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HERG1 channelopathies

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Abstract

Human ether a go-go-related gene type 1 (hERG1) K^+ channels conduct the rapid delayed rectifier K^+ current and mediate action potential repolarization in the heart. Mutations in *KCNH2* (the gene that encodes hERG1) causes LQT2, one of the most common forms of long QT syndrome, a disorder of cardiac repolarization that predisposes affected subjects to ventricular arrhythmia and increases the risk of sudden cardiac death. Hundreds of LQT2-associated mutations have been described, and most cause a loss of function by disrupting subunit folding, assembly, or trafficking of the channel to the cell surface. Loss-of-function mutations in hERG1 channels have also recently been implicated in epilepsy. A single gain-of-function mutation has been described that causes short QT syndrome and cardiac arrhythmia. In addition, up-regulation of hERG1 channel expression has been demonstrated in specific tumors and has been associated with skeletal muscle atrophy in mice.

Keywords

Cardiac electrophysiology; Cardiac potassium current; Ether-à-go-go; K^+ channel; Ventricular fibrillation

Introduction

KCNH2, the gene encoding the human ether a go-go-related gene type 1 (hERG1) K^+ channel, was discovered in 1994 [109]. Based on the biophysical properties of heterologously expressed channels, it was proposed that hERG1 channels conduct the rapid delayed rectifier K^+ current, I_{Kr} in cardiomyocytes [83,102]. I_{Kr} is one of several K^+ currents that mediate repolarization of vertebrate cardiomyocytes and is distinguished by its disproportionately rapid rate of inactivation compared to activation, its association with an inherited form of arrhythmia, and by its clinically significant pharmacology.

A reduction of I_{Kr} caused by long QT syndrome (LQTS)-associated mutations in *KCNH2* can induce ventricular arrhythmia and cause sudden cardiac death. As reviewed elsewhere [90], in noncardiac cells, ERG1 channels primarily contribute to maintenance of the resting potential. In addition to the heart, ERG1 expression has been identified in several regions of the brain [27], tumor cells [5,10,27], gastro-intestinal smooth muscle myocytes [21], pancreatic β-cells [79], lactotrophs [8], carotid body cells [68] and the inner ear [66]. However, with the exception of the infrequent association with epilepsy, *KCNH2* mutations are not known to cause disease in organs other than the heart. Several excellent and comprehensive reviews of hERG1 channels have recently appeared [47,70,75]. Here, the role of hERG1 channels in human disease is reviewed.

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hERG1 channel structure and accessory subunits

In humans, *KCNH2* is located on chromosome 7q35–36, and the coding region comprises 16 exons spanning approximately 34 kb of genomic sequence. The full-length hERG1 subunit (hERG1a) is composed of 1,159 amino acids with a predicted molecular mass of 127 kDa and has six transmembrane domains (S1–S6). hERG1a has a long (376 amino acids) N-terminus and residues 1–135 comprise the so-called "eag domain" that was crystallized and found to be the first eukaryotic example of a protein– protein interaction structure called a Per–Arnt–Sim (PAS) domain [58]. The function of the PAS domain in hERG1a is uncertain; however, LQTS-associated mutations in this region disrupt channel trafficking and accelerate the rate of deactivation [14,58], perhaps by disrupting its interaction with the S4–S5 linker of the channel [103]. The PAS domain can be phosphorylated [13,18] and needs to be properly folded for normal trafficking of the channel complex from the endoplasmic reticulum (ER) to the Golgi and cell surface [69]. An alternatively spliced variant of hERG1 (hERG1b) was isolated from mouse and human heart [50,51] and is composed of 819 amino acids with a predicted molecular mass of 94 kDa [39]. The N-terminus of hERG1b is only 36 amino acids and lacks the PAS domain but has an "RXR" ER retention signal sequence that prevents its trafficking to the surface membrane unless coassembled with hERG1a subunits [72]. In rodents, erg1a and erg1b has also been shown to coassemble in the brain [27]. The large C-terminus of both hERG1a and hERG1b contains a cyclic nucleotide binding domain (CNBD). Unlike cyclic-nucleotide gated channels, where binding of cyclic adenosine monophosphate (cAMP) to the CNBD is required for channel activation, cAMP has a relatively minor effect on hERG1 channel gating, causing a few millivolts shift in the voltage dependence of channel activation [18].

Similar to other Kv channels, functional hERG1 channels are tetrameric complexes formed by coassembly of four α-subunits, either hERG1a subunits alone or hERG1a plus hERG1b subunits [39,71,80]. In heterologous expression systems, hERG1 proteins can also coassemble with two ancillary β-subunits, MinK (KCNE1) and MiRP1 (KCNE2) [1,55]. The KCNEs are small transmembrane proteins (123–129 amino acids) with a single transmembrane domain. Although MinK most likely functions as the accessory subunit for KCNQ1 to form I_{Ks} channels in the heart [7,82], MinK can also modulate hERG1 channel density when overexpressed in heterologous expression systems [9,55]. MiRP1 was initially reported to alter the pharmacology and gating kinetics of hERG1 [1], and LQTS-associated mutations in MiRP1 alter hERG1 currents differently from wild-type MiRP1 [1,26,34,53]. However, the consequences and physiological significance of this interaction has been contested [110], and the effects of MiRP1 in heterologous expression studies are variable [3,54,110]. Moreover, it is not clear whether MiRP1 is expressed at high enough levels to affect hERG1 function throughout the heart as physiologically significant levels may be limited to pacemaker cells and Purkinje cells of the conduction system [73]. Most recently, it was reported that interaction of MiRP1 with KCNQ1 may be more physiologically significant than its association with hERG1. Along with MinK, MiRP1 can coassembly with KCNQ1 to form a heteromultimeric channel complex with a net result of decreased I_{Ks} conductance [36]. Moreover, targeted disruption of *kcne2* in mice suggests that constitutively active KCNQ1/MiRP1 channels are expressed in thyrocytes and that these channels are required for normal thyroid hormone biosynthesis [77]. Altered thyroid function might have a role in LQTS associated with mutations in *KCNE2*. Linkage of *KCNE2* mutations to ventricular arrhythmia and/or sudden cardiac death in a large kindred would go a long way towards substantiating the role of MiRP1 in LQTS.

Kinetics of channel gating determine role of hERG1 in action potential repolarization

Similar to other Kv channels, hERG1 is activated by voltage. The threshold for channel opening is about −50 mV, and the voltage required for 1/2 activation is about −30 mV. The single-channel conductance (γ) of hERG1 channels is 12.4 pS between −60 and −120 mV when determined with a $[K^+]_o$ of 120 mM [57,122]. At physiological levels of $[K^+]_o$ (5 mM), γ determined by nonstationary noise analysis is about 2 pS at 0 mV [44]. hERG1 channels also inactivate in a voltage-dependent manner with a half point of about −85 mV. Channel activation is slow, especially compared to the rapid onset of P-type inactivation that is proposed to be mediated by rearrangement of the selectivity filter [45]. The faster rate of inactivation results in a voltage-dependent reduction in whole cell conductance and a bell-shaped *I*−*V* relationship (Fig. 1). When the membrane is repolarized, channels recover from inactivation at a rate about ten times faster than the rate of deactivation. These kinetic features strongly affect the contribution of hERG1 to net current during the delayed repolarization phase typical of cardiac action potentials. Channel inactivation dominates at positive transmembrane potentials and greatly reduces the magnitude of hERG1 current at the peak of a cardiac action potential. During the plateau phase and continuing through phase 3 repolarization, channels recover from inactivation, and because deactivation is relatively slow, hERG1 current transiently increases in magnitude even as the electrochemical driving force for K^+ efflux is reduced.

Homotetrameric hERG1a channels deactivate slowly compared to homotetrameric hERG1b channels, whereas heteromultimeric hERG1a/1b channels deactivate at an intermediate rate that more closely matches the rate determined in native cardiomyocytes [50,51]. Slow deactivation associated with the hERG1a subunits was proposed to be mediated by an interaction between its N-terminal PAS domain and the S4–S5 linker [104], a structure that couples voltage sensor movement to opening and closing of the activation gate [52]. Deletion of the PAS domain greatly accelerates deactivation [58,95], and coexpression with an independent N-terminal domain (residues 1–135) can restore slow deactivation [28].

Discovery of the link between hERG1 channels and the long QT syndrome

The clinical condition known as “long QT syndrome” was initially reported in 1957 by Jervell and Lange-Nielsen [35] in children that were deaf–mute and had prolonged QT intervals, recurrent episodes of syncope, and a high incidence of sudden death. Six years later, Romano et al. [78] and Ward [108] independently described patients who also experienced syncope and sudden cardiac death but were not deaf. These initial studies indicated that at least some cases of ventricular arrhythmia associated with a prolonged QT interval were inherited. The clinical manifestations were described in detail, and treatment regimens were developed over the next 25 years, with the most significant contributions made by Moss, Schwartz, Vincent, and their colleagues [59–63,85,86,89]. In 1991, molecular genetic studies began to zero in on the genetic basis responsible for congenital forms of this disorder. The initial study by Keating, Vincent, and colleagues [42] linked the LQTS phenotype of a large kindred to a small region of chromosome 11 that later was shown to contain *KvLQT1* [105] (now called *KCNQ1*), a gene that encodes the α-subunits that coassemble to form I_{Ks} channels [7,82]. By 1997, mutations in four different ion channel genes were linked with inherited LQTS [19,98,99,105,106]. The rapid progress in the description of the molecular basis of LQTS and other channelopathies was paralleled by the discovery of new ion channels. Low stringency screening of a human hippocampal cDNA library for transcripts homologous with *eag*, a K^+ channel gene expressed in *Drosophila* and mammals [109], led to the discovery in 1994 of two new K^+ channel gene subfamilies: eag-related gene (*erg*) and eag-like (*elk*). A year later, mutations in the human *erg* gene (*HERG*) were associated with LQTS in multiple families [19]; soon afterwards, it was discovered that *HERG* (now called *KCNH2*) encodes the α-subunits of the K^+ channel that

conducts the cardiac rapid delayed rectifier K^+ current, I_{Kr} [83,102]. In 1997, two new members of the *erg* gene subfamily were discovered and named erg2 and erg3 [91]; hence, the original *HERG* gene is now more properly referred to as *HERG1*. There are currently 12 different recognized forms of inherited arrhythmia that include prolonged QT interval as a clinical symptom. The common name for each "syndrome" (LQT1–LQT12) is based on the chronological order that the corresponding gene or chromosomal locus was discovered (Table 1). Long QT syndrome caused by mutations in *KCNH2* was the second LQTS loci described and thus is called LQT2.

Clinical aspects of LQT2

LQTS often presents as unexplained seizures or syncope, and clinical diagnosis is confirmed by measurement of a prolonged QT interval on the body surface electrocardiogram (ECG). The QT interval is a measure of the time required for electrical repolarization of the ventricles. In addition to a prolonged QT interval, the hallmark ECG pattern for LQT2 is a notched (bifid) T-wave [117], but this feature is not observed in all patients with a confirmed LQT2 genotype. Syncope associated with LQTS is caused by a specific ventricular tachyarrhythmia called torsade de pointes ("twisting of the points") that is distinguished by sinusoidal twisting of the QRS axis around the isoelectric line of an ECG tracing. Torsade de pointes can either cease spontaneously or degenerate into ventricular fibrillation, a highly disorganized electrical activity that is life-threatening and is a major cause of sudden death. The incidence of congenital LQTS has not been accurately defined, but it has been estimated that as many as 1 in 2,500 people worldwide are affected [101]. Congenital LQTS is most often caused by dominant mutations in *KCNH2* or *KCNQ1*. In the vast majority of LQTS patients, the heart is structurally normal. An exception to this generality is LQT8, where gain-of-function mutations in the cardiac L-type Ca^{2+} channel gene (*CACNA1C*) cause developmental defects in addition to a severely prolonged QT interval [96,97].

For LQT2 patients, the most common trigger for arrhythmia appears to be emotional stress. In the most cited genotype–phenotype correlation study [88], Schwartz and colleagues reported that, in a sample of 177 symptomatic patients with LQT2, the majority of lethal or nonlethal cardiac events were associated with an increased sympathetic tone: 51% and 15% of the events were triggered by emotion and exercise, respectively. The other arrhythmia-related events (34%) occurred while the affected individuals were sleeping or resting with no obvious arousing stimulus. By contrast, the most common trigger for LQT1 (*KCNQ1* mutations) is exercise (68% of events), while most events associated with LQT3 (*SCN5A* mutations) occurred while the patients were asleep (55% of events). A very common trigger for LQT2-associated arrhythmia is a loud and unexpected noise, such as the buzzing of an alarm clock, or the ringing of a telephone or doorbell [112]. In the ECG illustrated in Fig. 2, a subject with confirmed LQT2 (mutation: G604S) was asleep when an alarm clock triggered multiple ventricular extrasystoles followed by torsade de pointes. A recently described but uncommon trigger for LQT2 is fever [2].

LQTS can also be acquired, either in association with chronic heart failure or an undesirable side effect of a drug that blocks hERG1 channels or interferes with their trafficking from the ER to the cell surface [22]. Other significant risk factors for congenital or acquired LQTS are hypokalemia, bradycardia, and female gender [43]. Not surprisingly, drug-induced arrhythmia is probably far more likely in subjects with congenital LQTS, regardless of the underlying mutation, but this association has been difficult to confirm [115]. For drugs (e.g., terfenadine) that are otherwise metabolized to a hERG1-inactive metabolite, a compromised liver function due to disease or mutations in specific CYP isoforms is also an important risk factor [22]. Inhibitors of CYP3A4 (e.g., erythromycin and other macrolide antibacterial agents) can also prevent metabolism of coadministered drugs such as terfenadine and cisapride to their hERG1-

inactive metabolites [22]. The consequences of drug-induced QT prolongation can be serious and closely resemble LQT2, with torsade de pointes arrhythmia, ventricular fibrillation, and sudden death [84]. Not long ago, drug-induced QT prolongation was a property actively sought as an antiarrhythmic mechanism, a so-called “class III” drug effect [93] that was later shown to be commonly mediated by blocking of hERG1 channels. Prolonged electrical refractoriness of the ventricle can prevent certain types of arrhythmia, but the proarrhythmic potential of this action is not trivial and prompted pharmaceutical companies to abandon discovery and development of drugs with this activity and to actively screen all noncardiac drugs for this unwanted side effect as a normal component of drug development.

The treatment of LQT2 is the same as for other forms of the disorder. The most common therapy is administration of beta-receptor blockers. The effectiveness of beta-blocker therapy was documented over a 5-year period in a large study with 869 LQTS patients, where syncope, aborted cardiac arrests, or death were reduced in the probands from 0.97 to 0.31 events per year, and in affected family members from 0.26 to 0.15 events per year [64]. Recently, activators of hERG1 channels have been discovered [29,40,119], but none of these compounds have been evaluated in a clinical trial to determine efficacy or safety. High-risk patients often receive left cardiac sympathetic denervation and/or an implantable cardioverter defibrillator. In the most comprehensive study involving 147 LQTS patients, left cardiac sympathetic denervation reduced cardiac events by ~90% [87].

Functional consequences of LQT2-associated hERG1 mutations

According to the on-line inherited arrhythmias database (http://www.fsm.it/cardmoc/), 291 different mutations in hERG1 were reported to cause LQT2 as of September 2009. However, this certainly underestimates the number of mutations that will eventually be discovered to cause LQT2, as evidenced by a report published in late September 2009 of an additional 159 unique *KCNH2* mutations in a sample comprising 2,500 LQTS phenotype-positive individuals and 903 genotype-positive cases [41]. This increases the known LQT2-associated mutations in *KCNH2* to a total of 450 and confirms that the location of the mutations in the hERG1 subunit is widespread (Fig. 3). In a sample of 226 genetically confirmed cases of LQT2, 62% were missense mutations, 24% were frameshift mutations, and the remaining 14% were nonsense, splice site, or inframe insertions or deletions in *KCNH2* [41]. Only a small percentage of *KCNH2* mutations have been characterized (and hence definitively verified) by a functional, in vitro electrophysiological analysis.

The functional consequences of hERG1 mutations are usually determined by comparing the current magnitude and other biophysical properties of heterologously expressed mutant channels with wild-type channels using the whole-cell voltage clamp technique. In addition, channel density at the surface membrane is often assayed using Western blots and antibodies to untagged or epitope tagged subunits. hERG1 proteins are core glycosylated in the ER. The mature glycosylation pattern is achieved in the Golgi before the protein can be adequately trafficked to the plasma membrane, and the difference sizes (135 kDa for core-glycosylated versus 155 kDa for mature protein) are used to quantify defects in folding and/or trafficking [120]. Export of hERG1 proteins from the ER and trafficking to the Golgi is dependent on the small GTPase Sar1 which regulates the formation of coat-associated protein complex II vesicles used during ER export [20]. LQT2-associated mutations in hERG1 can cause loss of function by reducing channel trafficking to the plasma membrane. As first described by Zhou et al. [120], hERG1 subunits with the LQT2-associated mutations Y611H or V822M are misfolded and retained in the ER in the core-glycosylated form. ER-retained subunits are then rapidly degraded by the ubiquitin–proteasome pathway. It is now known that defective protein folding, retention in the ER, or disrupted trafficking to the Golgi and surface membrane is the primary mechanism of loss of function caused by missense mutations in hERG1 [4]. Many of

these mutant channels can function, albeit with altered kinetic properties, if they can be induced to traffic to the membrane, either by reducing the incubation temperature during cell culture [69] or by pharmacological rescue with drugs that otherwise block the channel [24,76,116, 121]. Initial functional studies of mutant hERG1 channels were performed using heterologous expression in *Xenopus* oocytes incubated at low temperatures [81], leading to the erroneous conclusion that some mutations reduced current magnitude by affecting channel gating when actually the major defect was temperature-sensitive defective folding and reduced trafficking [69,121]. Some drugs such as arsenic trioxide (As_2O_3) and pentamidine can also reduce hERG1 channel trafficking, specifically by disrupting the association between hERG1 channels and their chaperone proteins [23,46]. Thus, drugs can reduce hERG1 function either by direct blocking of the channel pore or by reducing hERG1 protein trafficking to the cell membrane, prompting the development of assays for both activities [111].

Homozygous mutations in *KCNH2* are very rare and, when confirmed genetically, result in intrauterine death or live birth with severe QT prolongation [33,38]. Thus, heterozygous mutations in hERG1 are the norm for LQT2. For this reason, it is important to assay the defects caused by a specific heterozygous mutation in *KCNH2* by coexpression of mutant and wild-type hERG1 subunits. This approach is useful to determine if a particular missense mutation causes a dominant-negative suppression of channel density and/or function. For example, hERG1 subunits with the pore mutation G638S act like a “poison pill” in that it freely associates with normal hERG1 subunits and destroys the function of tetrameric channels that contain even a single mutant subunit [81]. Transgenic rabbits with the G628S mutation exhibited a >50% incidence of sudden arrhythmic death [12]. Surprisingly, rather than the expected compensatory increase in a repolarizing current, the reduction in I_{Kr} in these rabbits was accompanied by a decreased I_{Ks} [12]. More disruptive mutations (e.g., frame-shifts, premature stops, or deletions that produce truncated proteins) and even some missense mutations can cause haploinsufficiency, where mutant and normal subunits do not interact and only 1/2 of the total number of hERG1 channels are likely to be dysfunctional or absent (rapidly degraded).

Although certainly not as common as folding and trafficking defects (estimated to be the mechanism for up to 90% of missense mutations), some mutations reduce I_{Kr} by altering the properties of hERG1 channel gating. Mutations that enhance inactivation (e.g., G584S) [118] or accelerate the rate of deactivation (e.g., M124R or other mutations in the PAS domain) [92] reduce the outward current contributed by I_{Kr} during repolarization of the action potential. A nonsense mutation (e.g., R1014X) causes nonsense-mediated mRNA decay rather than a production of truncated protein [25].

In 2002, Moss and colleagues [65] tested the hypothesis that the location of specific mutations in the hERG channel protein might correlate with severity of disease. In 201 subjects with 44 different mutations, 35 subjects had mutations that were located in the pore region. Subjects with pore mutations (14 in total) had more severe clinical symptoms and experienced a two times higher frequency of arrhythmia-related cardiac events than did subjects with nonpore mutations. Although not confirmed with electro-physiological analyses, the pore mutants are more likely to cause a strong dominant-negative effect, either increasing the rate of degradation of multimeric subunit assemblies in the ER/Golgi or by preventing ion conductance if the channels are successfully exported from the Golgi to the plasma membrane.

Disorders other than LQTS associated with hERG1 channels

Short QT syndrome

Gain-of-function mutations in cardiac K^+ channel genes, including *KCNQ1* [32] and *KCNJ2* [74], can result in QT interval phenotype opposite to that of LQTS. Repolarization of cardiomyocytes is accelerated and is manifested as a short QT interval on the body surface

ECG. To date, one missense mutation in hERG1 (N588K) has been associated with short QT syndrome [11]. Asn588 is located in the S5-pore linker of the hERG1 subunit, and its mutation to Lys causes a positive shift in the voltage dependence of P-type inactivation. This shift reduces the extent of inactivation, and the resulting increase in outward current during the plateau phase of the action potential hastens repolarization of the ventricle and shortens the QT interval. The finding that gain-of-function mutations in hERG1 or other K^+ channels can cause lethal arrhythmia suggests that drugs or gene therapies designed to enhance repolarizing currents as a treatment for LQTS will have to be carefully tailored to prevent excess activity of the intervention.

Epilepsy

LQTS is frequently misdiagnosed as a seizure disorder or epilepsy, and patients are therefore often treated with antiepileptic drugs. As noted above, *KCNH2 (HERG1*) was initially discovered in the hippocampus [109], and it was later demonstrated that this gene is expressed in many regions of the central nervous system. Although it might seem intuitively obvious that mutations in *KCNH2* might cause CNS disorders, it was not until very recently that a clear link was made between hERG1 mutations and epilepsy. A recent case history [67] provides what may become a more common finding in the near future. The EEG of a 60-year-old man with a 40-year history of epilepsy (tonic–clonic seizure and syncope) demonstrated paroxysmal slow waves in response to intermittent photic stimulation. His epilepsy was treated with clonazepam and zonisamide, but he suffered three bouts of seizure during times that he was off this medication. After his most recent seizure episode, he underwent a cardiac evaluation. During ECG monitoring, he suddenly developed tonic–clonic seizures that was preceded by bradycardia and QT prolongation and that coincided with torsades de pointes arrhythmia. Subsequent genetic testing revealed a missense mutation (R534C) in *KCNH2* and a family history of sudden cardiac death. He has since been successfully treated with a beta-blocker and an implantable cardioverter defibrillator [67]. This example is not an isolated case. Johnson et al. [37] recently quantified the coexistence of LQTS and seizure activity in a well-defined cohort. In 343 unrelated LQTS probands, a history of seizures was more common in LQT2 (30 of 77, 39%) than all other subtypes of LQTS combined (11 of 106, 10%). Thus, an initial diagnosis of epilepsy in a patient experiencing syncope and seizure and subsequent prophylactic treatment with an antiepileptic drug (AED) may be inadequate—ECG monitoring could reveal the more complex clinical problem of epilepsy plus LQTS, requiring coadministration of an AED and a beta-blocker.

Based on the widespread distribution of hERG1 in the nervous system, it is somewhat surprising that mutations in KCNH2 have so rarely been associated with epilepsy and not to any other neurological disorder. Disease-causing mutations in hERG2 and hERG3 have also not been described. In rodents at least, erg2 and erg3 proteins are exclusively expressed in the nervous system [91], albeit sometimes in association with erg1 [27]. All three types of erg proteins can coassemble to form heteromultimeric channels in CHO cells [113,114]. Moreover, single-cell reverse transcription polymerase chain reaction has revealed that all three erg channel types are expressed in rat embryonic rhombencephalon neurons, and voltage clamp studies suggest that currents are conducted by heteromultimeric channels [30]. It is likely that additional neuropathies may eventually be attributed to dysfunction of hERG1 as well as hERG2 and hERG3 channels.

Up-regulation of hERG1 in cancer and atrophic skeletal muscle

Enhanced expression of hEAG and hERG1 channels has been detected in several human cancer cell lines [6,10], including neuroblastomas [56], rhabdomyosarcomas [94], monoblastic leukemias, mammary carcinomas, and colon carcinoma [17]. hERG1 is also expressed in lymphocytes [94] and primary tumors of several tissues including the endometrium [16] and

colon [48]. The clinical significance of these findings are uncertain and represents a typical chicken or egg conundrum; which came first, enhanced channel expression or altered cell cycle progression? Nonetheless, pharmacological evidence suggests that up-regulated eag/erg channel expression may be important. Specific channel blockers can reduce cell proliferation [17], and the channels are involved in regulation of tumor cell migration [48] and adhesion-dependent signaling [15,31].

Erg channel expression is also altered during muscle atrophy. Erg1a channels in mice are up-regulated in skeletal muscle 6 weeks after injection with Kb human esophageal cancer cells to induce muscle atrophy [107]. In the same study, erg1a was also up-regulated in the skeletal muscle of non-weight-bearing hind limbs of mice. Moreover, treatment of mice with astemizole (a potent hERG1 channel blocker) prevented muscle atrophy. Erg1a (but not erg1b) participates in the initiation of muscle atrophy in these mice by activating ubiquitin–proteasome proteolysis, but the molecular pathways involved in this regulation are not understood [107].

Developmental disorders

A specific LQT2-associated missense mutation in hERG1 (N629D) was originally discovered as a heterozygous mutation in a subject with typical LQT2. Heterologous expression revealed that the mutation alters ionic selectivity of the hERG1 channel [49], but the main dysfunction is reduced trafficking to the cell membrane [4]. Functional consequences of the N629D mutation other than LQTS have been investigated in transgenic mice. Homozygous N629D mutations cause cessation of spontaneous pacemaker activity and embryolethality at E11.5 [100]. Several developmental defects were also noted in these mice, including altered looping architecture of the heart, poorly developed bulbus cordis, distorted branchial arches, and enhanced apoptosis in the first branchial arch and cardiac outflow tract. It is unclear how the absence of functional hERG1 currents cause these developmental defects or if these changes are relevant to the embryolethality associated with other homozygous *KCNH2* mutations.

Summary

Although hERG1 channels are highly expressed in several tissues, the pathology associated with congenital mutations in *KCNH2* appear to be largely limited to the heart. Mutations in *KCNH2* are a common cause of LQTS. Most mutations cause loss of channel function by causing the subunits to misfold and/or decrease their trafficking to the plasma membrane. The role of hERG1 channels in epilepsy, cancer, and skeletal muscle atrophy are poorly understood but deserve further inquiry.

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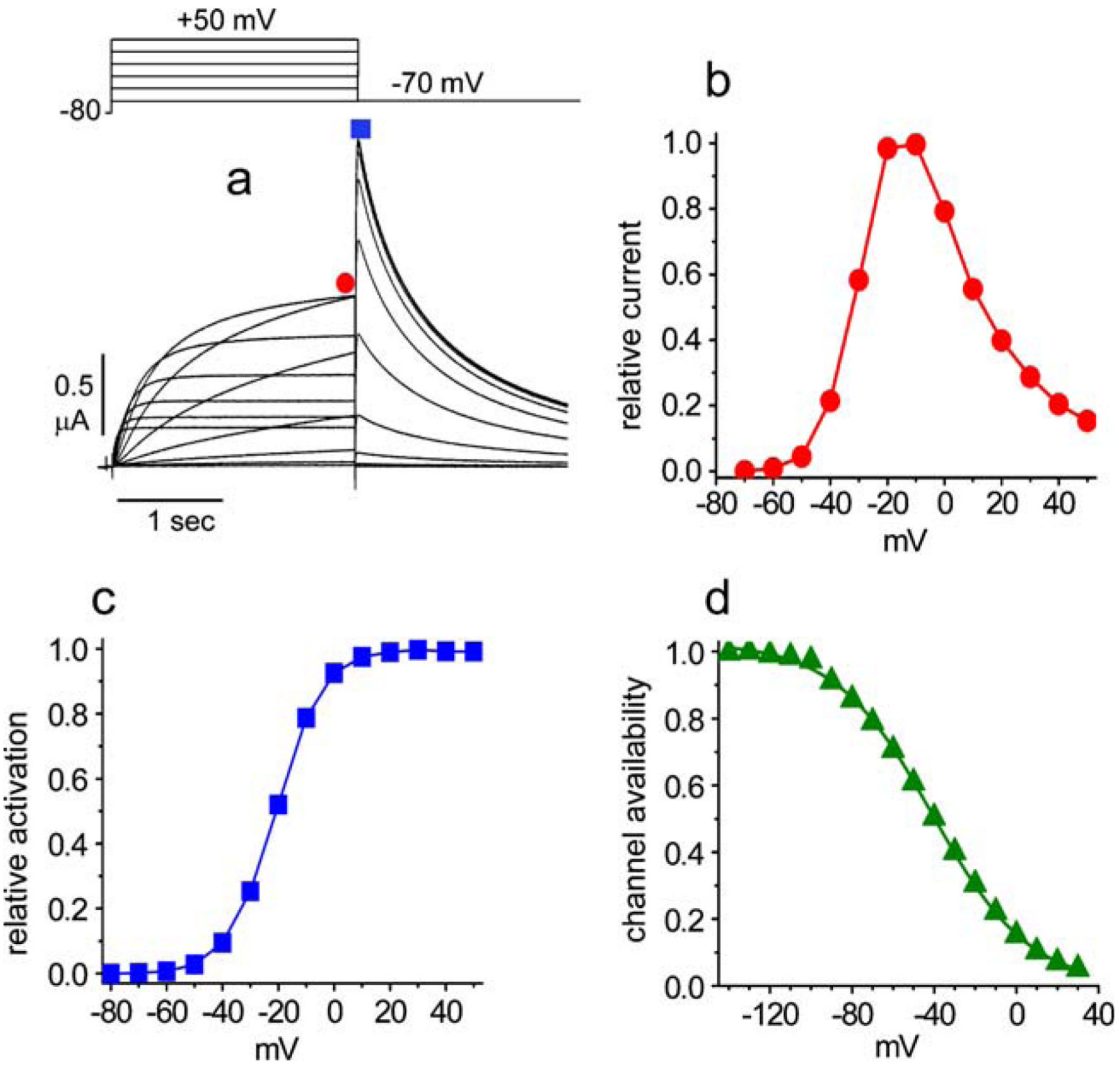

Fig. 1.

Biophysical properties of hERG1 channel currents. **a** Voltage clamp protocol (*upper panel*) and heterologously expressed hERG1 ionic currents (*lower panel*) recorded from a *Xenopus* oocyte. Currents were recorded at test potentials that ranged from −70 to +50 mV; deactivating ("tail") currents were measured at −70 mV. **b** Current–voltage (*I*−*V*) relationship for hERG1 currents measured at the end of test pulses, as indicated by *red circle* in **a**. **c** Voltage dependence of hERG1 current activation. The peak of tail currents measured at −70 mV (indicated by *blue square* in **a**) were normalized to the largest value and plotted as a function of the test potential. **d** Voltage dependence of hERG1 inactivation. Channel availability is decreased at positive potentials, resulting in a decreased magnitude of peak outward currents and the bell-shaped *I*−*V* relationship depicted in **b**

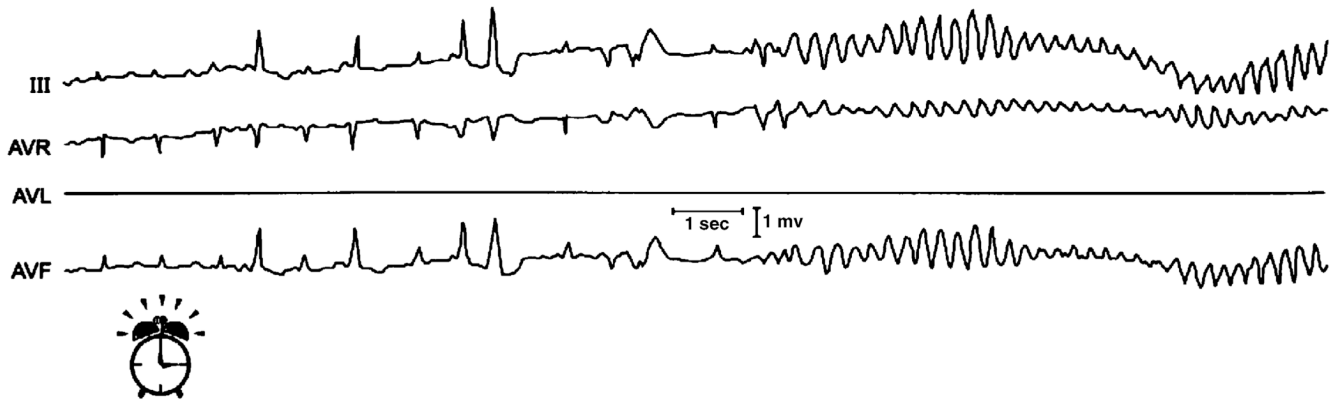

Fig. 2.
ECG recording of a sleeping LQT2 subject who was startled awake by the sudden noise from an alarm clock. Note the appearance of several ventricular extrasystoles and the long–short intervals of the QRS complexes immediately before the onset of torsade de pointes. Reproduced with permission from [112]

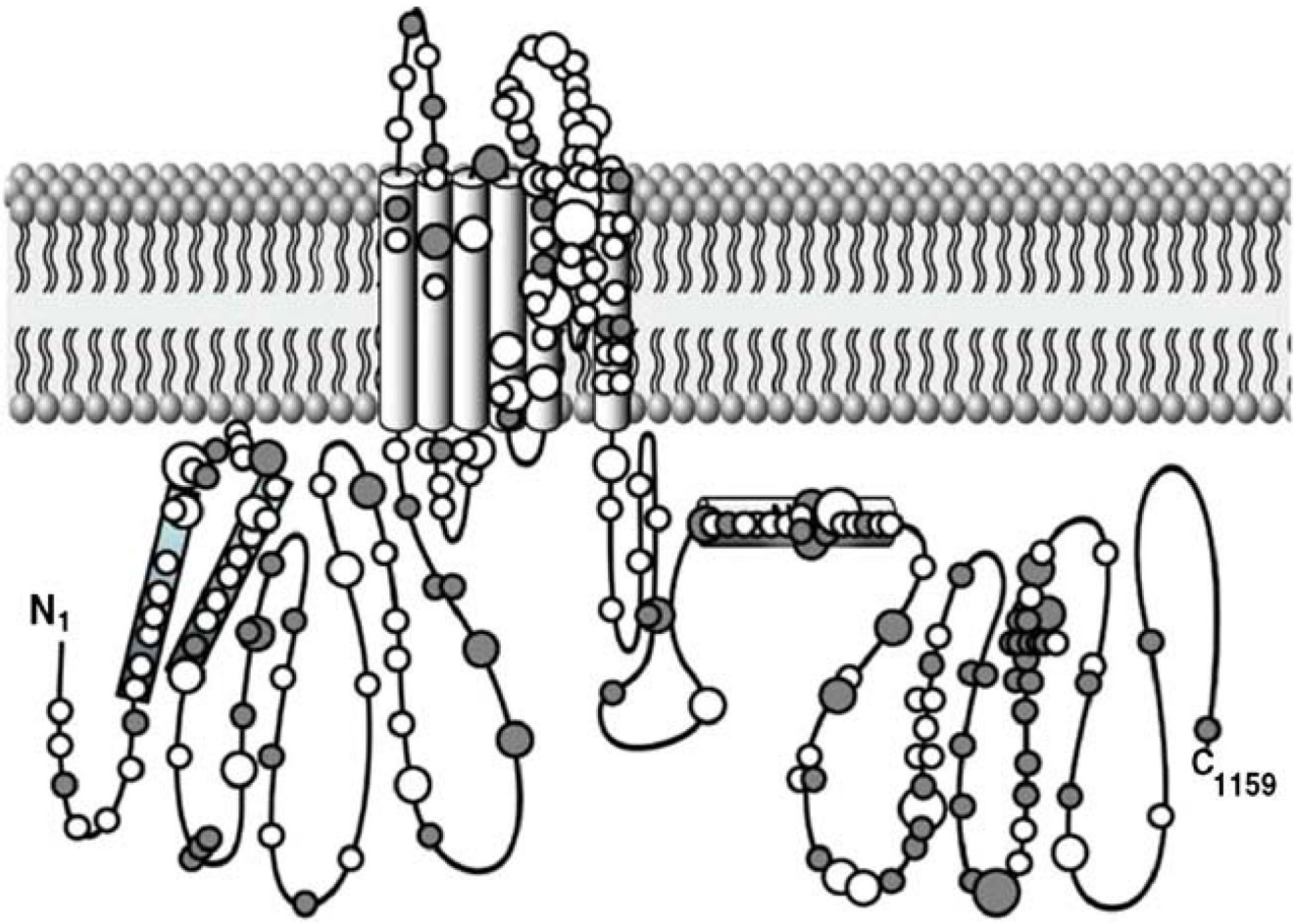

Fig. 3.

Diagram of a single hERG1 subunit, illustrating the widespread distribution in the location of LQT2-associated mutations. The subunit has six transmembrane segments and large intracellular N-terminal and C-terminal domains. Missense mutations are indicated by *open circles*; other types of mutations (i.e., frameshifts, deletions, splice site) are indicated as *filled circles*. The size of the symbol reflects the prevalence of a specific mutation (*smallest symbol* once; *largest symbol* >5 times). Reproduced with permission from [41]

Table 1

Congenital LQTS types, genes, and associated proteins. LQT1–LQT3 account for about 75% of "clinically robust" LQTS [101]. LQT9–LQT12 are extremely rare

Type	Human gene (alternative name)	Protein
LQT1	*KCNQ1 (KVLQT1)*	α-Subunit for slow delayed rectifier K channel
LQT2	*KCNH2 (HERG1)*	α-Subunit for rapid delayed rectifier K channel
LQT3	*SCN5A*	α-Subunit for Na channel ($Na_V1.5$)
LQT4[a]	*ANK2*	Ankyrin-B
LQT5	*KCNE1*	β-Subunit ("MinK") for slow delayed rectifier K channel
LQT6	*KCNE2*	β-Subunit ("MiRP1") for several K^+ channels
LQT7[a]	*KCNJ2*	α-Subunit for inward rectifier K channel (Kir2.1)
LQT8	*CACNA1C*	α-Subunit for L-type Ca channel
LQT9[a]	*CAV3*	Caveolin-3
LQT10	*SCN4B*	β-Subunit for Na channel ($Na_V1.5$)
LQT11	*AKAP9*	A-Kinase anchoring protein type 9 ("Yotiao")
LQT12	*SNTA1*	Alpha1-syntrophin

[a]These arrhythmia disorders are not always associated with prolonged QT intervals