Q**	**GOF**	**Cantu syndrome**	75, 76, 83
	c.3589C>T	R1197C	Uncertain	SUNDS	84
	c.3594G>A	M1198I	Uncertain	LVNC	85
	c.3605C>T	**T1202M**	**GOF**	**Cantu syndrome**	86
	c.4039 C > T	**R1347C**	**GOF**	**Cantu syndrome**	87
	c.4205C>G	S1402C	GOF	early repolarization syndrome	79
	c.4385C>G	**A1462G**	**GOF**	**Cantu syndrome**	88
	c.4537G>A	**A1513T**	**LOF**	**Dilated cardiomyopathy**	89
	4570–4572 delta InsAAAT	**L1524fs**	**LOF**	**Dilated cardiomyopathy**	89
	c.4640C>T	**T1547I**	**LOF**	**Atrial fibrillation**	90

Bold font: Causality implied/confirmed by functional analyses

Normal font: Association unchallenged, but lacking functional analyses

Italic font: Association challenged by additional studies