KCNH2-K897T Is a Genetic Modifier of Latent Congenital Long-QT Syndrome

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Background—Clinical heterogeneity among patients with long-QT syndrome (LQTS) sharing the same disease-causing mutation is usually attributed to variable penetrance. One potential explanation for this phenomenon is the coexistence of modifier gene alleles, possibly common single nucleotide polymorphisms, altering arrhythmia susceptibility. We demonstrate this concept in a family segregating a novel, low-penetrant KCNH2 mutation along with a common single nucleotide polymorphism in the same gene.

Methods and Results—The proband is a 44-year-old white woman with palpitations associated with presyncope since age 20, who presented with ventricular fibrillation and cardiac arrest. Intermittent QT prolongation was subsequently observed (max QTc, 530 ms), and LQT2 was diagnosed after the identification of a missense KCNH2 mutation (A1116V) altering a conserved residue in the distal carboxyl-terminus of the encoded HERG protein. The proband also carried the common KCNH2 polymorphism K897T on the nonmutant allele. Relatives who carried A1116V without K897T were asymptomatic, but some exhibited transient mild QTc prolongation, suggesting latent disease. Heterologous expression studies performed in cultured mammalian cells and using bicistronic vectors linked to different fluorescent proteins demonstrated that coexpression of A1116V with K897T together resulted in significantly reduced current amplitude as compared with coexpression of either allele with WT-HERG. Thus, the presence of KCNH2-K897T is predicted to exaggerate the IKr reduction caused by the A1116V mutation. These data explain why symptomatic LQTS occurred only in the proband carrying both alleles.

Conclusions—We have provided evidence that a common KCNH2 polymorphism may modify the clinical expression of a latent LQT2 mutation. A similar mechanism may contribute to the risk for sudden death in more prevalent cardiac diseases. (Circulation. 2005;112:1251-1258.)

Key Words: death, sudden ■ genetics ■ ion channels ■ long-QT syndrome ■ molecular biology

The congenital long QT syndrome (LQTS) is an inherited disorder characterized by prolongation of the QT interval and an increased risk for life-threatening ventricular arrhythmias.1,2 The disease is genetically heterogeneous and is caused by mutations in one of several genes including KCNQ1, KCNH2, KCNE1, and KCNE2 encoding potassium channel subunits, the cardiac sodium channel gene SCN5A, and the L-type calcium channel gene CACNA1C.3,4

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Clinical heterogeneity is a common feature in LQTS. Members of the same family who share the same mutation may have varying degrees of QT prolongation and widely different phenotypes, ranging from no symptoms to sudden death. This is usually attributed to variable penetrance,5 but the mechanisms underlying this phenomenon are not fully understood. In 4% to 8% of LQTS probands, compound mutations help explain exaggerated disease severity compared with other family members carrying single alleles.6,7 Another potential explanation is the coexistence of modifier alleles, possibly common single nucleotide polymorphisms (SNPs) that alter arrhythmia susceptibility. This hypothesis is supported by the observation that the KCNE1-D85N polymorphism, present in ≈1% of whites,8 appears to aggravate the LQTS phenotype in some of the families reported by Westenskow et al7 who carry KCNQ1 mutations. The proposed mechanism for these effects is additive reduction in channel function and associated repolarizing current.9

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In some cases of LQTS, the disease is latent or subclinical but can be unmasked by QT-prolonging drugs or metabolic derangements such as hypokalemia. In the absence of proarhythmic drugs and metabolic factors, subclinical LQTS may become clinically manifest in later generations if a second LQTS mutation is co-inherited. This appears to be true also for certain low-frequency SNPs in LQTS genes.

We present clinical, genetic, and electrophysiological evidence indicating that a very common nonsynonymous SNP (30% carrier frequency among whites) can also promote the clinical expression of a LQTS mutation having low penetrance. This further validates the concept of genetic modification of LQTS by a common variant and carries important practical implications.

Methods

PatientAscertainment

A 44-year-old, white Italian woman presented to IRCCS Policlinico San Matteo for clinical care after cardiac arrest caused by ventricular fibrillation. After informed consent was obtained by using a protocol approved by the Ethics Review Board of the Policlinico San Matteo, Pavia, blood was collected from the proband and members of her extended family for isolation of DNA.

MutationalScreening

Genomic DNA was extracted from peripheral blood leukocytes by using standard methods and diluted to 50 ng/μL. All coding exons of KCNQ1, KCNH2, SCNS5A, KCNE1, and KCNE2 were amplified by polymerase chain reaction, using previously published primer pairs or additional primers with annealing temperatures of 53° to 69°C (sequences available on request). Amplicons were screened for mutations and to exclude polymerase errors. Wild-type HERG and the second LQTS mutation are coinherited. This appears to be true also for certain low-frequency SNPs in LQTS genes.

Site-DirectedMutagenesis

The two alleles identified in this study, A1161V and K897T, were constructed in a recombinant HERG cDNA, using polymerase chain reaction site-directed mutagenesis. The final constructs were assembled in bicistronic mammalian expression plasmids (pRES2-EGFP, pRES2-DsRed, BD Biosciences-Clontech) in tandem with an internal ribosomal entry site (IRES) and either enhanced green fluorescent protein (EGFP) or DsRed for use as indicators of successful transfection. All constructs were sequenced to verify the mutation and to exclude polymerase errors. Wild-type HERG and the variant alleles were subcloned into pIREs-EGFP and pIREs-DsRed for use in coexpression experiments.

CellCulture andElectrophysiology

Chinese hamster ovary cells (CHO-K1, ATCC) were grown at 37°C in 5% CO2 in F-12 nutrient mixture medium supplemented with 10% fetal bovine serum (Atlanta Biologicals), 2 mmol/L-glutamine, and penicillin (50 U/mL)–streptomycin (50 μg/mL). Unless otherwise stated, all tissue culture media were obtained from Life Technologies. Cells were transiently transfected by using Fugene-6 (Roche Diagnostics, Indianapolis, IN) with 3 μg plasmid DNA. In coexpression experiments, cells were cotransfected with 3 μg of each plasmid. After transfection (48 to 72 hours), fluorescent cells were selected by epifluorescence microscopy (green for single transfections, yellow for cotransfections) for use in whole-cell patch-clamp recording experiments. Nontransfected CHO cells grown under these conditions did not exhibit measurable endogenous potassium currents with the recording conditions used for this study.

Whole-cell currents were measured in the broken-patch, whole-cell configuration of the patch-clamp technique, using an Axopatch 200B amplifier (Axon Instruments Inc, Foster City, CA). The bath solution consisted of (in mmol/L): NaCl 145, KCl 4, MgCl2 1, CaCl2 1.8, glucose 10, HEPES (N-[2-hydroxyethyl]piperazine-N’-[2-ethanesulfonic acid]) 10, adjusted to pH 7.35 with NaOH, ~275 mOsmol/kg. The pipette solution consisted of (in mmol/L): KCl 110, ATP-K3, 5, MgCl2, 2, EDTA (ethylenediaminetetraacetic acid) 10, HEPES 10, adjusted to pH 7.2 with KOH, ~265 mOsmol/kg. The pipette solution was diluted 7% to 10% with distilled water to prevent activation of swelling-activated currents. Patch pipettes were pulled from thick-wall borosilicate glass (World Precision Instruments, Inc) with a multistage P-97 Flaming-Brown micropipette puller (Sutter Instruments Co) and fire-polished. Pipette resistance was 1 to 4 mol/Lf, and as reference electrode, a 1% to 2% agar-bridge with composition similar to the bath solution was used. Whole-cell current traces were filtered at 5 kHz and acquired at 1 to 2 kHz. All chemicals were purchased from Sigma Chemicals.

The holding potential was −80 mV, and whole-cell currents were measured from −80 to +70 mV (in 10-mV steps) 1990 ms (activation) and 2200 ms (tail currents) after the start of the voltage pulse. The access resistance and apparent membrane capacitance were estimated as described by Lindau and Neher. Pulse generation, data collection, and analyses were done with Clampex 8.1 (Axon Instruments, Inc). Statistical comparisons were made by using the Student t test, and significance was assumed for P<0.05.

Results

ClinicalPhenotype

The proband had palpitations associated with presyncopal episodes since age 20 years and a cardiac arrest caused by ventricular fibrillation at age 44. She had no exposure to medications with proarhythmic effects. No specific trigger for the episode of cardiac arrest was identified, as she was quietly sitting in the car while her husband was driving. Subsequent investigations including brain and chest CT scans, echocardiography, coronary angiography, cardiac MRI, a standard clinical electrophysiological study, and flecainide challenge test were all normal. Shortly after cardiac arrest, serum potassium was 3.5 mEq/L but was subsequently found to be in the normal range. A surface resting ECG was normal, with a QTc of 425 ms. A diagnosis of idiopathic ventricular fibrillation was made, prompting implantation of an internal defibrillator and initiation of β-blocker therapy. During a follow-up 12-lead, 24-hour ECG recording, periods of bifid T waves in leads V3 through V5 and prolonged QTc (maximum QTc, 530 ms) were observed (Figure 1). During most of the recording, however, the morphology and QTc duration were normal, indicating that the patient had a labile QT interval. An exercise stress test showed a normal rate adaptation of ventricular repolarization: in basal condition at a heart rate of 77 bpm, QTc was 450 ms and did not increase at peak exercise when heart rate reached 111 bpm. A subsequent ECG showed a basal QTc of 470 ms, with negative T waves in leads V1 through V4, and prolonged QTc up to 510 ms in V4, during a hyperventilation test (Figure 2).

Family history was negative for syncope or sudden cardiac death, although one sibling of the proband was a stillborn.
Identification of a Novel KCNH2 Mutation

We screened DNA from the proband for mutations in all coding exons of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2, using DHPLC. An abnormal elution profile was identified in one fragment encompassing KCNH2 exon 15 amplified from the proband, but this was not observed in 130 control white individuals. Sequence analysis revealed a heterozygous missense mutation that results in an alanine-to-valine substitution at position 1116 (designated A1116V, Figure 3A). This amino acid lies within the distal carboxyl-terminus of the encoded protein (HERG) and is highly conserved among homologous sequences of several species including human, mouse, rat, and dog (Figure 3B). A second KCNH2 variant (K897T) was identified in the proband. This is a common polymorphism with an estimated prevalence in white populations up to 33%,8,21,22

Segregation of KCNH2 Variants

Segregation of A1116V and K897T in the proband’s family indicates that the two variants are located on separate KCNH2 alleles (Figure 4). Mutation screening revealed that A1116V but not K897T was present in a brother and in his two children. All A1116V carriers other than the proband were asymptomatic with normal baseline QT intervals (Figure 5). Twelve-lead, 24-hour Holter recordings were completely normal in the brother (Figure 5B) and showed rare transient episodes of mild QTc prolongation in a 22-year-old niece (maximum QTc, 480 ms, Figure 5C). A 9-year-old nephew had a borderline normal QTc during most of the recording, but brief periods of biphasic or notched T waves in leads V5 through V6, and prolonged QTc in all leads were observed (Figure 5D). However, the QTc was always <500 ms in the nephew, and QTc prolongation occurred only during periods of increased heart rate. The hyperventilation test was normal in the brother but induced QT prolongation in both niece (maximum QTc, 490 ms) and nephew (maximum QTc, 480 ms). The hyperventilation test is a useful clinical tool able to increase the sensitivity of standard ECG in detecting mutation carriers.23 The K897T polymorphism was also identified in the proband’s son and in one of her sisters. Both of these K897T carriers were asymptomatic, with normal QTc intervals by standard ECG and during the hyperventilation test. One of the proband’s brothers refused medical contact. The genetic status of her parents could not be ascertained because they had died.

Biophysical Characterization of KCNH2 Variants

We studied the functional features of both variants separately and together by using whole-cell patch-clamp recording of recombinant HERG heterologously expressed in cultured CHO-K1 cells. Functional characterization of A1116V revealed significantly reduced activating and tail current densities at positive potentials when compared with wild-type HERG (WT-HERG) (Figure 6, A through C, P<0.05). Similarly, expression of K897T generated current densities that were significantly less than WT-HERG at potentials greater than +10 mV (Figure 6, B and C, P<0.05). Tail current density was 50% lower in cells expressing A1116V

Figure 1. ECG recordings from the proband. Morphology and QTc duration were normal during most of the recording (A); however, there were also transient episodes of bifid T waves in leads V3 through V6 (B) and prolonged QTc (maximum QTc, 530 ms) (C).

Figure 2. Hyperventilation test in the proband. The baseline ECG showed a QTc of 470 ms, with negative T waves in V3 through V6. During hyperventilation, QTc prolonged to 510 ms in V3 and the repolarization abnormalities were magnified. QTc represents the mean value of five consecutive beats.
compared with cells expressing WT-HERG but only 25% lower in cells expressing K897T (Figure 5C). Comparing the two variants with one another, activating and tail current densities for A1116V were significantly less than K897T at positive potentials (Figure 6, B and C; \(P<0.05\)). A significant shift in the voltage dependence of activation was also observed for A1116V (\(V_{1/2}, -5.1 \pm 2.4 \text{mV}\)) compared with WT-HERG (\(V_{1/2}, +1.1 \pm 1.7 \text{mV}\); Figure 6D; \(P<0.05\)) but there was no significant shift observed for K897T. More detailed analyses of kinetic properties demonstrated that A1116V exhibits slower recovery from inactivation, whereas the time course and voltage dependencies of inactivation and deactivation were indistinguishable among the three alleles (see online-only Data Supplement Figure). We conclude that both A1116V and K897T cause mild channel dysfunction, but A1116V has greater functional impairments.

Because the proband carried both A1116V and K897T on separate alleles, we examined the effects of coexpressing both variants in the same cells. To demonstrate expression of both constructs in a single cell, we coupled expression of the variant HERG alleles to either EGFP or DsRed fluorescent proteins by using bicistronic IRES vectors and identified coexpressing cells by yellow fluorescence (combined EGFP and DsRed). Coexpression of either A1116V or K897T with WT-HERG did not significantly alter the magnitude of activating currents (Figure 7A). By contrast, cells coexpressing A1116V and K897T together exhibited significantly lower current density compared with WT-HERG alone at potentials greater than \(-10 \text{mV}\). Current density at positive potentials was also lower in cells coexpressing both variant alleles compared with coexpression of A1116V or K897T with WT-HERG (Figure 7A). Tail current density was significantly lower in cells coexpressing both variant alleles compared with coexpression of A1116V or K897T with WT-HERG (Figure 7A). Tail current density was significantly lower in cells coexpressing A1116V and K897T compared with WT-HERG alone, coexpression of K897T and WT-HERG, and coexpression of A1116V and WT-HERG at positive potentials (Figure 7B). There was no significant shift in the voltage dependence of activation observed in any of these experiments (Figure 7C). On the basis of these findings, we determined that the K897T polymorphism exaggerates the reduction in \(I_K\) caused by A1116V.

**Discussion**

The present findings provide clinical, molecular, and in vitro electrophysiological evidence that a very common KCNH2 polymorphism can act as a genetic modifier of the clinical severity of the LQTS.

The genetic basis of symptomatic and apparently sporadic LQTS in a middle-aged woman was determined to be a novel heterozygous missense mutation (A1116V) in KCNH2 cosegregating with the common KCNH2-K897T variant on the opposite allele. Other family members carrying only one of these variants were asymptomatic, but some showed evidence of subclinical disease associated with A1116V.

Biophysical characterization revealed that the degree of functional HERG impairment in the heterozygous condition for A1116V is relatively mild compared with other LQTS mutations causing the full phenotypic expression of LQTS. This is consistent with the concept that A1116V is associated with a latent form of LQTS. However, when coexpressed with K897T, a more substantial reduction in HERG activity was observed. These findings are concordant with the clinical observation that symptomatic LQTS occurred only in the proband carrying both variant alleles. Because K897T is a common polymorphism and by itself has not been associated with LQTS, we propose that this allele acts as a genetic modifier to promote the clinical expression of the disease caused by A1116V.

**Genetic Modifiers of LQTS**

Inherited disorders are said to exhibit incomplete penetrance when less than 100% of mutation carriers exhibit disease manifestations. This is very common in autosomal-dominant LQTS, and current wisdom posits the existence of modifier genes to partly explain this phenomenon. Despite widespread acceptance of this notion, there have been very few specific genetic modifiers identified in LQTS or other inherited...
arrhythmia syndromes. Makielski and colleagues reported that H558R, a common SCN5A polymorphism present in 20% to 30% of whites, modifies the in vitro activity of the SCN5A-M1766L mutation when present together. These studies provided tenable mechanisms for intramolecular complementation, but the practical significance of the data were limited by the absence of genetic evidence that the two variants occurred on the same allele in subjects with LQTS. Homozygosity for SCN5A-H558R has also been shown to provoke conduction system disease associated with the mutation SCN5A-T512I in a young child. A related example involves the observation of atrial standstill associated with

Figure 5. Characteristics of asymptomatic KCNH2-A1116V carriers. A, Partial family tree from Figure 3. The A1116V mutation but not K897T was identified in one brother and his two children. B, Normal QTc in the brother recorded during 12-lead, 24-hour ECG monitoring. C, The 22-year-old niece had a normal baseline QTc, but during a 24-hour ECG recording, rare transient episodes of mild QTc prolongation were observed (maximum QTc, 480 ms). D, The 9-year-old nephew had a normal baseline QTc, but during 24-hour ECG recording, periods of biphasic or notched T waves in leads V3 through V6 and prolonged QTc were observed. However, QTc was always <500 ms and prolongation occurred only during increased heart rate.

Figure 6. Functional characterization of A1116V and K897T HERG variants. A, Representative traces illustrating potassium currents observed in CHO cells transiently transfected with WT-HERG or A1116V (horizontal and vertical scale bars represent 1000 ms and 225 pA, respectively). B, Current-voltage relation for potassium current densities (normalized to membrane capacitance) measured in CHO cells expressing WT-HERG (WT, solid circles, n=9), K897T (open circles, n=9), or A1116V (solid squares, n=8). C, Current-voltage relation for amplitude of peak tail current densities after repolarization to -50 mV for WT-HERG (WT, solid circles, n=9), K897T (open circles, n=9), or A1116V (solid squares, n=8). D, Normalized current-voltage relation for peak tail current densities for WT-HERG (WT, solid circles, n=9), K897T (open circles, n=9), or A1116V (solid squares, n=8). Data were recorded at test potentials ranging from -80 to +70 mV stepped in 10-mV increments from the holding potential of -80 mV for 2000 ms, followed by repolarization to -50 mV for 2000 ms. Data are shown as mean±SEM.
SCN5A-D1275N in a Dutch family cosegregating a common connexin-40 promoter haplotype. As discussed earlier, coinheritance of KCNJ1 mutations with the common variant KCNE1-D85N predisposes to greater degrees of QT prolongation and more severe symptoms in two of the families reported by Westenskow et al. Inherited predisposition to hypokalemia caused by renal salt wasting has also been observed as an unusual form of genetic modification of LQTS associated with a KCNJ1 mutation.

Genetic factors other than the primary mutation may worsen the severity of LQTS or, as illustrated by the case we present here, expose latent disease. In the situation where a modifier allele unmask an otherwise subclinical form of LQTS, the correct diagnosis is extremely difficult without the support of genetic testing and segregation analysis of the extended pedigree. Even identification of the novel A1116V mutation did not suffice in explaining the occurrence of LQTS in the proband we report here. Although the occurrence of ventricular fibrillation in the absence of physical exercise is consistent with the current knowledge regarding genotype-phenotype correlation in LQT2, the location of the A1116V mutation (C-terminus) is usually associated with a mild or benign form of LQTS rather than the presenting symptom of cardiac arrest observed in this case. Only when the coinheritance of the common polymorphism K897T was considered did the genetic data coincide with clinical observations.

The electrophysiological characterization of A1116V and K897T, alone and in combination, provided additional evidence to support the hypothesis that coinheritance of both variants is necessary for clinically overt disease. A1116V produces a significant but less dramatic reduction in $I_{Ks}$ than other LQTS-associated KCNH2 mutations. This is consistent with individuals carrying only A1116V exhibiting either a normal QTc or transient signs of modest QT prolongation. K897T also reduced $I_{Ks}$ but to a lesser degree than A1116V and only at a voltage of 10 mV or greater. Coexpression of the two variants led to a significantly greater reduction of $I_{Ks}$ compared with that produced by each individual allele. The reduction in $I_{Ks}$ caused by the coexpression of A1116V and K897T was evident at voltages that are relatively close to the membrane potential during the action potential plateau. This explains why the actual loss of repolarizing current was of sufficient magnitude to produce, even transiently, major QT prolongations and electrical instability in the proband.

The functional studies reported here were performed in the absence of accessory subunits such as KCNE2. Recent experimental evidence has questioned whether KCNE2 acts as an obligate $\beta$-subunit for KCNH2, and other investigations have demonstrated that this protein has very restricted cardiac expression. It is conceivable that coexpression of KCNE2 might influence the functional behavior of the KCNH2 mutant, but the physiological relevance would be uncertain.

**Clinical and Functional Significance of KCNH2-K897T**

The KCNH2-K897T variant has previously attracted the interest of several investigators, but there has been inconsistent evidence for association of this allele with a clinical phenotype. This is a common SNP in whites with a minor allele frequency of 24% and 33% of the general population is heterozygous. The proportion of other ethnic groups that are heterozygous for K897T is lower (7% to 8% in Asian, black, and Hispanic populations).

This variant may have an impact on the QT interval. Pietila and colleagues found that K897T was associated with longer QT intervals in middle-aged women. Similarly, Paavonen et al. reported on a group of LQT1 patients, all carrying the same KCNJ1 mutation (G589D), who exhibited longer QT intervals on exercise if they also carried the K897T allele. By contrast, Bezzina et al. reported that QTc was...
shorter among control subjects homozygous for K897T. Although the latter study surveyed a large population (n=1382), which increases the statistical power, the actual differences in QTc were small (10 ms).

Similarly, previous heterologous expression studies to determine the functional impact of K897T are not in complete agreement. Anson et al.\textsuperscript{36} using human embryonic kidney cells, observed several differences between K897T and WT-HERG channels. K897T channels activated at more negative potentials, inactivated, and recovered from inactivation faster compared with WT channels. These authors proposed that the small decreases (10% to 30%) of current observed for K897T potentials, inactivated, and recovered from inactivation faster cells, observed several differences between K897T and WT-HERG channels could cause a subtle increase in action potential duration. Using similar methodology, Paavonen and colleagues\textsuperscript{37} reported a smaller current density, slower inactivation, and reduced expression of the K897T variant compared with wild-type. The authors speculate that these changes could lead to increased arrhythmia susceptibility in settings of reduced repolarization. By contrast, Bezzina et al.\textsuperscript{30} concluded that K897T might decrease action potential duration slightly, leading to accelerated repolarization and shorter QT intervals, based on computer simulations incorporating their own electrophysiological observations. Finally, Scherer et al.\textsuperscript{37} found no difference between K897T and WT-HERG when experiments were performed in Xenopus oocytes.

Our findings are consistent with the majority of the studies described above, particularly in that expression of the K897T variant resulted in slightly lower current density compared with WT-HERG. Similar to several of the previous studies, our work used cultured mammalian cells; however, we used bicistronic IRES plasmids that enabled greater certainty in coexpression experiments. The small decreases in current density that we observed for K897T in both the homozygous and heterozygous states are not expected to cause disease alone but may accentuate the effects of reduced repolarization reserve in certain settings such as QT-prolonging drugs or coinheritance of an LQTS mutation.

Implications for Risk Stratification in LQTS
Our study contributes to the “proof of concept” that common polymorphisms can act as genetic modifiers of the clinical severity in familial arrhythmogenic disorders. The novel and unexpected finding is that the clinical manifestations of LQTS can be exacerbated also by a polymorphism with a very high prevalence (30%) in the general population.

The importance of this concept should not be underestimated. Clearly, other SNPs will be identified that are able to modify LQTS risk, and as a result, further studies will be required to determine the clinical significance of other SNPs, as well as K897T, as they are demonstrated to act as genetic modifiers. Molecular genetics integrated with clinical cardiology is progressively offering new clues for a better management of patients at risk for sudden death.

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