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**SPOTLIGHT REVIEW**

# Heritable arrhythmias associated with abnormal function of cardiac potassium channels

**Lia Crotti [1,2,3,4]*, Katja E. Odening[5,6,7], and Michael C. Sanguinetti [8]**

[1]Center for Cardiac Arrhythmias of Genetic Origin, Istituto Auxologico Italiano, IRCCS, Milan, Italy; [2]Laboratory of Cardiovascular Genetics, Istituto Auxologico Italiano, IRCCS, Milan, Italy; [3]Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano, IRCCS, San Luca Hospital, Milan, Italy; [4]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [5]Department of Cardiology and Angiology I, Heart Center University of Freiburg, Medical Faculty, Freiburg, Germany; [6]Institute of Experimental Cardiovascular Medicine, Heart Center University of Freiburg, Medical Faculty, Freiburg, Germany; [7]Department of Cardiology, Translational Cardiology, Inselspital, Bern University Hospital, and Institute of Physiology, University of Bern, Bern, Switzerland; and [8]Department of Internal Medicine, Nora Eccles Harrison Cardiovascular Research and Training Institute, University of Utah, Salt Lake City, UT, USA

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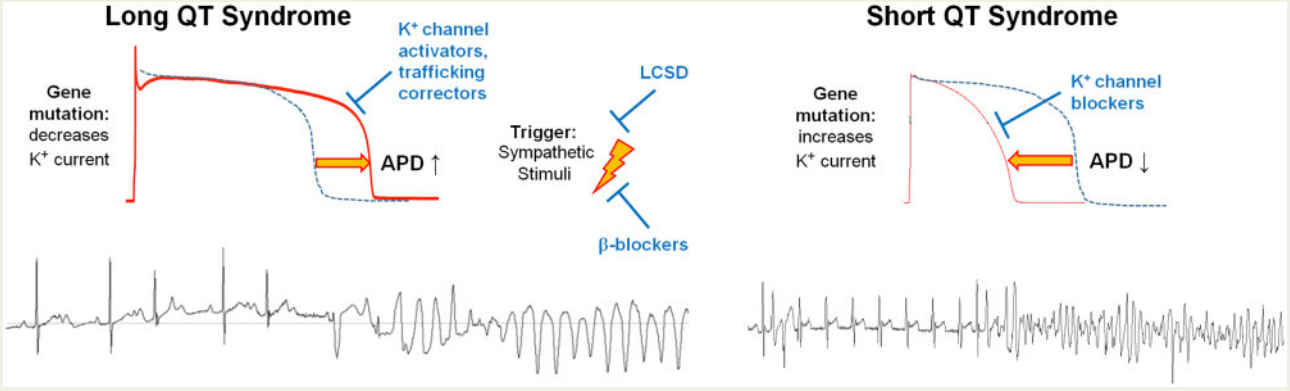
## Abstract

Cardiomyocytes express a surprisingly large number of potassium channel types. The primary physiological functions of the currents conducted by these channels are to maintain the resting membrane potential and mediate action potential repolarization under basal conditions and in response to changes in the concentrations of intracellular sodium, calcium, and ATP/ADP. Here, we review the diversity and functional roles of cardiac potassium channels under normal conditions and how heritable mutations in the genes encoding these channels can lead to distinct arrhythmias. We briefly review atrial fibrillation and J-wave syndromes. For long and short QT syndromes, we describe their genetic basis, clinical manifestation, risk stratification, traditional and novel therapeutic approaches, as well as insights into disease mechanisms provided by animal and cellular models.

## Graphical Abstract




**Keywords** Long QT syndrome • Short QT syndrome • Potassium channels • Atrial fibrillation • Sudden cardiac death

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* Corresponding author. Tel: +39 02 619112374; fax: +39 02 619112956, E-mail: l.crotti@auxologico.it

# 1. Potassium currents in the heart: functional roles in repolarization and arrhythmias

## 1.1 A plethora of $K^+$ channels in the heart

Cardiomyocytes express a wide variety of $K^+$ channel proteins that conduct at least 11 different types of $K^+$ selective currents. This diversity includes three delayed rectifier currents ($I_{Kr}$, $I_{Ks}$, and $I_{Kur}$), three inward rectifier currents ($I_{K1}$, $I_{KATP}$, and $I_{KACh}$), two transient outward currents ($I_{tof}$ and $I_{tos}$), two intracellular cation-activated currents ($I_{KNa}$ and $I_{KCa}$), and at least one 'background leak' current ($I_{Kleak}$). The primary physiological functions of these currents are to maintain the resting membrane potential ($I_{K1}$), mediate repolarization of action potentials ($I_{tof}$, $I_{tos}$, $I_{Kur}$, $I_{Kr}$, and $I_{Ks}$), or to promote repolarization in response to an elevation of $[Na^+]_i$ ($I_{KNa}$), $[Ca^{2+}]_i$ ($I_{KCa}$), or a reduction in the $[ATP]_i/[ADP]_i$ ratio ($I_{KATP}$). In the past few decades, the molecular identity of the channels that conduct these currents have been identified, and the specific contribution of each channel type to cardiac excitability and mechanisms of their modulation by accessory subunits and intracellular messengers have been defined. The voltage-gated $K^+$ (Kv) or ligand-gated channels that conduct $I_{tof}$, $I_{tos}$, $I_{Kur}$, $I_{Kr}$, $I_{Ks}$, $I_{KNa}$, and $I_{KCa}$ function as tetrameric complexes that are formed by coassembly of four identical or highly similar α-subunits that each contain six transmembrane segments (S1–S6) that constitute two distinct functional domains. The S1–S4 segments form a voltage-sensing domain, and the S5–S6 segments from each subunit surround the central cavity of the channel and provide the transmembrane conduit for selective $K^+$ flux. Inwardly rectifying $K^+$ (Kir) channels that conduct $I_{K1}$, $I_{KATP}$, and $I_{KACh}$ are formed by coassembly of four smaller subunits that each have two transmembrane segments equivalent to the pore-forming S5–S6 of Kv channels. In addition, functional Kv and some Kir channels also include accessory (β) subunits that modulate gating and/or trafficking of channels to the cell membrane. The relative magnitudes of each $K^+$ current varies as a function of both time and voltage during a cardiac action potential and is schematically illustrated in *Figure 1* for a human atrial and ventricular myocyte.

## 1.2 Molecular identity and physiological roles of delayed rectifier $K^+$ channels

Cardiac delayed rectifier $K^+$ currents are distinguished from one another based on their relative rates of activation onset: $I_{Ks}$ is slow, $I_{Kr}$ is rapid, and $I_{Kur}$ is ultra-rapid. $I_{Ks}$ is conducted by Kv7.1 (*KCNQ1*) channels[2] that are coupled to a variable number of minimal $K^+$ (minK) β-subunits (*KCNE1*) that each have a single transmembrane domain (gene names are indicated in italics). Kv7.1 channels activate fast in response to membrane depolarization and also inactivate at potentials >0 mV. In contrast, $I_{Ks}$ conducted by Kv7.1/minK channels activate much more slowly and do not inactivate[3] and thus, outward current increases throughout the plateau phase of the action potential and reaches its peak amplitude during the onset of Phase 3 repolarization. $I_{Kr}$ is conducted by channels formed by coassembly of four Kv11.1 subunits (*KCNH2* or *HERG1*)[4,5] and is characterized by a rapid rate of activation (relative to $I_{Ks}$) and even faster rate of inactivation, a property that greatly limits the magnitude of outward current during Phase 2 (plateau) of the action potential. Kv11.1 channels recover from their non-conducting, inactivated state to a conducting (open) state during Phase 3 repolarization, resulting in an enhanced current despite the reduced electrochemical driving force for $K^+$. In the mammalian heart, $I_{Kr}$ channels include full-length subunits (Kv11.1a) that coassemble with a smaller, alternatively spliced variant (Kv11.1b) that accelerate the rate of channel closure.[6] $I_{Kur}$ is restricted to the atria in the human heart[7] and is conducted by Kv1.5 (*KCNA5*) channels that activate with extremely fast kinetics and can also exhibit voltage-dependent inactivation when associated with ancillary subunits (Kvβ1.2, Kvβ1.3, or Kvβ2.1) that alter gating kinetics and modulate channel trafficking to the plasma membrane.[8]

## 1.3 Molecular identity and physiological roles of transient outward $K^+$ channels

Cardiac transient outward $K^+$ current ($I_{to}$) is very rapidly activated during the upstroke of the action potential and then more slowly inactivates. The kinetic properties of $I_{to}$ promote the initial and short-lived period of repolarization (Phase 1) that precedes and modulates the duration and amplitude of the plateau (Phase 2) of action potentials (*Figure 1*). Two types of $I_{to}$ are distinguished in the heart based on their relative rates of recovery from inactivation.[9] $I_{tof}$ recovers fast and is conducted by channels composed by coassembly of Kv4.3 (*KCND3*) and/or Kv4.2 (*KCND2*) α-subunits. $I_{tos}$ recovers slowly from inactivation and is conducted by Kv1.4 (*KCNA4*) channels. In the human heart, Kv4.3 is coassembled with KChiP2 (*KCNIP2*) ancillary subunits that modulate channel gating and control the trafficking of channels to the cell surface.[10,11]

## 1.4 Molecular identity and physiological roles of inward rectifier $K^+$ channels

Kir channels exhibit marked inward rectification, meaning that inward currents activated at potentials negative to the $K^+$ equilibrium potential ($E_K$) increase as a linear function of voltage, whereas outward currents activated at potentials positive to $E_K$ exhibit a progressively reduced slope conductance that culminates in very little sustained current during the plateau phase of a cardiac action potential. Reduced outward current at positive potentials is caused by voltage-dependent block of Kir channels by intracellular polyamines and $Mg^{2+}$.[12] All Kir channels are constitutively activated by phosphatidylinositol-4,5-bisphosphate ($PIP_2$).[13] Cardiac $I_{K1}$ is mediated by Kir2 channels, mainly Kir2.1 (*KCNJ2*) but also Kir2.2 (*KCNJ12*) and Kir2.3 (*KCNJ4*) that are constitutively open and thus, are largely responsible for setting the resting membrane potential of atrial and ventricular myocytes to a potential close to $E_K$.[14] $I_{K1}$ is smaller in atrial than in ventricular myocytes and is relatively absent in myocytes in the sinoatrial node (SAN) and atrioventricular node that consequently have a less negative maximal diastolic potential. $I_{KACh}$ is restricted to the atrium and is conducted by channels formed by Kir3.1 (*KCNJ3*) and Kir3.4 (*KCNJ5*) α-subunits.[15] $I_{KACh}$ is activated by extracellular binding of acetylcholine to M2 muscarinic receptors and results in shortening of action potential duration (APD) in atrial myocytes and a hyperpolarization and slowing of the firing rate of SAN cells. $I_{KATP}$ channels are hetero-octomeric complexes, formed by coassembly of four Kir6.2 (*KCNJ11*) and/or Kir6.1 (*KCNJ8*) α-subunits plus four SUR2A or SUR1 accessory subunits.[16] $K_{ATP}$ channels are activated by intracellular MgADP, inhibited by intracellular ATP ($IC_{50} \sim 50$ μM), and regulation by the ATP/ADP ratio is modified by channel phosphorylation and $PIP_2$.[17] $K_{ATP}$ channels are normally in a closed state but are readily activated and can dramatically shorten APD during conditions that reduce $[ATP]_i$ such as hypoxia or ischaemia.

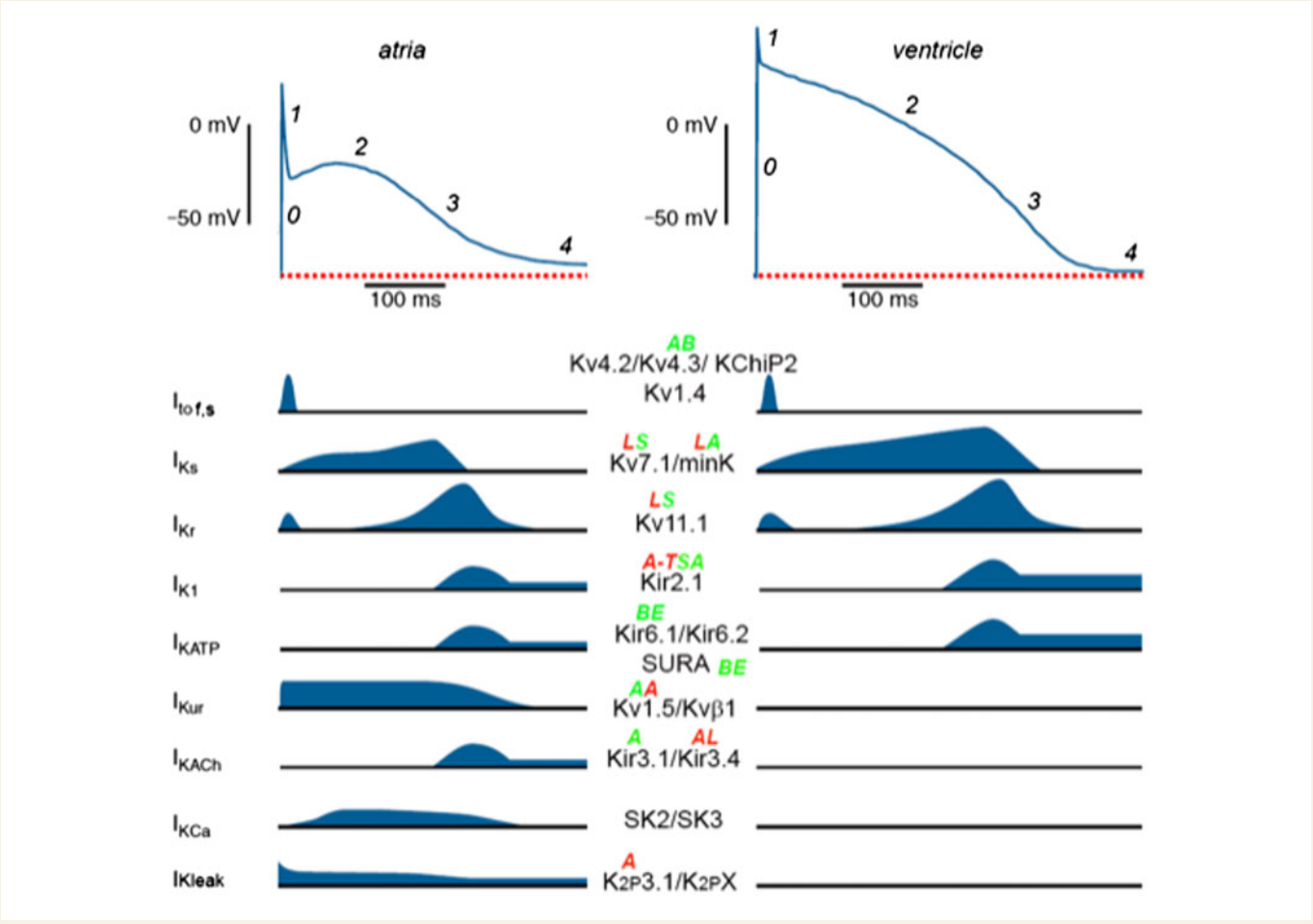


**Figure 1** Multiple potassium ion currents mediate repolarization of human cardiomyocytes. Upper panels indicate the timing of the different phases *0–4* of a typical atrial (left) and ventricular (right) action potential. Lower panel shows approximate amplitude of each current throughout the duration of the action potentials. Current name is indicated at the far left. The primary $K^+$ channel subunits that form channels that conduct these currents is indicated in the centre (in black text); cardiac arrhythmia known to be associated with a specific subunit is also indicated according to the code: ***A***, atrial fibrillation; ***A–T***, Anderson–Tawil syndrome; ***B***, Brugada syndrome; ***E***, early repolarization syndrome; ***L***, LQTS; ***S***, SQTS; Colour of text indicates type of mutation, either a gain of function (green) or loss of function (red). Note that current magnitude can vary significantly under different conditions; for example, $I_{KATP}$ and $I_{KNa}$ (not shown) can range from unmeasurable under normal physiological conditions to very large during anoxia. Modified with permission from Schmitt *et al.*[1]

## 1.5 Molecular identity and physiological roles of cation-activated and leak $K^{\pm}$ channels

Cardiac myocytes also express channels that conduct intracellular cation-activated currents ($I_{KCa}$, $I_{KNa}$) and a background 'leak' current ($I_{Kleak}$). Large conductance $Ca^{2+}$-activated (BK) channels are located in mitochondrial membranes, but sarcolemma $I_{KCa}$ is conducted by small conductance $Ca^{2+}$-activated $K^+$ (SK) channels SK1–SK3 (*KCNN1-3*)[18] that are expressed primarily in atrial myocytes where they are activated in response to elevated $[Ca^{2+}]_i$ subsequent to the opening of sarcolemma L-type and sarcoplasmic reticulum RyR $Ca^{2+}$ channels. $Ca^{2+}$ activates SK channels by binding to calmodulin that constitutively interacts with the C-termini of SK α-subunits.[19] In human atria, SK2 and SK3 expression levels are ∼10-fold higher than that of SK1, and electrical remodelling associated with chronic atrial fibrillation (AF) reduces their expression by ∼50%.[20] $I_{KNa}$ is conducted by $K_{Na}1.2$ (*KCNT2*) channels that are expressed in the sarcolemma and perhaps mitochondrial membranes of cardiomyocytes.[21] Although $K_{Na}1.2$ channels have a very high conductance, the outward current conducted by these channels is predicted to be quite small except under severe ischaemia when $[Na^+]_i$ can increase significantly. Opening of these channels in the mitochondria has been proposed to counteract opening of the mitochondrial permeability transition pore and thus protect against ischaemia–reperfusion injury.[22] $I_{Kleak}$ is the term used here to describe the prominent background $K^+$ current in atrial myocytes. It is likely that several two-pore domain $K^+$ ($K_{2P}$) channels that are voltage independent and gated by pH, lipids and membrane stretch contribute to this current. In the human heart, $K_{2P}3.1$ (TASK1, KCNK3) channels were initially reported to be expressed predominantly in the atria,[23] where they can form as homodimers or heterodimers when partnered with $K_{2P}9.1$ (TASK-3, KCNK9).[24] More recently, it was reported that at least 10 different $K_{2P}$ channels are expressed, albeit at low levels, in the human ventricle.[25] The specific role(s) of these channels in ventricular repolarization is unclear, but APD prolongation was noted after RNAi-mediated knockdown of $K_{2P}2.1$, $K_{2P}3.1$, $K_{2P}6.1$, and $K_{2P}17.1$ expression in human iPSCs

differentiated into cardiomyocytes.[25] A role for K2P2.1 in arrhythmogenesis is also suggested by the finding that mRNA and protein levels are down-regulated in heart failure and AF.[26]

Ion channels are regulated by a plethora of molecular interactions with accessory subunits, kinases, chaperones, signalling networks, etc. that affect their levels of expression, intracellular trafficking, rates of turnover, and single channel gating properties such as open probability and rates of activation and inactivation. Most cardiac $K^+$ channels are modulated by phosphorylation by one or more enzymes such as PKA, PKC, CaMKII, or Src.[1] As one example, $I_{Ks}$ channels are bound to the A kinase-anchoring protein AKAP9,[27] which in turn recruits the binding of PKA, protein phosphatase 1 (PP1), phosphodiesterase 4D3,[28] and adenylyl cyclase 9 to the channel complex.[29] $I_{Ks}$ channels also interact with calmodulin, $PIP_2$ and ATP that stabilize the channel in an open state.[30–32] For in depth descriptions of the myriad ways in which cardiac $K^+$ channels can be regulated, the reader is directed to several extensive review articles on this topic.[1,33,34]

The discovery of mutations in genes that encode many $K^+$ channel subunits has provided unique insights into the molecular mechanisms and pathophysiology associated with genetic forms of AF and ventricular fibrillation (VF). In general terms, loss of function mutations in $K^+$ channel subunits results in a delayed time course of cardiac repolarization (e.g. long QT syndrome, LQTS), whereas gain of function mutations results in a faster rate of cardiomyocyte repolarization (e.g. AF and short QT syndrome, SQTS). Heterozygous missense mutations are the most common cause of $K^+$ channelopathies and most of these single amino acid substitutions cause a loss of normal function, either by causing protein misfolding and early degradation, hindering trafficking of the channel to the cell membrane or by altering gating in a manner that reduces net conductance (e.g. altered kinetics or voltage dependence of activation or inactivation). Below we present a brief consideration of AF and J-wave syndromes, followed by a more in-depth discussion of LQTS and SQTS. Finally, it should be noted that $K^+$ channel mutations can also cause a wide spectrum of human diseases beyond cardiac arrhythmia. Notable examples are epilepsy,[35] diabetes,[36] ataxia,[37] and Cantu syndrome that includes atrioventricular (AV) node block.[38]

# 2. Atrial fibrillation and J-wave syndromes

## 2.1 Atrial fibrillation

Several $K^+$ channels have been reported to be associated with rare forms of genetic AF, including Kv1.5, Kv4.2, Kv4.3, Kir2.1, Kir3.4, and $K_{2P}3.1$. The first $K^+$ channel associated with AF was Kir2.1 (*KCNJ2*) where a gain of function mutation (V93I) was detected in all affected members of a Chinese kindred.[39] The following year, the first report for Kv1.5 (*KCNA5*) was a heterozygous E375X mutation predicted to result in a loss of function by introducing a premature stop codon that eliminates the S4-terminus region of the channel subunit.[40] Early-onset nocturnal paroxysmal AF in a family was found to be caused by a point mutation (S447R) that resides in a PKC phosphorylation site of Kv4.2 (*KCND2*) channels.[41] This mutation increased $I_{tof}$ magnitude by slowing inactivation and enhancing membrane expression of channels. A point mutation (A545P) in Kv4.3 (*KCND3*) increases peak-current density and slows the onset of inactivation of $I_{tof}$.[42] A role for $I_{KACh}$ in AF has been suggested by the initial finding that common polymorphisms in Kir3.4 (*KCNJ5*) are associated with lone AF,[43] and more recently by the report of five rare mutations in both Kir3.1 (*KCNJ3*) and Kir3.4 (*KCNJ5*) in patients with sporadic AF.[44] One gain of function mutation (N83H) in Kir3.1 enhances constitutively active $I_{KACh}$ (M2 receptor stimulation not required),[44] a cellular phenotype noted previously in atrial myocytes isolated from AF patients.[45] Most recently, a gain of function mutation in Kir3.4 was reported to cause sinus node dysfunction in a large family.[46] Point mutations in Kv β-subunits minK related protein 2, MiRP2 (*KCNE3*),[47] and MiRP4 (*KCNE5*)[48] have also been reported in single patients with AF. KCNE subunits are especially interesting because they modulate the gating of several different Kv channels,[49] a feature that also makes it difficult to define the mechanisms underlying their pathology in AF. Loss of function variants in $K_{2P}3.1$ has also been associated with AF in a few patients.[50]

## 2.2 J-wave syndromes

The term J-wave syndromes was recently suggested to describe ventricular arrhythmia associated with both Brugada syndrome and early repolarization syndrome (ERS) that are characterized by VF and elevation and notching of the J-point (a deflection immediately following the QRS complex) on the electrocardiogram (ECG).[51] These arrhythmias are very rarely related to an enhanced outward $I_{to}$ or $I_{KATP}$ resulting from gain of function mutations in Kv4.3 (*KCND3*)[52] or Kir6.1 (*KCNJ8*),[53] or loss of function mutations in the Kv4.3 β-subunit MiRP2 (*KCNE3*).[54] Most recently, a *de novo* mutation in Kv4.3 (G306A) was reported from an ERS-associated proband and shown to increase the magnitude of $I_{to}$ and slow the rate of its onset and recovery from inactivation.[55]

# 3. Long QT syndrome

LQTS is a genetically transmitted cardiac disease characterized by prolonged QT interval of the surface ECG, caused by a prolonged duration in the plateau phase of ventricular action potentials.[56] Prolonged repolarization can result from a reduction of outward currents, particularly $I_{Kr}$ and $I_{Ks}$ or by an enhancement of inward $Na^+$ or $Ca^{2+}$ currents during Phase 2 or 3 of the action potential. Patients affected by LQTS have a structural normal heart, but are at high risk of life-threatening arrhythmias, because the prolongation of repolarization may result in subsequent re-activation of $Ca^{2+}$ or $Na^+$ currents, which in turn may generate an early after depolarization (EAD) and promote triggered electrical activity at the end of repolarization[56] (*Figure 2*). The typical arrhythmia in LQTS patients is Torsades de Pointes (TdP), a tachyarrhythmia that can self-terminate or degenerate into VF.[56] Clinically, the patients can suffer palpitations, syncopal events or sudden cardiac death (SCD), usually starting from childhood or teen age. An appropriate diagnosis is mandatory as effective therapies are available and prevention of SCD is possible.[56]

## 3.1 Molecular mechanisms

Two main hereditary variants of LQTS are known; the autosomal dominant Romano–Ward syndrome,[57] with a prevalence of 1:2000 live births[58] and the recessive Jervell–Lange Nielsen (JLN) syndrome, in which a more severe cardiac phenotype is associated with congenital deafness.[59]

Seventeen genes are currently associated with LQTS (LQT1–LQT17) and among these, seven encode for $K^+$ channel subunits or for proteins that modulate $K^+$ channel function. In absolute numbers, mutations in $K^+$ channel genes are responsible for the vast majority of LQTS cases. Specifically, *KCNQ1* and *KCNH2* encoding Kv7.1 and Kv11.1 α-subunits

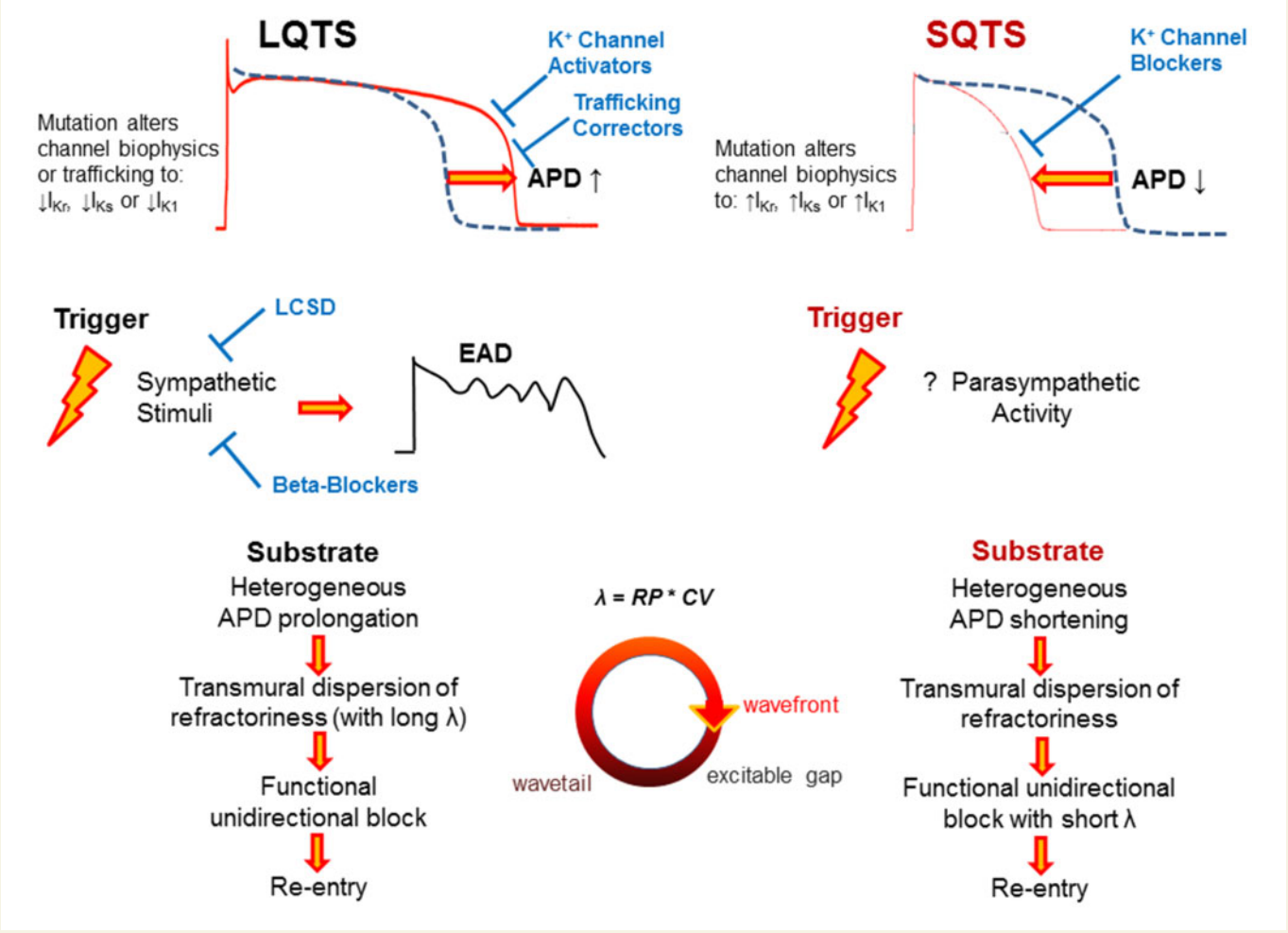


**Figure 2** Arrhythmia mechanisms and therapeutic targets in LQTS and SQTS. Left panel: long QT syndrome (LQTS); right panel: short QT syndrome (SQTS). Potential therapeutic targets are indicated in blue. In SQTS, cardiac arrest often occurs during sleep, suggesting a parasympathetic trigger. Formula indicates factors determining re-entry formation as wavelength ($\lambda$) = refractory period (RP) * conduction velocity (CV). ↑, increase; ↓, decrease; APD, action potential duration; $I_{K1}$ inward rectifier potassium current; $I_{Kr}$ rapid delayed rectifier potassium current; $I_{Ks}$ slow delayed rectifier potassium current.

of $I_{Ks}$ and $I_{Kr}$ channels are responsible for LQT1 and LQT2. Together, mutations in these genes account for 80% of all LQTS cases. Perturbation in $I_{Ks}$ and $I_{Kr}$ can also occur when β-subunit genes as *KCNE1* (LQT5 or JLN) and *KCNE2* (LQT6) are mutated. These are responsible for less than 5% of all LQTS cases[60,61] and LQT5 is usually associated with a low penetrant form of the disease.[62] Other rare genetic subtypes characterized by a reduction in outward $K^+$ current are LQT7 or Andersen–Tawil syndrome (due to mutations in *KCNJ2* that reduce $I_{K1}$), LQT11 (due to mutation in *AKAP9*, the gene encoding for Yotiao, an $I_{Ks}$ channel modulator), and LQT13 (due to mutation in *KCNJ5* that reduces $I_{KACh}$).[56]

LQTS mutations can affect multiple properties of channel function (as reviewed in detail in Ref.63) Mechanisms of reduced Kv7.1/minK or Kv11.1 channel function include protein misfolding, misprocessing in the endoplasmic reticulum, disrupted trafficking of channels to the cell surface, reduced $K^+$ permeation, and altered channel gating, such as enhanced inactivation, slower activation or faster deactivation. A single virulent mutation in only one subunit of a tetrameric Kv and Kir channel can sometimes have a 'poison pill' effect and result in complete dominant-negative suppression of channel function. For example, missense mutations in the intracellular C-helix of Kv11.1 that interrupts its interaction with minK subunits decreases $I_{Ks}$ density and also impairs $PIP_2$ modulation, causing a depolarizing shift of channel activation.[64]

## 3.2 Clinical presentation

The clinical presentation of LQTS varies significantly in different patients—ranging from no symptoms to sudden death. Arrhythmic events are usually triggered by an increase in sympathetic activity and therefore, the most typical presentation is a syncopal event during emotional or physical stress in a young and otherwise healthy individual. In LQT1 subjects, cardiac events typically occur during exercise, with swimming being a specific trigger in one-third of the cases.[65] Conversely, in LQT2, the predominant trigger is emotional stress, with sudden auditory stimuli being pathognomonic for this genetic subgroup.[65] LQT2 patients are also more susceptible to QT prolonging drugs and electrolyte unbalances and female patients are at higher risk in the post-partum period[56] and during menopause transition and post-menopausal periods.[66]

**Table 1 Long QT syndrome diagnostic criteria**

| | Points | | Points |
|---|---|---|---|
| **Electrocardiographic findings**[a] | | **Clinical history** | |
| QTc[b] | | Syncope[c] with stress | 2 |
| ≥480 ms | 3 | Syncope[c] without stress | 1 |
| 460–479 ms | 2 | Congenital deafness | 0.5 |
| 450–459 ms (in males) | 1 | | |
| QTc 4th min of recovery from exercise stress test ≥480 ms | 1 | **Family history** | |
| Torsade de pointes[c] | 2 | Family members with definite LQTS[d] | 1 |
| T-wave alternans | 1 | Unexplained SCD below age 30 among immediate family members[d] | 0.5 |
| Notched T wave in three leads | 1 | **SCORE ≤1 point: low probability of LQTS** | |
| Low heart rate for age[e] | 0.5 | **SCORE 1.5–3 points: intermediate probability of LQTS** | |
| | | **SCORE ≥3.5 points high probability of LQTS** | |

Adapted from Schwartz and Crotti.[67]
[a]In the absence of medications or disorders known to affect these electrocardiographic features.
[b]QTc calculated by Bazett's formula.
[c]Mutually exclusive.
[d]The same family member cannot be counted in both.
[e]Resting heart rate below the 2nd percentile for age.

Basal ECG, exercise stress test and 12-lead 24-h Holter monitoring are all extremely important to identify the main electrocardiographic features of the disease. Typical features on surface ECG include QTc prolongation (>440 ms for men and >460 ms for women after puberty) and alteration of T-wave morphology that can be biphasic, bifid or notched.[56] Typically, LQT1 patients tend to have broad-based T waves; while biphasic or notched T waves are more frequently observed in LQT2 patients. LQTS-related ECG features associated with major electrical instability include T-wave alternans and functional 2:1 AV block. T-wave alternans is a beat-to-beat alternation of the polarity and/or amplitude of the T wave,[56] while the 2:1 functional 'pseudo' AV block is usually seen in neonates or young children who have a particularly prolonged QT, leading to conduction block within the refractory ventricle.

In case of borderline QTc, it is very important to evaluate the QT behaviour during an exercise stress test and 24 Holter recording to make a diagnosis. Indeed, both the inability of QT to shorten during exercise and QT prolongation during the recovery phase have been identified as typical features of affected patients, particularly with LQT1.[67] Specifically, the presence of a QTc ≥480 ms at the fourth minute of recovery is one of the diagnostic criteria of the disease.[67] Regarding ECG Holter recording, phases of clear QT prolongation and variability in the morphology of the T wave could be highly suggestive or diagnostic for the disease. Furthermore, 24-h Holter recording may provide prognostic information; i.e. identification of T-wave alternans, pronounced QT prolongation, or frequent sudden pauses with abnormal repolarization abnormalities in the subsequent beat are all negative prognostic factors. Echocardiography in LQTS patients never show major structural abnormalities; however, subtle mechanical abnormalities do exist and correlate with arrhythmic risk.[68–71]

Among potassium channel-related LQTS, there are two syndromic forms with peculiar features. The JLN syndrome is a severe variant of LQTS, in which the cardiac phenotype is combined with congenital deafness[72] due to the presence of homozygous or compound heterozygous mutations in *KCNQ1* (LQT1) or *KCNE1* (LQT5) genes.[59] Patients with JLN syndrome present with a malignant phenotype: 90% of them are symptomatic (often already at paediatric age), the QTc is markedly prolonged (on average 557 ± 65 ms) and conventional therapies have limited efficacy, leading to the recommendation of early implantable cardioverter-defibrillator (ICD) implantation, even in children. JLN subgroups at lower risk are those with a QTc <500 ms, those asymptomatic during the first year of life and those with *KCNE1* mutations.[59]

The Andersen–Tawil syndrome (ATS), also referred to as LQT7 (mutations in *KCNJ2*), is characterized by prominent U waves on the ECG that are often difficult to distinguish from truly prolonged QT, ventricular arrhythmias and potassium-sensitive periodic paralysis. Affected patients may also present mild or prominent dysmorphic facial and limb features.[73,74] Ventricular arrhythmias range from premature ventricular beats to short runs of polymorphic ventricular tachycardia (VT) and no specific trigger has been identified.[73,74] It is quite debated if ATS should be considered as LQTS variant, as a true QT prolongation is frequently not present and arrhythmogenesis might be related to a different mechanisms than conventional LQTS.[75] Epilepsy is another extra-cardiac manifestation that can be observed in some LQTS cases[76]; specific examples include patients with severe heterozygous loss of function mutations in *KCNH2*[77] or *KCNQ1*.[78]

## 3.3 Diagnosis and risk stratification

The diagnosis of LQTS can be made if a Schwartz score (based on electrocardiographic features, familial and personal history[67]) of ≥3.5 points is found (*Table 1*), or in presence of a QTc ≥500 ms in repeated 12-lead ECGs.[79] These criteria do not allow the identification of silent mutation carriers. Therefore, an LQTS diagnosis can also be made in presence of an unequivocally pathogenic mutation.[79]

The main differential diagnosis is the so-called acquired long QT syndrome (aLQTS), in which QT prolongation is caused either by drugs, bradycardia or hypokalaemia. Also in aLQTS a genetic predisposition can be identified, and $K^+$ channel genes play a predominant role.[80]

Risk stratification in LQTS is based on clinical and genetic factors.[81] Patients symptomatic for cardiac events (syncope or cardiac arrest) are unquestionably at higher risk of recurrences if not adequately treated,[82] with those having events in the first year of life being the most severe cases.[83] Another major risk factor is a QTc >500 ms,[84] with additional malignant ECG features being T-wave alternans, 2:1 AV block and sinus pauses followed by particularly prolonged QT intervals. In the LQT1

subgroup, autonomic parameters have been identified in a few studies as useful in risk stratification, such as reduced baroreflex sensitivity or reduced heart rate reduction during the first minute of recovery from an exercise stress test.[85,86] Carrying two independent mutations[87] or having JLN syndrome[59,72] is associated with an increased arrhythmic risk, but even in the presence of a single disease-causing mutation the risk can be influenced by the gene involved,[84] the location of the mutation in the protein,[88,89] and sometimes by the specific mutation.[90]

As in many inherited disorders, there is considerable variability of disease expressivity in LQTS; i.e. even within members of the same family carrying the same disease-causing mutation, clinical manifestation can be very different. Such an interpersonal variation is partially attributed to genetic modifying factors, such as single-nucleotide polymorphisms (SNPs) that may attenuate or aggravate the pathological manifestation of the principal disease-causing mutation, thereby conferring protection or increased risk, respectively.[91] A large number of modifier SNPs have been described since 2005,[92] most of them affecting $K^+$ channel function/expression[92–95]; however, SNP evaluation is not yet integrated into clinical practice. Among different modifier SNPs so far described, those more strongly and reproducibly associated with arrhythmic risk in multiple studies[96–98] are those on *NOS1AP*, a gene encoding for CAPON, an anchoring protein for the neuronal isoform of NO-synthase that is abundantly expressed in cardiac myocytes and highly relevant to intracellular $Ca^{2+}$ handling.[99]

Apart from the genetic modifiers other factors so far identified as possible modulator of disease severity are medications that could influence QT interval (www.crediblemeds.org) and therefore arrhythmic risk, alterations in serum potassium and magnesium levels, autonomic nervous system variations,[85,86] and hormonal changes.[56,66]

## 3.4 Therapy

The first line therapy for LQTS is β-adrenergic receptor blockers that should be started upon initial diagnosis as SCD can be the first manifestation of the disease in 12% of untreated patients.[56] Not all β-blockers are equally effective and nadolol and propranolol should be considered the β-blockers of choice, being associated with a lower risk of recurrences compared to metoprolol.[100] However, in a recent study, nadolol appeared to be more effective than propranolol, and this could be due to the better compliance obtained with nadolol (requiring only once a day administration instead of three times) and the fact that propranolol is particularly used in very small children at higher risk.[81] In LQT3 patients with a QTc >500 ms it is recognized by current guidelines that mexiletine, a $Na^+$ channel blocker, should be added to β-blocker therapy whenever a QT shortening of at least 40 ms is observed during an acute oral test.[79] Interestingly, a recent study also reported a significant QT shortening by mexiletine in LQT2 patients, suggesting a possible antiarrhythmic effect also in this genetic subgroup.[101]

Whenever patients remain at high risk despite a full dose of β-blockers, or when β-blockers are not tolerated, left-cardiac sympathetic denervation (LCSD) should be considered. LCSD is a surgical procedure, that can also be performed with a thoracoscopic approach, that requires the removal of the first four thoracic ganglia (T1–T4), leaving intact the cephalic portion of the left stellate ganglion to avoid the Horner's syndrome.[56] The rational for LCSD is mainly based on its antifibrillatory effect and on the major reduction of norepinephrine release without interfering with heart rate.[102] In a cohort of high-risk LQTS patients that underwent LCSD, the procedure showed a 91% reduction in cardiac events and produced a mean QTc shortening of 39 ms, pointing to an action on the arrhythmic substrate as well as on its trigger.[103] Indeed, LCSD reduces the inhomogeneous norepinephrine release in the ventricle with a consequent reduction of the dispersion of repolarization and therefore of the QTc.[104] In LQTS, an ICD is needed in a minority of the patients; those with a previous cardiac arrest and with recurrences despite full antiadrenergic therapy (possibly including LCSD).[105] Asymptomatic patients should not be implanted with an ICD, unless despite optimal therapy a QTc >550 ms is present together with signs of high electrical instability (i.e. T-wave alternans, 2:1 AV block, very long sinus pauses with subsequent beats showing aberrant T-wave morphology and further QT prolongation).[105]

## 3.5 Cellular and animal models

Animal models for $K^+$ channelopathies are very useful to investigate pathophysiological mechanisms of arrhythmogenesis on multiple levels (from cellular/tissue to whole heart and animal), to test the role of genetic background in altering the arrhythmic phenotype and to test novel therapies. However, the major limitation of animal studies is the partially limited clinical translation due to some species differences in cardiac electrical function.[106] Transgenic mouse models representing LQT1 or LQT2 (with knock-out or dominant-negative loss-of-function mutations of human voltage-gated $K^+$ channels *KCNQ1* or *KCNH2*) have failed to mimic the human disease phenotype, particularly lacking spontaneous VT, VF, and SCD. The main reason is due to difference in the predominant repolarizing voltage-gated $K^+$ channel currents responsible for cardiac repolarization in murine and human cardiomyocytes.[107]

Rabbits represent a species with more pronounced similarities to human cardiac electrophysiology, e.g. with $I_{Kr}$ and to a lesser degree, $I_{Ks}$ as main drivers of cardiac repolarization.[106,108] Several different transgenic rabbit models for LQTS have been generated based on a dominant-negative overexpression of human mutated $K^+$ channels; e.g. LQT1 (KCNQ1-Y315S), LQT2 (KCNH2-G628S),[109] and LQT5 (KCNE1-G52R).[110] In LQT1 or LQT2 rabbit cardiomyocytes, the repolarizing currents $I_{Ks}$ (LQT1) or $I_{Kr}$ (LQT2) were completely eliminated, resulting in a prolongation of APD, ventricular refractoriness, and QT prolongation in both,[109,111] and the development of spontaneous VT and SCD in LQT2[109] (*Figure 3*). In transgenic LQT5 rabbit cardiomyocytes, in contrast, the biophysical properties of $I_{Ks}$ and $I_{Kr}$ were altered with accelerated deactivation kinetics,[110] but overall $I_{Ks}$ and $I_{Kr}$ current densities were not reduced. Consequently, these rabbits exhibited only a partial phenotype with no significant prolongation of whole heart APD and only a very slightly prolonged QT interval.[110]

Studies in transgenic LQT1 and LQT2 rabbits have strengthened our insights into the importance of spatial and temporal heterogeneities of repolarization as a pro-arrhythmic 'substrate' and the key role of increased sympathetic activity as a 'trigger' for EAD and LQTS-related arrhythmias. Indeed, in LQT2 rabbit hearts, a pronounced dispersion of repolarization was identified in left and right ventricles,[109,111,113] causing unidirectional functional block and re-entry formation as the initiating mechanism of VT/VF.[109] In addition, in LQT2 hearts, a dynamic spatio-temporal dispersion of repolarization with discordant alternans in adjacent regions developed at physiological heart rates and preceded onset of VT/VF.[114] In contrast, in LQT1 hearts with a more homogeneously prolonged APD within the left ventricle at normal heart rates,[109,111,113,115] VT/VF did not develop spontaneously nor could it be induced, suggesting a protective effect of a homogeneous APD prolongation. When LQT1 hearts were further stressed, however, by continuous tachypacing to induce cardiac tachymyopathy,[116] or complete AV block,[117] APD dispersion increased, spatially discordant alternans developed and VT/VF was easily inducible.[116]

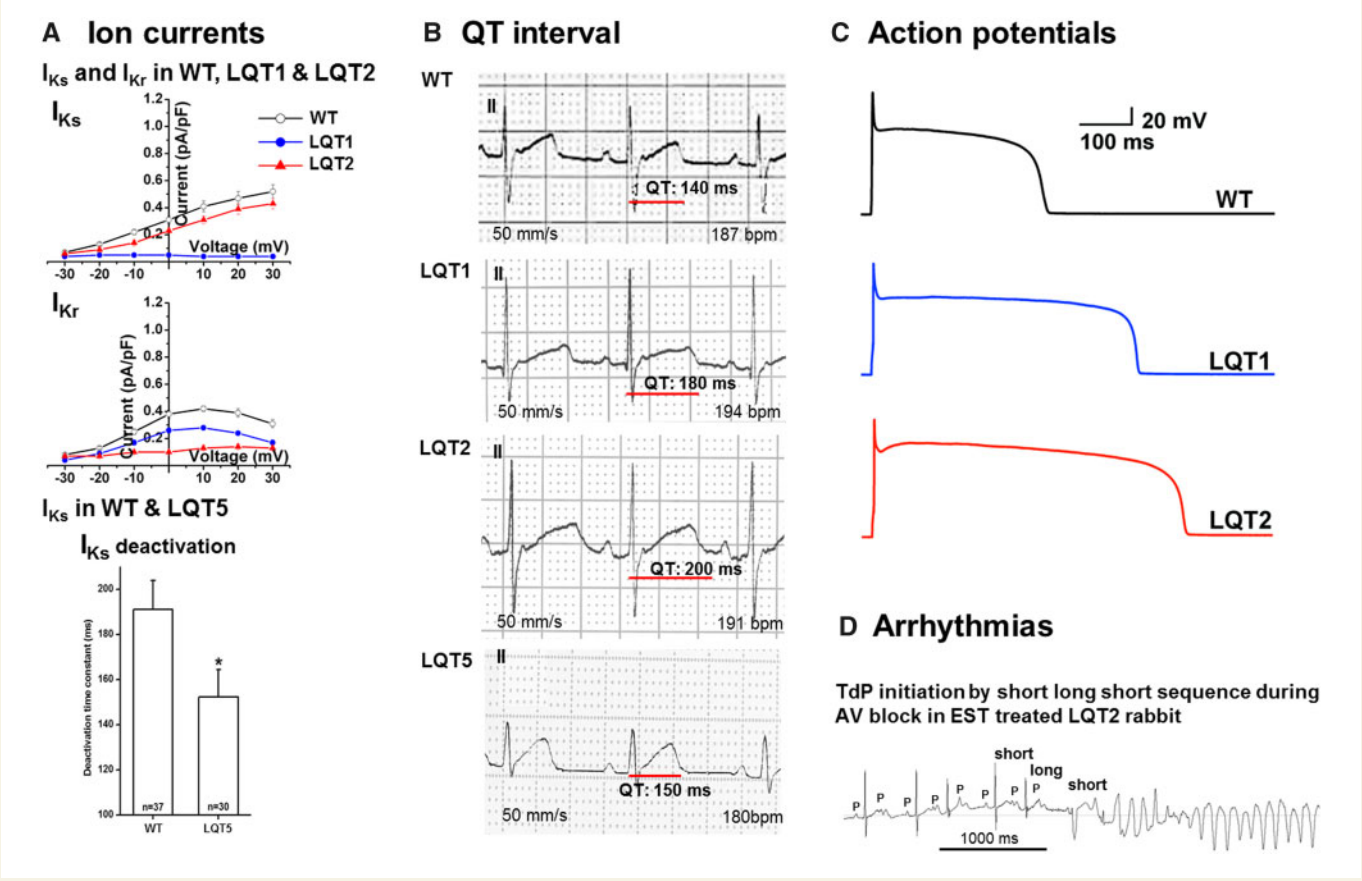


**Figure 3** Transgenic LQTS rabbits. (*A*) Upper panel: IV-curves of $I_{Ks}$ and $I_{Kr}$ currents in cardiomyocytes isolated from WT, LQT1, and LQT2 rabbit hearts, indicating loss of $I_{Ks}$ in LQT1 and loss of $I_{Kr}$ in LQT2 (modified with permission from Brunner *et al.*[109]) Lower panel: $I_{Ks}$ deactivation time constant is reduced in transgenic LQT5 cardiomyocytes compared to WT. (modified with permission from Major *et al.*[110]) (*B*) Representative ECG tracings indicating differences in QT interval in WT, LQT1, LQT2, LQT5 rabbits (ECG from WT, LQT1, and LQT2 modified with permission from Brunner *et al.*[109]) (*C*) Cellular action potentials in cardiomyocytes from LQT1 and LQT2 hearts demonstrate prolonged APD (modified with permission from Brunner *et al.*[109]) (*D*) Spontaneous TdP in oestradiol-treated LQT2 rabbit initiated by short-long-short sequence during episode of 'pseudo' AV block due to pronounced prolongation of ventricular refractoriness (modified with permission from Odening *et al.*[112]).

Studies in transgenic LQT1 and LQT2 rabbit models have also been instrumental in evaluating the pro-arrhythmic, harmful, or anti-arrhythmic, beneficial effects of frequently utilized drugs,[111,115,118] circulating metabolites,[119] or hormones in LQTS.[112,120] Moreover, several mechanisms underlying pro-arrhythmic effects of oestradiol and anti-arrhythmic, protective effects of progesterone have been identified in LQT2 rabbit models—the latter being based on shortening of repolarization, reduction of EAD formation, and $Ca^{2+}$ stabilizing effects.[112] These studies suggest that progesterone-based therapies may be considered as novel anti-arrhythmic add-on approaches in female LQTS patients. Recently, potential harmful, pro-arrhythmic effects of postpartum hormones oxytocin and prolactin via $I_{Ks}$-inhibition have been revealed in the LQT2 rabbit models[120] that might contribute to the clinical observation of an increased postpartum arrhythmic risk - particularly in LQT2.[91]

In recent years, evidence has accumulated that in LQTS mechanical function is subclinically altered with impaired diastolic relaxation and prolonged contraction duration.[68–70] Using *phase-contrast*-based magnetic resonance imaging, a regionally heterogeneous reduced diastolic function was demonstrated in transgenic LQT2 rabbits,[113] thus supplementing clinical findings with important insights into regional mechanical heterogeneity. In addition, a spatial correlation between the extent of electrical dysfunction (prolongation of APD) and impaired diastolic function[113] and a correlation between the extent of mechanical dysfunction and arrhythmic risk was revealed.[121] These experimental as well as first clinical data on differences in the extent of mechanical function among symptomatic and asymptomatic subjects[71] suggest a potential future role for the assessment of mechanical dysfunction for risk stratification in LQTS. Moreover, the extent of mechanical dysfunction and its heterogeneity might not only reflect the extent of electrical dysfunction but may also be causatively linked to arrhythmia formation via mechano-electrical feedback.

Another animal model frequently used in long QT related research is the zebrafish.[122] Zebrafish share pronounced similarities with human cardiac electrophysiology in terms of ventricular AP shape, AP/QT duration, and repolarizing ion currents—namely $I_{Kr}$.[123,124] Furthermore, as the zebrafish is similarly sensitive to pharmacological modulations by $I_{Kr}$-blocking drugs, it has emerged as a model for drug safety testing.[125,126] Rather than inducing LQTS by genetic manipulation of known disease causing mutations—as done in the rabbit and mouse LQTS models

highlighted in the previous sections—spontaneous LQTS zebrafish mutants caused by mutations in zERG, the zebrafish ortholog of KCNH2, do exist and can be identified in phenotype-based screening approaches.[125,127] Among them, the zebrafish *breakdance* mutant, which carries the trafficking deficient *KCNH2*-I59S mutation, recapitulates several features of severe forms of human LQT2 including spontaneous EADs, and 2:1 AV block due to pronounced ventricular AP prolongation.[127,128] Using this zebrafish model in a relatively high-throughput chemical screen has resulted in the identification of flurandrenolide and the novel compound 2-MMB, which are both able to rescue trafficking and may lead to novel therapeutic approaches of LQTS.[128] In addition to chemical screens for discovery and testing of novel drugs, zebrafish have also been used for phenotype-based screens to identify novel genes and gene networks implicated in the regulation of cardiac repolarization.[129]

Animal models always show some species differences compared to human pathophysiology. Therefore, human diseases should ideally be studied in human organs, tissues, or cells. In recent years, induced pluripotent stem cell (iPSC) technologies have thus been utilized to investigate human iPSCs differentiated into cardiomyocytes (iPSC-CMs) derived from LQTS patients. Specifically, in 2010 and 2011, it was demonstrated in proof of principle studies that the three main genetic forms of LQTS can be modelled in iPSCs derived from patients' fibroblasts.[130–132] Moretti *et al.*[130] were the first to study iPSC-CMs obtained from an LQT1 patient carrying the *KCNQ1*-R190Q mutation, demonstrating that the cells recapitulated the electrophysiological features of the disease (i.e. altered $I_{Ks}$ activation and deactivation resulting in prolonged APD and increased susceptibility to catecholamine-induced tachyarrhythmia). Itzhaki *et al.*[131] created iPSC-CMs from an LQT2 patient, carrying the *KCNH2*-A614V missense mutation, again recapitulating clinical features and showing the usefulness of the system to evaluate potential pharmacologic treatments. More recently, a drug repurposing strategy was tested in LQT2 iPSC-CMs. Specifically, the drug Lumacaftor, already approved for clinical use in patients with cystic fibrosis harbouring the most common mutation for this disease (CFTR-Phe508 deletion), was tested in LQT2 cardiomyocytes carrying mutations with or without trafficking defect.[133] Lumacaftor corrects the trafficking defect induced by the CFTR-Phe508 deletion, through a still unknown mechanism, thus it was hypothesized that it might also correct trafficking defects caused by *KCNH2* mutations ('class 2' mutations).[133] Indeed, Lumacaftor reduced the field potential duration (analogous to QT interval at the cellular level) only in iPSC-CMs with trafficking deficient *KCNH2* mutations.[133] A Phase II clinical study on two adult patients in whose cardiomyocytes the drug proved efficacious found that the drug shortened QTc by ~30 ms, an encouraging effect but less than expected from data with iPSC-CMs.[134] Larger clinical studies are clearly warranted to provide more conclusive evidence of the efficacy of Lumacaftor in LQT2.

### 3.6 Novel therapies

Two novel therapeutic approaches for LQTS have been studied in recent years. Molecules that correct protein trafficking defects represent the first approach. Despite being effective in vitro, their major limitation is their non-specificity and toxicity, and thus, are not suitable for clinical practice.[135] The only promising drug of this group so far identified is Lumacaftor, that was originally discovered and validated for cystic fibrosis, and later proved to rescue HERG trafficking defects in vitro[132] and to reduce the QTc in the first two LQT2 patients in which it was tested.[133] Another strategy tested successfully in iPSC-CMs was the allele-specific RNA interference rescues.[136] However, applying an RNA-based drug to patients will require more effort. The second approach is represented by clinically untested compounds that activate $I_{Ks}$ or $I_{Kr}$. ML277 is a selective KCNQ1 activator[137] that enhances $I_{Ks}$ by stabilizing the activated state of the channel[138] and shortens APD of patient iPSC-CMs-harbouring a loss of function mutation in KCNQ1.[139] Several $I_{Kr}$ activators have been identified, such as RPR-260243 that slows the rate of Kv11.1 channel deactivation,[140] and several compounds that markedly enhance outward $I_{Kr}$ by inhibiting channel inactivation, including ICA-105574,[141] ML-T531,[142] and AZSMO-23.[143] PD-118057 increases channel open probability of Kv11.1 and shifts its voltage dependence of inactivation to more positive potentials.[144] NS1643 increases both $I_{Kr}$ peak and tail currents[145] and shortens APD and QT in transgenic LQT2 rabbits.[146] However, all of these compounds affect cardiac ion channels other than Kv11.1 and it is also unclear whether their effects on $I_{Kr}$ can be limited to prevent excessive (and thus potentially pro-arrhythmic) shortening of the QT interval.

## 4. Short QT syndrome

### 4.1 Clinical presentation

SQTS is a rare, but potentially lethal congenital channelopathy characterized by accelerated cardiac repolarization and shortened QT interval (QTc < 320–340 ms).[147,148] The phenotype of SQTS patients is highly variable—ranging from completely asymptomatic to those presenting with various arrhythmia-associated symptoms such as dizziness, syncope, or even SCD.[148] In the worst cases, patients may develop SCD in infancy (sudden infant death syndrome).[149] Forty percent of patients present with SCD due to VT/VF as their initial symptom.[148] Of note, gender differences in the arrhythmia free survival over longer follow-up were reported with significantly higher VT/VF/SCD rates among female SQTS patients than males.[148,150]

In addition to ventricular arrhythmia, patients are prone to develop early-onset, familial AF,[147] with variable AF prevalence reported in different SQTS families ranging from 10% to over 60%[151,152] and pronounced genotype differences in AF risk.[153] The reduced penetrance with a clinically manifest phenotype observed in (only) around 80% of mutation-positive subjects[153] and the marked variability in disease phenotype,[154] indicate a potential role of genetic modifiers and remodelling as determinants of disease severity.

### 4.2 Molecular mechanisms

Since its first description in 2000,[155] causative mutations have been identified in six different genes: SQTS types 1–3 are associated with gain-of-function mutations in *KCNH2*, *KCNQ1*, and *KCNJ2*, encoding Kv11.1, Kv7.1, and Kir2.1 channels respectively[156–158] (*Figure 3*), whereas SQTS types 4–6 are caused by loss-of-function mutations in $Ca^{2+}$ channels. Mechanisms of $K^+$ channel gain of function include reduced inactivation, faster activation, slowed deactivation or constitutive opening (failure to close). In SQT1, missense mutations such as N588K[156] or T681I[159] in Kv11.1 cause a dramatic shift (e.g. +50 mV for T618I) in the voltage required for half-maximal channel inactivation, resulting in a pronounced enhancement of outward $I_{Kr}$ during the plateau phase of the action potential and a markedly shorter APD. In addition to faster ventricular repolarization, SQT2 is characterized by AF and sinus bradycardia and is caused by missense mutations in Kv7.1 such as V307L[157] that enhance the rate of channel activation, or V141M[154] that greatly slows deactivation (channel closure) by altering voltage sensor-pore coupling.[160] SQT3 caused by missense mutations in Kir2.1 (e.g. D172N, V93I, E299V) is characterized by tall and asymmetrical T waves[39,158,161] and AF in many,

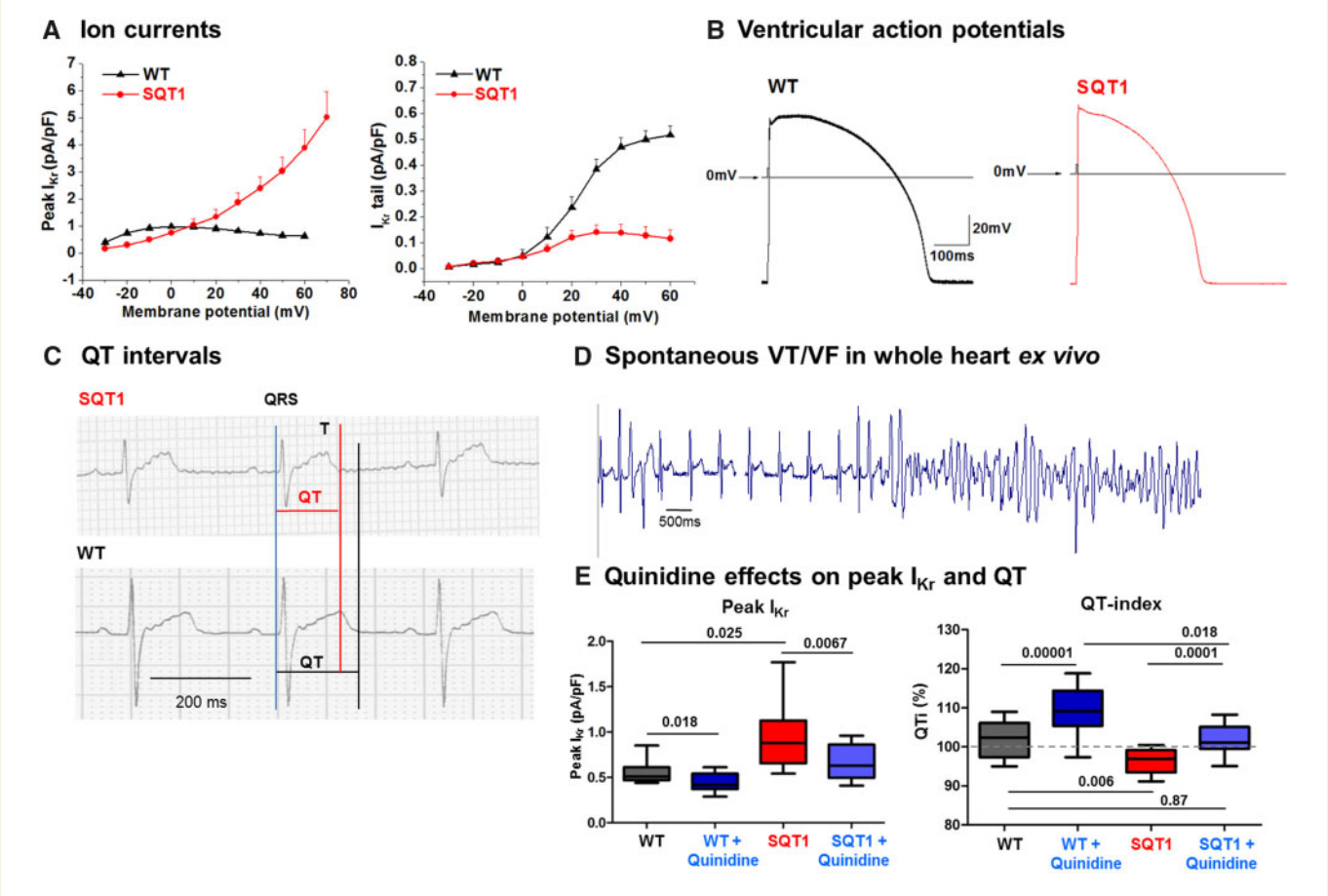


**Figure 4** Transgenic SQTS rabbits. (*A*) Increased peak $I_{Kr}$, due to impaired inactivation at positive membrane voltages (left panel) and decreased $I_{Kr}$ tail (right panel) in SQT1 cardiomyocytes. (*B*) Representative cellular action potential recordings in ventricular cardiomyocytes indicating shortened APD in SQT1. (*C*) Representative surface ECG recordings indicating shortened QT interval in SQT1. (*D*) Episode of spontaneous VT in Langendorff-perfused SQT1 heart *ex vivo*. (*E*) Quinidine reduces peak $I_{Kr}$ in SQT1 cardiomyocytes thereby normalizing the heart rate corrected QT-index (from 95% to 100%) (modified with permission from Odening *et al.*[169]).

but not all patients. These missense mutations all increase outward currents (i.e. reduce extent of inward rectification) conducted by Kir2.1 channels. The SQT3-associated gain of function mutation in Kir2.1, K346T enhances cardiac $I_{K1}$ amplitude by reducing channel protein ubiquitylation and its interaction with caveolin 2, effects that enhance channel targeting to, and stability in, the surface membrane.[162]

## 4.3 Diagnosis and risk stratification

The diagnostic work-up includes (repetitive) 12-lead ECG, 24-h Holter ECG as well as exercise testing. The 2015 European Society of Cardiology (ESC) Guidelines for the prevention of SCD[163] suggest that a diagnosis should be reached in all patients with a QTc ≤340 ms, while when the QTc is between 340 and 360 ms, SQTS can be diagnosed only in the presence of at least one additional criterion that could be either presence of a pathogenic mutation, family history of SQTS, family history of SCD below age 40 or survival of a VT/VF episode in the absence of heart disease. The Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndrome[79] has suggested a slightly lower cut-off (QTc ≤ 330 ms). However, it is worth noting that for QTc to be diagnostic it should always be below the indicated cut-off value and not only in bradycardic conditions and thus, a 12-lead 24-h Holter evaluation is very important. Another typical feature of affected individuals is the reduced rate-adaptation of QT during exercise testing (more shallow QT/HR relationship) with an absolute QT shortening that should be <60 ms.[164] Finally, other ECG characteristics that could support the diagnosis are the PR depression and a JTp between 90 and 120 ms.[165]

Importantly, to date, reliable risk stratification strategies to identify SQTS patients at risk for lethal arrhythmias/SCD are lacking. Inducibility of AF and VT/VF during electrophysiological studies is increased (60%)[166]; however, its clinical relevance for risk stratification remains unclear. Scoring systems, which include clinical parameters, ECG criteria and/or electrophysiological work-up (including programmed ventricular stimulation) have not yet helped to identify pro-arrhythmic risk factors and high-risk patients.[147,148] The only strong predictor of recurrent ventricular arrhythmias is survived/resuscitated cardiac arrest.[148]

## 4.4 Cellular and animal models

Despite the first description of SQTS in 2000,[167] our knowledge on arrhythmia mechanisms, triggers, and consequences for risk stratification is limited, likely due to the small number of SQTS cases (<200)

characterized to date. The lack of knowledge regarding this disorder increases the importance for the development of cellular and animal models that recapitulate the SQTS phenotype to elucidate arrhythmogenic mechanisms, to identify risk factors and to develop novel therapies.

Until recently, only drug-induced SQTS animal models were available with limited translational potential. The first available genetic animal model for SQTS was the zebrafish model *reggae* (expressing the missense mutation L499P in zERG) that results in similar dysfunction in $I_{Kr}$ biophysical properties as that observed in human SQT1[168] as well as a shortened QT. Recently a transgenic rabbit model for SQT1 carrying the disease-specific human mutation *KCNH2*-N588K was generated and characterized.[169] This SQT1 rabbit model mimics the human disease phenotype on all levels (from ion current, cellular, tissue, and whole-heart levels to *in vivo*) with shortened QT, more shallow QT/RR slope, shortened atrial and ventricular refractoriness and APD, as well as increased VT/VF and AF inducibility. This phenotype results from an increase in steady-state $I_{Kr}$ due to impaired channel inactivation[169] (*Figure 4*). Cellular experiments revealed that the multi-channel blocker quinidine normalized QT and APD in SQT1 rabbits by reducing the pathologically enhanced $I_{Kr}$. Electrical remodelling was also observed in $I_{K1}$ and $I_{Ks}$, effects that contribute to the electrical disease phenotype. These unanticipated effects on other currents warrants further investigation and may be causatively linked to phenotypic variability in human subjects.

The first human iPSC-CM genetic models of SQT1 were developed from human skin fibroblasts of different SQT1 patients carrying *KCNH2*-N588K or *KCNH2*-T618I missense mutations.[170–172] These SQT1 iPSC-CMs resemble the expected patient's cellular phenotype with shortened APD, and spontaneous arrhythmic events. In confluent two-dimensional iPSC-derived cardiac cell sheets of *KCNH2*-N588K iPSC-CMs, arrhythmogenesis could be visualized, revealing increased inducibility of sustained spiral waves, accelerated and stabilized rotors, increased rotor rotation frequency, increased rotor curvature, and increased rotor complexity.[170] Treating the cells with quinidine abolished the arrhythmic events and prolonged APD,[171,172] indicating that SQT1 iPSC-CMs are useful tools for further mechanistic and therapeutic studies.

### 4.5 Traditional therapies

As SQTS survivors of SCD continue to be at high risk for developing recurrent ventricular arrhythmias,[148] ICDs are the standard, guideline-recommended therapy for these patients.[173] However, due to the short QT and the peaked T-wave morphology, the risk for T-wave oversensing-induced inappropriate shocks are relatively high in SQTS patients.[174] Although appropriate shocks are documented in up to 17.5% of SQTS patients, the rate of complications is even higher with up to 54% in patients during a median follow-up time of 67.4 months.[175] Supportive drug therapies may provide additional protective effects, as recently shown for hydroquinidine that prolonged/normalized the QT interval and effectively prevented ventricular arrhythmias in SQTS patients.[176] However, known side effects of hydroquinidine such as gastrointestinal intolerance may lead to non-compliance in many patients, and the drug may not be effective in all genotypes - as previously described for other drugs such as sotalol.[177,178]

### 4.6 Novel therapies

SQTS caused by a gain of function mutations in Kv11.1 or Kv7.1 channels could conceivably be treated with blockers or gating modulators that reduce net outward conductance of the mutant channel or other $K^+$ channels that contribute to action potential repolarization. Already approved drugs may have utility in SQTS. Examples include chloroquine for SQT3 because of its ability to block both wild type and mutant Kir2.1 channels,[179] or a combination of $K^+$ and $Na^+$ channel blockers that together prolong both effective refractory period and wavelength for re-entry.[180]

## 5. Conclusions

Normal $K^+$ channel function is essential to maintain electrical stability in the heart. Gene mutations that alter the assembly, trafficking, turnover or gating of cardiac $K^+$ channels can cause LQTS, SQTS, J-wave syndromes and AF. Although remarkable progress in our understanding of the genetic and physiological basis of these inheritable $K^+$ channelopathies have been elucidated in the past 25 years,

mechanism-based therapies are largely missing. We anticipate that a more complete understanding of the molecular basis of mutation-induced channel dysfunction, additional transgenic animal models, as well as advances in gene-therapy techniques will provide insights that yield novel arrhythmia-specific, and in some cases, channel mutation-specific therapies in the future.

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