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ATP-sensitive Potassium Currents in Heart Disease and Cardioprotection

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K_{ATP} and cardiovascular disease: The theoretical case

Cardiovascular K_{ATP} and cardioprotection

Since their discovery in cardiac myocytes over 30 years ago, it has been recognized that K_{ATP} channels provide a very large potential ionic conductance in the surface membranes of all muscle cells. Under normal metabolic conditions, cardiac K_{ATP} channels are predominantly closed, and they do not significantly contribute to cell excitability. However, these channels can open when exposed to a severe metabolic stress such as anoxia, metabolic inhibition or ischemia. By shortening the action potential, K_{ATP} activation will reduce Ca^{2+} entry and inhibit contractility[1], thereby reducing energy consumption, potentially protecting the cell. Such a preservation 'strategy' is naturally self-limiting - if too many myocytes stop contracting, the heart will stop pumping and the animal will die, but it has always been a reasonable notion that temporary protection of a small number of cells, or region of the heart, against the damage of Ca^{2+}-overload during ischemia, is a likely beneficial consequence of K_{ATP} channel activation.

In the vasculature, activation of K_{ATP} channels will hyperpolarize the membrane potential, leading to inhibition of voltage-sensitive Ca^{2+}-channels and lowering of intracellular Ca^{2+}, resulting in vasodilation[2].

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Disclosures

None

Cardiac K_{ATP} channels and arrhythmia

Opening of cardiac K_{ATP} channels both shortens the action potential and reduces the refractory period, such that channel activation could establish an arrhythmogenic substrate supporting reentry. Hence inhibition of K_{ATP} could be a way to stop or even prevent arrhythmias. Because K_{ATP} channels tend to open only when cell metabolism is inhibited, any agents that inhibits K_{ATP} activity should specifically target channels only during ischemia, leaving non-ischemic myocardium unaffected. On the other hand activation of cardiac K_{ATP} channels has consistently been shown to protect the heart from damage during ischemia, by limiting Ca^{2+} entry.

The molecular basis of K_{ATP} channels

K_{ATP} channels are heterooctameric complexes of 4 pore-forming Kir6 channel-forming subunits, each associated with one regulatory SUR subunit. Two Kir6-encoding genes, *KCNJ8* (Kir6.1) and *KCNJ11* (Kir6.2)[3,4], and two SUR genes, ABCC8 (SUR1) and ABCC9 (SUR2)[4–6] encode mammalian K_{ATP} subunits, but alternative RNA splicing can give rise to multiple SUR protein variants (e.g. SUR2A and SUR2B) that confer distinct physiological and pharmacological properties on the channel complex[7,8]. Interestingly, the genes for Kir6.2 and SUR1 are located next to each other on human chromosome 11p15.1[4] suggesting an as yet unrecognized co-regulation at the gene level. In addition, the genes for Kir6.1 and SUR2 are also adjacent to one another on chromosome 12p12.1[6,9], implicating an evolutionary duplication. In heterologous expression, both Kir6.2 and SUR1 subunits co-assemble in a 4:4 stoichiometry[4] to generate the functional K_{ATP} channel[10–12]. Similarly, biochemical studies confirm that the SUR2 protein variants, SUR2A and SUR2B, also coassemble with Kir6 subunits[3,13–15], presumably in a similar octameric arrangement.

Crystallographic studies of bacterial and eukaryotic Kir channels[16,17][new] demonstrate a conserved architecture of Kir channels with two transmembrane helices (M1, M2) bridged by an extracellular loop that generates the narrow portion of the pore and controls ion selectivity. As with other ABCC proteins, SURs contain two six-helix transmembrane domains, TMD1 and TMD2 and two cytoplasmic nucleotide binding folds (NBFs), but also contain an additional N-terminal TMD0 domain that is critical for trafficking and gating of the channel complex[18]. The details of the physical connection between Kir6 and SUR subunits remains unknown, but electron micrography and intersubunit FRET studies of complete K_{ATP} complexes suggest an intimate packing of 4 SUR and 4 Kir6.x subunits[19,20].

The key regulatory features of K_{ATP} channels are rapid and reversible closure by cytoplasmic ATP, and activation by nucleotide tri- and diphosphates[21]. In the absence of other nucleotides, the free [ATP] that causes half-maximal channel inhibition is in the micromolar range. Since intracellular ATP concentrations are in the low millimolar range and change little under physiologic conditions, [ATP] is probably always sufficient to almost fully inhibit channel activity. Channel activation then arises from the activating effects of Mg-nucleotides, particularly MgADP, on the SUR subunit[22]. Nucleotide regulation is probably the key molecular regulator of K_{ATP} channel activities, although other second messenger systems and regulators[23] may be involved in control of channel activity and channel-dependent pathologies.

Cardiovascular tissue distribution of K_{ATP} channel subunits

From studies in heterologous expression systems where SUR and Kir6 subunit expression can be controlled, it is apparent that all possible subunit combinations can and do occur. Post-translational quality control mechanisms have been described that ensure the appropriate octameric composition of the channel[24,25], yet there is no evidence that these mechanisms discriminate between subunits. There have been relatively few studies to examine the transcriptional regulation of K_{ATP} subunits and still little is known about what specific factors might control K_{ATP} structure, although members of the forkhead transcription factor family and HIF-1α have been shown to regulate the expression of some subunits (as well as metabolic enzymes)[26,27].

Kir6.1 and Kir6.2, as well as SUR2 and SUR1, are all expressed in the heart[3,28–30]. There is now good evidence that in mouse hearts, SUR1 and Kir6.2 are major constituents of the atrial myocyte sarcolemmal K_{ATP}, whereas SUR2A and Kir6.2 generate ventricular K_{ATP}[31,32]. However, in hearts of larger animals, including humans, both SUR1 and SUR2A subunits probably contribute to sarcolemmal channels in both atrial and ventricular myocytes[33] (Fig. 1). The situation may be more complex in critical subregions of the heart, including nodal and conduction cells. K_{ATP} channel currents have been detected throughout the pacemaking and conduction systems[34–36]. Low K_{ATP} single channel conductances in rabbit SA node cells and mouse conduction cells[34] suggests a role for Kir6.1 in generating the channel pore in these tissues, yet sarcolemmal K_{ATP} is abolished in Kir6.2$^{-/-}$ SA node cells[37] indicating a necessary requirement for Kir6.2. The identity of the SUR component of K_{ATP} in conducting and pacemaker tissues is unknown, although K_{ATP} channels in nodal cells do respond to the relatively SUR2-specific openers cromakalim and pinacidil, suggesting a major role for SUR2[34–36].

K_{ATP} channel density is relatively low in vascular smooth muscle (VSM) compared to cardiac myocytes[38,39] and the biophysical and pharmacological properties are quite variable, reflecting variable expression of K_{ATP} subtypes between vascular beds[40–47]. There is considerable variation in reported single channel conductances[43,44,48–52], although low-conductance channels (unitary conductances from 20–50 pS) may represent the predominant K_{ATP} channel subtype, with a more limited distribution of medium- and high conductance K_{ATP} channels (50–70 pS and >200 pS, respectively)[53]. Importantly, and unlike classic K_{ATP} channels of the heart[3,54] or pancreas[4,55], the predominant VSM K_{ATP} conductances are inactive in isolated membrane patches, and require nucleotide diphosphates (ADP, UDP, GDP) in the presence of Mg^{2+} to open, leading to their functional designation as 'nucleotide-dependent' K^+-channels, or K_{NDP} channels[46,56,57]. Heterologously expressed Kir6.1/SUR2B channels recapitulate many of these biophysical properties of native VSM K_{ATP}/K_{NDP}[9,13,58–61]. Thus the Kir6.1/SUR2B channel may represent the predominant VSM K_{ATP}, but other subtypes are also likely to be expressed in specific vascular beds, separately or in combination with Kir6.1/SUR2B subunits[56] (Fig. 1).

Finally, it is important to note that K_{ATP} channels are also prominent in lymphatic muscle. While the classical understanding was that fluid flow in the lymphatic system was passive, it is now clear that lymphatic vessels are lined by smooth muscle. Contractility of these vessels

is clearly sensitive to K_{ATP} activation[62], with a pharmacological profile that is consistent with the major subunits expressed in lymphatic muscle being Kir6.1 and SUR2[63].

Cardiovascular disease and K_{ATP} mutations

Predictions from genetically modified animals

Murine knockout models of each of the four K_{ATP} channel genes have been generated and extensively analyzed. Knockout of Kir6.2 or SUR1 results in a loss of glucose-dependent insulin secretion, modeling features of hyperinsulinism in humans[64,65]. Conversely, knockout of Kir6.1 or SUR2 leads to a vascular hypercontractility phenotype[30,66]. The key features are baseline hypertension, coronary artery vasospasm and sudden cardiac death. $SUR2^{-/-}$ mice treated with the Ca^{2+} channel blocker nifedipine exhibit a reduction in coronary artery vasospasm, implicating abnormally elevated $[Ca^{2+}]_i$ due to loss of hyperpolarizing K_{ATP} current as causal in the hypercontractility[66]. Collectively, these K_{ATP}-null mice recapitulate clinical features of the human disorder of Prinzmetal (or variant) angina, but several studies have failed to demonstrate any association of human coronary vasospasm or hypertension with LOF mutations in Kir6.1 or SUR2[67,68], even though linkage analysis indicates that there are associated genes within the same locus as Kir6.1 and SUR2[69].

We have extensively explored the potential for K_{ATP} gain-of-function (GOF) action in the heart and vasculature by transgenic introduction of mutant Kir6.1 and Kir6.2 channels that are very insensitive to closure by ATP[70–72]. Under aMHC control, GOF subunits expressed in the heart generate channels that still remain closed under all but extreme circumstances, and cause little overt malfunction, with no decrease in cardiac action potential duration, nor decrease in contractility[70,72]. Curiously, we find that in ventricular myocytes from these animals there is actually dramatically enhanced Ca^{2+} current,[73] which may be a compensatory response to an initial or local action potential shortening. These studies also reveal that overexpressing the SUR1 isoform the myocardium has an effect to prolong the PR interval[74], and that when Kir6.2 GOF is expressed together with SUR1, second and third degree AV block, progressing to ventricular and supra-ventricular arrhythmias and death[74,75].

While the phenotype of animals expressing K_{ATP} GOF in the heart is complex, expression of Kir6.1 GOF mutants in smooth muscle (under smooth muscle HC promoter control) leads to enhanced K_{ATP} activity in vascular smooth muscle, and a clear reduction of systolic and diastolic blood pressures[71], paralleling the effects of KCOs in human hypertensive patients.

K_{ATP}-associated human disease

Thus animal studies have provided a clear prediction of hypertensive or hypotensive consequences for K_{ATP} LOF or GOF, respectively, in smooth muscle, but rather complex and contradictory predictions regarding K_{ATP} mutations in the heart. This may help explain why, until recently, there has been little evidence for human cardiovascular disease resulting from K_{ATP} gene mutations (Table 1). Gain- and loss-of function mutations in *KCNJ11* (Kir6.2) and *ABCC8* (SUR1), which encode the predominant K_{ATP} channel subunits in pancreatic β-

cells and in neurons[76], are now well understood to underlie neonatal diabetes and congenital hyperinsulinism, respectively[77]. However, and despite evidence for expression of these subunits in cardiac myocytes, there is no published evidence for any cardiovascular problems in these patients.

Sequence analysis of DNA from necropsy tissue on sudden infant death syndrome (SIDS) cases identified coding mutations in *KCNJ8* (Kir6.1), an in-frame deletion (E332del) and a missense mutation (V346I), both in the distal C-terminus of Kir6.1. Reduced channel activity was reported from expressed mutant channels, leading the authors to conclude that loss-of-function mutations in Kir6.1may be one cause of SIDS[78], through as yet unexplained mechanisms. There have also been two reports of SUR2 loss of function mutations leading to cardiac disease[79,80]. In each case, the mutations were identified in the C-terminal exons and would therefore lead to a disruption of the second nucleotide binding fold of SUR2A, and hence reduction of nucleotide stimulation of channel activity, without affecting SUR2B. In the first report, the single patient with the mutation presented with long-standing atrial fibrillation originating in the vein of Marshall, with normal cardiac morphology and contractile features[80]. In the second report, two individuals with two distinct mutations presented with heart failure due to idiopathic dilated cardiomyopathy[79]. There have been no subsequent reports of similar genetic defects, and further evidence for causal association of Kir6.1 or SUR2 LOF mutations with disease is lacking.

Several studies reported a single *KCNJ8* mutation (encoding S422L in Kir6.1) protein to be associated with the ‘J-wave’ phenomenon, characterized by abnormalities in the J-point of the ECG and early repolarization syndrome (ERS). First reported by Haissaguerre et al[81], subsequent studies have reported association of this variant with atrial fibrillation (AF)[82], as well as additional Brugada syndrome and early repolarization syndrome patients[83,84]. However, a recent study has reported that this variant is relatively common in individuals of Ashkenazi Jewish origin and it remains unclear whether the reported associations are causal[85].

More recently, it has become clear that mutations in both *ABCC9* (encoding SUR1) and *KCNJ8* (Kir6.1) are associated with Cantu syndrome (CS)[86]. (MIM 239850), or hypertrichosis-osteochondrodysplasia-cardiomegaly syndrome, a distinctive multi-organ disease[87–90]. In many cases, the mutations are *de novo*, but autosomal dominant inheritance also occurs[91]. The conclusion that these mutations all lead to gain-of K_{ATP} channel function has been confirmed in several studies[87,89,92], which demonstrate reduced sensitivity to ATP inhibition or enhanced activation by MgADP in each case.

Cantu Syndrome: Multiple tissue symptoms

Perhaps most striking about this recent discovery is that so many of the CS features are not trivially predictable, and in the heart, the resultant phenotypes are even counter to any naïve predictions. Since first being recognized as a unique syndrome in 1982[86], a constellation of features has been described in CS patients[91,93–100] (Table 2). Multiple cardiovascular features include cardiac enlargement, concentric hypertrophy of the ventricles and pericardial effusion. Some patients have required pericardiocentesis and even pericardial stripping to prevent reaccumulation of the pericardial effusion. Multiple vascular

consequences include pulmonary hypertension secondary to partial pulmonary venous obstruction has been reported, associated with severe mitral valve regurgitation that spontaneously resolved[95]. A significant number of patients have had patent ductus arteriosus (PDA) requiring surgical closure, as well as bicuspid aortic valves with and without stenosis. Lymphedema involving the lower extremities may develop over time, and in one patient, lymphangiogram demonstrated dilated lymphatic vessels in the legs with delayed lymphatic drainage[101]. Interestingly, diazoxide, minoxidil and other related K_{ATP} channel openers that are used to treat severe refractory hypertension can also result in similar features as unexplained side effects, including hypertrichosis, pericardial effusion, edema, and even coarsening of the facial featuresl[102,103]. Teratogenic effects of minoxidil, including marked hypertrichosis, dysmorphic facial features, low blood pressure, and transposition of the great vessels and pulmonary bicuspid valvular stenosis, have been reported in the offspring of minoxidil-treated mothers[104,105]. These observations first led to the suggestion that CS might result from gain-of-function (GOF) in K^+ channel activity[91].

Normally, abrupt increase in oxygen tension and falling PGE2 and PGI2 levels lead to inhibition of voltage-gated K channels and contraction of smooth muscle fibers in the ductus arteriosus, resulting in wall thickening and lumen obliteration after birth. Persistence of the PDA in Cantu syndrome patients may thus be readily explained as a consequence of maintained vessel dilation due to K_{ATP} overactivity. More generally, mechanisms of persistent PDA are not clear[106], but the enhancement of a K current in smooth muscle presents an obvious potential explanation in Cantu syndrome patients. Altered vascular tone may also underlie pericardial effusion, but the reason for cardiomegaly is not obvious. Cardiomegaly reported in most cases of Cantu Syndrome is due to increased myocardial mass (hypertrophy) with larger cardiac chambers but with normal systolic function, and this does not fit the diagnostic criteria of dilated or hypertrophic cardiomyopathy[107], and may be a secondary response to reduced vascular tone[108]. Similarly, the reason for osteochondrodysplasia and facial dysmorphology is not obvious, and the mechanism by which minoxidil causes hair growth has remained controversial[109]. While CS patients show no evidence of orthostatic blood pressure problems, systematic analysis of patient blood pressures does show that these are physiologically below the norm for age (G.K. Singh, M.D. Levin, D.K. Grange, C,G. Nichols, unpublished). Through opening vascular K channels and dilation of blood vessels, the supply of oxygen, blood and nutrients to the hair follicle may be increased, causing follicles in the telogen phase to shed and be replaced by new thicker hairs in a new anagen phase. However, there is also evidence that SUR2 isoforms are present in follicular dermal papillae [110] and while the new realization definitively ties the hair growth to an action on K_{ATP} channels, it does not immediately prove where the action is.

K_{ATP} manipulation in heart disease

Perhaps no other channels in the heart carries more potential and promise than K_{ATP} channels for breaking the link between myocardial ischemia and cardiac arrhythmia. Since the first report detailing the presence of K_{ATP} in cardiac myocytes was published[111], the possibility that this channel 1) determines the electrical behavior of the heart during ischemia and 2) might protect the heart has been well recognized. Nevertheless, efforts to

exploit the "cardiac K_{ATP}" channel to ameliorate arrhythmia and moderate damage of the myocardium during ischemia have yet to mature.

As genetic variation in humans, and manipulation in animals, has made clear, cardiac sarcolemmal K_{ATP} channels are normally predominantly closed in physiological conditions, and application of channel-blocking sulfonylureas generally has little or no effect on the ventricular action potential[112]. Because K_{ATP} channels in different regions of the heart have different composition, it is likely that they will be operative under different conditions *in vivo*. For example, shortening of the Purkinje action potential may be greater than that of the ventricular action potential at the same ATP/ADP ratio, given that SUR2B and Kir6.1 may be prominent in these cells[113]. K_{ATP} channels composed of SUR1 and Kir6.2, as in the mouse atrium[32], will have still different activating conditions.

When metabolism is inhibited, the action potential can shorten markedly and contraction can be inhibited as a result of K_{ATP} activation[1,114,115]. K_{ATP} activation during ischemia is likely to be cardioprotective, since reduction of APD and contraction may preserve ATP stores that would otherwise be consumed during the contractile cycle. In support of this idea, treatment with the K_{ATP} opener pinacidil during ischemia increases cellular ATP and energy stored as creatine phosphate[116]. AP shortening is absent in Kir6.2$^{-/-}$ hearts, and the time to contractile failure is prolonged but the time to onset of rigor contracture is reduced[117]. Diastolic Ca^{2+} overload, myocardial damage, and increased mortality are also observed in isoproterenol-challenged Kir6.2$^{-/-}$ myocytes[118]. In addition to highlighting the acute protective effect of K_{ATP} activation, Kir6.2$^{-/-}$ animals show increased mortality and exaggerated hypertrophy in response to pressure overload [119,120], and to mineralocorticoid/salt challenge[121]. Together, these studies suggest that decreased K_{ATP}, by stopping the protective 'unloading' that K_{ATP} activation leads to, should tend to cause Ca overload and perhaps hasten the transition to heart failure under stressed conditions. However, other studies seem to contradict a cardioprotective role. Both SUR2- (SUR2$^{-/-}$) and SUR1-knockout (SUR1$^{-/-}$) mice were found to be more tolerant of global ischemia-reperfusion than control mice, with reduced infarct sizes[122,123]. Since the SUR2$^{-/-}$ mice have a marked reduction of ventricular sarcolemmal K_{ATP} channels, the enhanced cardioprotection is opposite the expected phenotype (i.e. impaired protection). Cardioprotection in SUR2$^{-/-}$ mice might conceivably be due to concomitant loss of the SUR2B component of vascular K_{ATP} channels, but similar cardioprotection in SUR1$^{-/-}$ mice[123] could not be explained by such a mechanism.

Potential for therapeutic modulation of cardiovascular K_{ATP} activity

There is tremendous potential for modulation of K_{ATP} channel activity in general and more importantly perhaps, in a tissue-specific manner, since there is already a rich pharmacology, not only of channel inhibitors but also channel openers (KCOs). KCOs have been used in two major clinical settings: (1) to block insulin secretion in conditions of hyperinsulinema, and (2) as antihypertensives.

Sulfonylureas have seen widespread use as glucose lowering agents in type 2 diabetes. K_{ATP} channel inhibitory drugs have not reached clinical acceptance in the cardiovascular arena,

the expectation being that blockade of cardiac K_{ATP} channels may be detrimental in conditions of myocardial ischemia, during which these channels can open and are presumed to be protective, as discussed above. This debate is still not resolved[124,125]. The association of Cantu Syndrome with K_{ATP} GOF holds the promise that sulfonylureas or other blockers should be an effective therapy. It is generally accepted that most sulfonylureas are physiologically more potent inhibitors of SUR1-dependent K_{ATP} than SUR2A-dependent channels, although there has been little careful comparison of effect on SUR1- versus SUR2B-dependent channels. There has been a long-standing dogma that the drug HMR1098 is a cardiac specific K_{ATP} blocker, although direct head-to-head comparison confirms that it is also a more effective blocker of SUR1-dependent than SUR2A-dependent K_{ATP} channels[31,32,126]. Relative efficacies of HMR1098 versus other sulfonylureas in specific physiological conditions may be important to understand, since it is conceivable that specific K_{ATP} inhibitors could successfully counteract the symptoms of Cantu syndrome, without significantly affecting blood glucose control, a key issue if K_{ATP} channel inhibition is to be a viable treatment for the disease.

Further implications and future prospects

It is now recognized that the subunit make-up of the family of K_{ATP} channels is more complex and labile than originally thought[15,127]. The growing association of Kir6.1 and SUR2 variants with specific cardiovascular electrical and contractile derangements and the clear association with Cantu syndrome firmly establish the importance of appropriate activity in normal function of the heart and vasculature. Further studies of patients with some or all symptoms of Cantu syndrome will reveal new mutations in K_{ATP} subunits and perhaps in proteins that regulate K_{ATP} synthesis, trafficking, or location, all of which may ultimately benefit therapeutically from the unique pharmacology of K_{ATP} channels.

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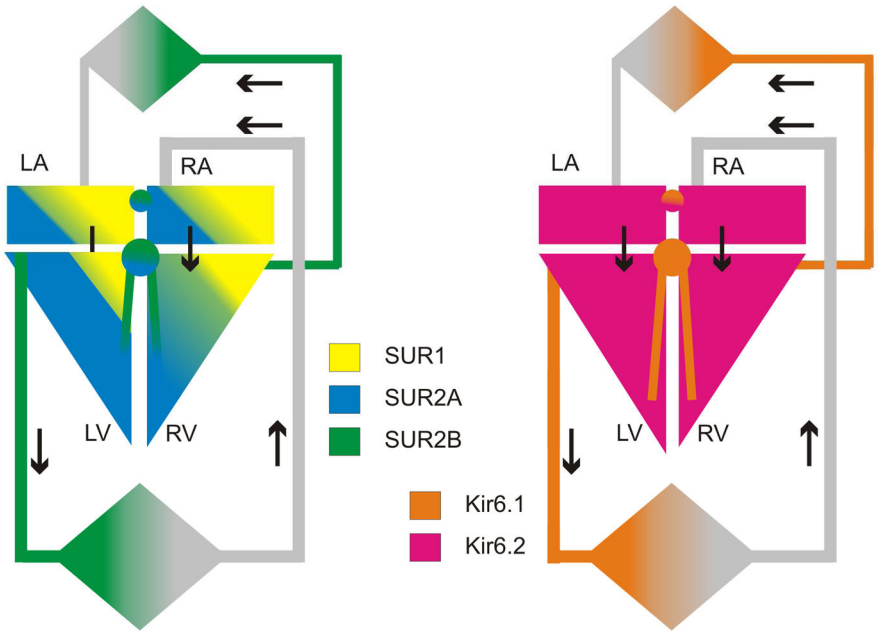

Figure 1. Cardiovascular K_{ATP} channel distribution

Schematic representation of K_{ATP} channel subunit distribution in the cardiovascular system. SUR2A and to a lesser extent SUR1 are prominent in ventricular chambers (LV, RV), whereas SUR1 is more prominent in atrial chambers (LA, RA), and SUR2B is prominent throughout the vasculature. Kir6.2 is found throughout the myocardium, with Kir6.1 more prominent in conducting tissue and in the vasculature.

Table 1

REPORTED ASSOCIATION OF DISEASE WITH K_{ATP} CHANNEL MUTATIONS

Gene	Clinical condition	Features	# of reported affected individuals	Refs
KCNJ8 **(Kir6.1)**	J-wave syndrome	S422L mutation. Reportedly gain-of- function (GOF). Abnormalities in the J- point of the ECG, and including Brugada syndrome (BrS) and early repolarization syndrome (ERS), including VF and AF	9	81_83
	SIDS	In-frame deletion (E332del) and loss- of-function mutation (V346I), through as yet unexplained mechanisms.	2	78
	Cantu Syndrome	GOF mutations associated with complex multi-organ disease (See Table 2)	2	89,90
KCNJ11 **(Kir6.2)**	Neonatal diabetes	Multiple GOF mutations cause inhibition of insulin secretion. No cardiovascular phenotype	>100	128
	Congenital hyperinsulinism	LOF mutations cause hypersecretion of insulin. No cardiovascular phenotype	>10	77,128
ABCC8 **(SUR1)**	Neonatal diabetes	Multiple GOF mutations cause inhibition of insulin secretion. No cardiovascular phenotype	>100	128
	Congenital hyperinsulinism	Multiple LOF mutations cause hypersecretion of insulin. No cardiovascular phenotype	>100	77,128
ABCC9 **(SUR2)**	AF	Isolated case of LOF mutation assicated with AF originating in the vein of Marshal	1	80
	Idiopathic dilated cardiomyopathy	Two cases with distinct LOF mutations associated with heart failure due to idiopathic dilated cardiomyopathy	2	79
	Cantu syndrome	GOF mutations associated with complex multi-organ disease (See Table 2)	>25	87,88

Data from Refs [77_83,87_90,128].

Table 2

MAJOR CLINICAL FEATURES OF CANTU SYNDROME

Neonatal Features
Neonatal macrosomia
Maternal polyhydramnios
Macrocephaly
Craniofacial dysmorphology
Coarse facial appearance (can be confused with a storage disoder)
Epicanthal folds
Broad nasal bridge
Anteverted nostrils
Long philtrum
Wide mouth with full lips
Macroglossia
High or narrow palate
Gingival hyperplasia
Hair
Congenital generalized hirsutism
Thick scalp hair
Thick and/or curly eyelashes
Excessive hair growth on forehead, face, back and limbs
Cardiovascular
Cardiomegaly
Concentric hypertrophy of the ventricles
Normal ventricular contractility
Pericardial effusion
Pulmonary hypertension
Partial pulmonary venous obstruction
Mitral valve regurgitation
Congenital anomalies
Patent ductus arteriosus
Bicuspid and/or stenotic aortic valve
Skeletal abnormalities
Thickened calvarium
Narrow shoulders and thorax
Pectus carinatum
Broad ribs
Platyspondyly and ovoid vertebral bodies
Hypoplastic ischium and pubic bones
Erlenmeyer-flask-like long bones with metaphyseal flaring

Delayed bone age
Skin and joints
Loose and/or wrinkled skin, especially in neonates
Deep palmar and plantar creases
Persistent fingertip pads
Hyperextensibility of joints
Lymphatic system
Lymphedema, onset usually in adolescence or adulthood
Gastrointestinal
Pyloric stenosis
Increased risk for upper gastrointestinal bleeding