New Mechanism Contributing to Drug-Induced Arrhythmia
Rescue of a Misprocessed LQT3 Mutant

Kai Liu, MD; Tao Yang, PhD; Prakash C. Viswanathan, PhD; Dan M. Roden, MD

Background—The cardiac sodium channel (SCN5A) mutation L1825P has been identified in a patient with drug-induced torsade de pointes precipitated by the I_Kr blocker cisapride. Although L1825P generates late sodium current typical of SCN5A-linked long-QT syndrome (LQT3) in vitro, the patient reported had a normal QT interval before administration of the drug. To address this discrepancy, we tested the hypothesis that this mutant channel is not processed normally.

Methods and Results—CHO cells transfected with L1825P displayed significantly reduced peak I_{Na} (209 ± 36 versus 23 ± 5 pA/pF; P < 0.05). Confocal imaging and cell-counting studies using epitope-tagged constructs demonstrated that cell surface expression of the mutant was only ~9% of wild-type. Incubating transfected cells with cisapride partially rescued misprocessing to 30% of wild-type. As a result, “late” sodium current increased with cisapride from 1.2 ± 0.11 to 5.04 ± 0.77 pA/pF (P < 0.05).

Conclusions—L1825P fails to generate QT prolongation because it does not reach the cell surface. Moreover, the data suggest that cisapride caused torsade de pointes not only by blocking I_{Ks} but also by rescuing cell surface expression of the mutant channel, further exaggerating the LQT3 phenotype. This not only represents a new mechanism in the drug-induced long-QT syndrome but also strongly supports the concept that variable cell surface expression contributes to clinical variability in the LQT3 phenotype. (Circulation. 2005;112:3239-3246.)

Key Words: ion channels ■ arrhythmia ■ long-QT syndrome

Mutations in at least 8 genes have been reported as causes of the congenital long-QT syndrome (LQTS).1–4 SCN5A encodes the α-subunit of the cardiac-specific voltage-gated sodium channel, and mutations in this gene have been linked to the LQT3 form of the disease. A common mechanism in LQT3 is impaired fast inactivation that leads to persistent “late” sodium current (I_{Na}), a phenotype referred as “gain of function.” By contrast, other SCN5A-related arrhythmia syndromes, such as Brugada syndrome or conduction system disease, arise from reduced peak I_{Na}, caused by mutations that have been called “loss of function.” One increasingly well-recognized mechanism underlying reduced sodium current in the Brugada syndrome and conduction disease is misprocessing of mutant channels, with retention in the endoplasmic reticulum (ER) and thus failure to reach the cell surface.5–8

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Although mutations in multiple genes can cause LQTS, the “acquired” form (aLQTS) is almost always a result of drug-induced block of the cardiac delayed rectifier potassium current I_{Ks}.9,10 In some cases, development of the characteristic arrhythmia torsade de pointes after administration of an I_{Ks} blocker has been the first clue to the diagnosis of subclinical congenital LQTS.11–14 Mutations in KCNQ1 (LQT1) and KCNH2 (LQT2), each encoding a component of delayed rectifier K⁺ current, are the most common causes of the congenital LQTS and have been reported in the acquired form as well. When such aLQTS-associated mutations are studied in vitro, the K⁺ current changes have been modest, an observation consistent with a near-normal baseline QT but enhanced risk for aLQTS.11,15 This is one example of a situation we have called “reduced repolarization reserve.”16

Three SCN5A mutations have been reported in aLQTS.17–19 One, resulting in L1825P in the SCN5A C-terminus, was identified in a patient whose baseline ECG showed a normal QT interval and right bundle-branch block.17 However, administration of the potent I_{Ks} blocker cisapride provoked marked QT prolongation and torsade de pointes. Characterization of this mutant in a heterologous expression system demonstrated noninactivating late I_{Ks} typical of LQT3. The report also indicated that peak I_{Na} was reduced compared with wild-type (WT). Accordingly, we hypothesized that this variant did not traffic normally to the cell surface, which might explain the lack of baseline QT interval prolongation. In the course of these studies, we also identified a new effect of the culprit drug, cisapride, to rescue L1825P misprocessing. Taken together, the data demonstrate for the first time a
pharmacological rescue of a misprocessed LQT3 mutant as a disease mechanism in aLQT3 and thereby implicate variable cell surface expression as a modulator of the LQT3 phenotype.

Methods

Generation of Expression Vectors and Transient Transfection in CHO Cell Lines

The SCN5A DNA (Gen Bank accession No. NM000335), a gift from Dr Al George, was subcloned into the pBK-CMV vector (Stratagene). The L1825P construct was prepared using the QuickChange site-directed mutagenesis kit (Stratagene) according to the manufacturer's instructions. Recombinant PCR was used to introduce the FLAG (DYKDDDDK) epitope into the domain I extracellular S1–S2 linker in frame after nucleotide position 653, between Pro 153 and Pro 154. All constructs were sequenced to verify the desired mutation and epitope and to ensure the lack of other introduced variations.

Cultured Chinese hamster ovary (CHO) cells were transiently transfected with constructs described above using FuGENE6 (Roche Applied Science). A plasmid encoding the enhanced green fluorescent protein (pEGFP-N3, BD Bioscience Clontech) was cotransfected in electrophysiology experiments to identify transfected cells.

Cells were grown for 48 hours after transfection before study. In drug rescue experiments, cisapride (Sigma-Aldrich Inc) was added to the culture media at concentrations ranging from 1 mmol/L to 1 μmol/L, after which the cells were studied in cisapride-free conditions. For confocal microscopy imaging, cells were split 24 hours after transfection, transferred to a Laboratory-Tek II chamber slide system (Nalge Nunc International), and grown for another 24 hours.

Electrophysiology

Whole-cell voltage clamp was performed at room temperature with 2-MΩ patch microelectrodes and an Axopatch 200A amplifier. The extracellular bath solution contained (in mmol/L) NaCl 145, KCl 4.0, MgCl₂ 1.0, CaCl₂ 1.8, glucose 10, and HEPES 10; the pH was 7.4, adjusted with NaOH. The pipette (intracellular) solution contained (in mmol/L) NaF 10, CsF 110, CsCl 20, EGTA 10, and HEPES 10; adjusted with CsOH. Cells were held at pH 7.4, adjusted with CsOH. The pipette (intracellular) solution contained (in mmol/L) NaF 10, CsF 110, CsCl 20, EGTA 10, and HEPES 10; the pH was 7.4, adjusted with CsOH. Cells were held at -120 mV, and activating currents were elicited with depolarizing pulses from -100 to +50 mV in 10-mV increments. Specific clamp protocols are indicated with the data. Late current was measured as the mean between 95 and 100 ms after the initiation of the depolarization, normalized to cell surface, and presenting with the data. Late current was measured as the mean between 95 and 100 ms after the initiation of the depolarization, normalized to cell surface, and presented with the data.

Flow Cytometry and Quantification of Cell Surface Expression

Transfected CHO cells were harvested by incubation with PBS, pH 7.4, containing 0.5 mmol/L EDTA for 10 minutes at room temperature, followed by 2 washes with TBS. Cell surface staining was performed as described above using FITC-conjugated anti-FLAG M2 antibody. After an extensive washing step, the cells were examined for FITC-labeled, FLAG-tagged channel expression by fluorescence-activated cell sorting (FACS) on a FACSCalibur bench-top analyzer (BD Bioscience), using CellQuest (BD Bioscience) for data acquisition and analysis. FLAG-tagged channel expression was quantified by converting the geometric mean fluorescence intensity from each cell preparation to the number of

Immunoblot Analysis

Whole-cell lysates were collected 48 hours after transfection with FLAG-tagged WT or L1825P constructs as previously described. The same amount of protein extract (20 μg each for controls, WT, or L1825P) was loaded into 4% to 12% precast NuPAGE gels (Invitrogen Corp) and then separated by SDS-PAGE under reducing conditions. After electrophoresis, proteins were transferred to a Hybond polyvinylidene difluoride membrane (Amersham Biosciences Corp), blocked with 5% nonfat milk in TBS-T (TBS with 0.05% TWEEN-20) at room temperature for 1 hour, and incubated with horseradish peroxidase-conjugated anti-FLAG M2 monoclonal antibody (1:300; Sigma) in TBS-T at room temperature for 1 hour. After an extensive wash with TBS-T, the immunoreaction between the antibody and the FLAG antigen of the tagged channel was visualized using the ECL system (Amersham Bioscience Corp).

Immunocytochemistry

Transfected CHO cells were washed with Tris-buffered saline (TBS, pH 7.4) twice and fixed with a freshly prepared mixture of methanol:acetone (1:1) for 1 minute. For surface staining, cells were incubated with mouse anti-FLAG M2 monoclonal antibody–FITC conjugate (1:300; Sigma-Aldrich Inc) in TBS with 2% BSA for 1 hour at room temperature, followed by extensive washing with TBS and mounting on glass coverslips.

To study intracellular localization, fixed cells were permeabilized and blocked with preincubation in 0.2% Triton X-100, 2% BSA, and 5% goat serum TBS at room temperature for 30 minutes. After the blocking solution had been washed out, cells were incubated with the same amount of the FITC-conjugated anti-FLAG antibody as described above for 1 hour. After being washed, these cells underwent ER staining with a primary rabbit polyclonal antibody to calnexin (1:200; Novus Biologicals Inc) and a secondary goat polyclonal antibody to rabbit IgG conjugated with Cy3 (1:200; Novus Biologicals Inc); there was a 1-hour incubation period in each step followed by a wash.

Fluorescent probe–labeled cells were examined using a Zeiss LSM510 confocal laser-scanning inverted microscope (Carl Zeiss) equipped with an argon-krypton laser beam. A 63×1.4 plan-achromat oil objective lens with a 1.5 numerical aperture was used. FITC and Cy3 fluorophores were excited at λ of 488 and 543 nm at 50% laser power with detector gain set to 900. Fluorescence was filtered by BP505-550 and LP560 filters, respectively.

In Figure 1, Effects of the L1825P mutation on sodium current. A, Whole-cell Na⁺ current (I Na) from CHO cells expressing WT SCN5A or L1825P. Representative traces were recorded with test potentials of 100-ms duration from -100 to +50 mV in 10-mV increments and from a holding potential of -120 mV. B, Example of late I Na from WT and L1825P elicited by a test depolarization pulse from -120 mV to -20 mV for 100 ms. Late I Na was measured as the mean between 95 and 100 ms after the initiation of the depolarization, normalized to cell surface, and presented in pA/pF.
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the conductance of sodium Na, as shown in Figure 1B, was obtained with L1825P (WT, 209 ± 36 pA/pF, n = 9; L1825P, 23 ± 3 pA/pF, n = 11; P < 0.05). Finally, despite the reduction in peak current and in line with the previous report, a robust noninactivating (late) I_{Na} was introduced into the Luo-Rudy model as described previously. To examine the effect of L1825P mutation, the biophysical consequences of the mutation were introduced into the formalism of the sodium channel. Briefly, peak inward current was reduced by a factor of 10 to reflect the lower expression of L1825P,

the voltage dependence of activation (represented by the m gate) was shifted by −9 mV, and the steady-state inactivation (represented by the h and j gates) was shifted by −11 mV. The sustained inward component of current (as observed in LQT3 mutant channels) was simulated as described earlier. Slowing of inactivation was simulated by increasing the time constant of inactivation by a factor of 1.5. For action potential simulations, a heterozygous condition (50/50 mixture of mutant and WT channels) was assumed to reflect equal penetrance. The effect of cisapride was simulated by decreasing the conductance of I_{Na} by 85%, whereas for the rescue of L1825P by cisapride, L1825P current was scaled to 30% of WT without affecting other gating parameters.

Luo-Rudy Simulation
Simulations were conducted using the single-cell formalism of the theoretical dynamic model of a mammalian ventricular action potential (Luo-Rudy model). The transient inward potassium current, I_{Kr}, was introduced into the Luo-Rudy model as described previously. To examine the effect of L1825P mutation, the biophysical consequences of the mutation were introduced into the formalism of the sodium channel. Briefly, peak inward current was reduced by a factor of 10 to reflect the lower expression of L1825P,

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Statistical Analysis
Data are expressed as mean ± SD (standard deviation of the mean). Statistical significance was determined using the Student t test for comparisons of 2 means or using ANOVA for comparisons of multiple means. Differences were considered statistically significant with a probability value of P < 0.05.

Results
L1825P Generates Reduced Peak Current
Figure 1A shows sodium currents recorded from CHO cells expressing WT or L1825P channels. Fewer GFP-positive L1825P cells actually displayed any current (9 of 12 for WT versus 11 of 40 for L1825P, P < 0.05). Furthermore, peak L1825P current was greatly reduced compared with WT (WT, 209 ± 36 pA/pF, n = 9; L1825P, 23 ± 3 pA/pF, n = 11; P < 0.05). Finally, despite the reduction in peak current and in line with the previous report, a robust noninactivating (late) I_{Na} was simulated by decreasing the conductance of I_{Na} by 85%, whereas for the rescue of L1825P by cisapride, L1825P current was scaled to 30% of WT without affecting other gating parameters.

Reduced Cell Surface Expression of L1825P
One obvious explanation for these results is that L1825P might not be processed correctly, as has been reported for a number of Brugada syndrome mutations. To test this idea, an extracellular FLAG epitope was introduced into both WT and L1825P channels and their cellular localization studied. Figure 2A shows staining in nonpermeabilized cells with the FITC-conjugated anti-FLAG antibody. Staining in WT-transfected cells indicates that the WT-FLAG channels are localized to the plasma membrane. By contrast, little staining was observed on the
surface of the cells transfected with L1825P-FLAG. Quantification of cell surface expression by FACS and MESF (Figure 2B) in >15 000 cells in 3 separate experiments revealed a 91% reduction of the L1825P mutant (MESF values: WT, 329 812 ± 2320, n = 3; L1825P, 30 136 ± 2086, n = 3, P < 0.05). Western blots of whole-cell extracts (Figure 2C) showed comparable protein levels for WT and L1825P, indicating that the L1825P channel protein was synthesized but did not reach the cell surface. Further support for this idea is presented in Figure 2D, showing that in permeabilized cells, the staining pattern of the L1825P channel overlapped nearly completely with that of the ER-resident protein calnexin, in contrast to the cell surface expression seen clearly in the parallel WT experiment.

Mutant Cell Surface Expression Is Partially Rescued by Cisapride
Misprocessing of mutant cell surface proteins is an increasingly well-recognized mechanism underlying loss-of-function phenotypes in diseases like the congenital long-QT syndromes, the Brugada syndrome, and cystic fibrosis.5–8,26–30 In these settings, ER retention of presumably misfolded proteins has been rescued by incubation with a range of small-molecule and other interventions.8,28,30–34 Accordingly, we evaluated the effects of incubation with cisapride, the culprit drug in torsade de pointes in the L1825P mutation carrier. Figure 3A shows that the presence of cisapride in the culture media for 48 hours had no effect on WT I Na but increased peak I Na of the L1825P mutant in a concentration-dependent manner (from 1 nmol/L to 1 μmol/L), as summarized in Figure 3B. The same results were obtained when the study was repeated in tsA-201 cells, in which the mutant was originally characterized. The effect of cisapride was studied further by confocal imaging as above; Figure 3C shows that culturing the L1825P channel with 1 μmol/L cisapride resulted in greater surface immunostaining compared with L1825P alone; quantification demonstrated a 3-fold enhancement of expression in MESF values (L1825P+ Cisapride 1 μM).

Figure 3. Cisapride facilitates L1825P channel membrane expression in a dose-dependent manner. A, Current traces for WT and L1825P recorded after 48 hours of cell culture with a range of concentrations of cisapride. B, Summary data of peak I Na densities from WT and L1825P without or with cisapride at the indicated concentration during cell culture. Peak I Na was elicited at −20 mV from a holding potential of −120 mV and normalized to cell capacitance and presented as pA/pF. When cells expressing L1825P were studied, only those that generated detectable I Na were counted; the majority (>75%) generated no I Na. C, Immunostaining (anti-FLAG, green) of L1825P-FLAG–transfected cells. Top, Rescued surface labeling when incubated with 1 μmol/L cisapride for 48 hours. Bottom, FACS analysis as in Figure 2B. Cell surface expression with cisapride culture was increased 3-fold compared with no cisapride conditions.

Figure 4. L1825P late I Na is increased relative to the peak I Na in the presence of 1 μmol/L cisapride during cell culture. A, Examples of WT and L1825P late I Na recorded from cells pretreated with 1 μmol/L cisapride. B, Summary data for the WT and L1825P late I Na with or without 1 μmol/L cisapride. *P < 0.05 vs L1825P.
Cisapride Has No Gating Effect on Either WT or L1825P Channel

Previous studies showed that acute cisapride exposure did not change the kinetics of the \( I_{\text{Kr}} \) in either WT or L1825P. In this study, however, we determined the effects of longer exposure to the drug. Figure 5 shows that this longer cisapride exposure did not alter WT or L1825P gating; the differences between the 2 channels in time constants and in voltage dependence of inactivation are those previously reported.\(^\text{17}\)

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cisapride, 100±4070, n=3, \( P<0.05 \). Although this effect might be expected to “rescue” a Brugada syndrome phenotype, it may also increase late current and thus worsen the LQT3 phenotype. Indeed, late current increased in proportion to peak current (Figure 4: L1825P, 1.2±0.11 pA/pF, n=11; L1825P+cisapride, 5.04±0.77 pA/pF, n=8; \( P<0.05 \)), as would be expected with rescue of cell surface expression.

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Prolonged Action Potential Duration by Cisapride in Simulation

Figure 6 shows the results of action potential reconstructions using the Luo-Rudy model under 4 different conditions: WT; mutant (50% WT and 50% L1825P channels, modeled using late currents from Figure 4); mutant with superimposed \( I_{\text{Kr}} \) block (the recognized cisapride effect\(^\text{35}\)); and mutant with superimposed \( I_{\text{Kr}} \) block+L1825P rescue. Incorporating the mutant produces minimal action potentials and is the only one with an early afterdepolarization. This finding highlights the new mechanism we have identified as a contributor to drug-induced arrhythmia in this setting: action potential prolongation caused by \( I_{\text{Kr}} \) block by cisapride is exaggerated by rescue of misprocessed mutant channels.
Figure 6. The effect of L1825P mutation on action potentials using the Luo-Rudy model. A heterozygous formulation of sodium channels (50% WT and 50% mutant) has a minimal effect on action potential duration (blue). In the presence of an \( I_{\text{Kr}} \) blocker (cisapride), there is significant action potential prolongation (green). Incorporation of rescue of sodium channels because of cisapride (red) augments action potential prolongation and causes an early afterdepolarization, indicated by the arrow.

Discussion

Acquired LQTS occurs in up to 8% of patients treated with certain antiarrhythmics, and much less commonly with a wide range of “noncardiovascular” drugs, including certain antibiotics, antipsychotics, antihistamines, and the prokinetic gastrointestinal agent cisapride. For virtually all culprit drugs, which share few structural features, block of the repolarizing current \( I_{\text{Kr}} \), that is the mechanism underlying action potential prolongation. In a minority of cases, the acquired form of the disease is the first manifestation of subclinical congenital long-QT syndrome.

In this study, we found that L1825P, previously identified and characterized as a subclinical LQT3 mutation discovered by challenge with the potent \( I_{\text{Kr}} \) blocker cisapride, is not processed normally to the cell surface. Such misprocessing is an increasingly well-recognized mechanism in diseases such as Brugada syndrome, diabetes insipidus, and cystic fibrosis involving membrane proteins; and is well described in common forms of LQTS-linked loss-of-function mutations in potassium channel genes. However, this mechanism has been reported in only 1 case of the congenital LQT3 caused by gain-of-function mutations in the cardiac sodium channel gene \( SCN5A \). Furthermore, we also observed an unexpected dose-dependent effect of cisapride to rescue in cytoplasmic misprocessing of the L1825P channel.

Initial studies of this variant revealed a spectrum of gating defects typically seen in other LQT3 mutants, including a prominent late (noninactivating) plateau inward current underlying QT prolongation. Thus, L1825P would be predicted to generate QT prolongation in the baseline ECG in mutation carriers; however, this was not observed in the reported proband. Such dissociation between genotypes and clinical phenotypes is increasingly well recognized in LQTS, and the studies we performed suggest a novel mechanism in LQT3: we find that L1825P is retained in the ER, and its forward trafficking to the plasma membrane is enhanced by chronic treatment of the \( I_{\text{Kr}} \) blocker cisapride, as opposed to the null effect after the acute exposure in the original report. Consequently, we postulate that with cisapride challenge, L1825P mutants retained in the ER were transported to the cell surface; however, in this case, restored membrane integration contributed to an increased QT-prolonging defect attributable to increased persistent late \( I_{\text{Kr}} \). Thus, in this case, cisapride prolonged QT not only by blocking \( I_{\text{Kr}} \) but also by exacerbating the LQT3 phenotype.

Trafficking-defective \( SCN5A \) mutations have been reported in patients with loss-of-function in vitro phenotypes associated with \( SCN5A \)-related congenital arrhythmia syndromes. Although disruption of surface expression is the common feature for these variants, the nature of the clinical symptom did not always correlate with the reported in vitro characteristics. Trafficking mutation carriers of G1743R, R1432G, and R1232W/T1620M displayed Brugada arrhythmias with right precordial ST-segment elevation; this phenotype was absent in the conduction disorder caused by a similar trafficking defect of a frameshift truncated protein (5280delG). In addition, a congenital LQT3 mutation (M1766L) discovered in a symptomatic newborn was also determined to exhibit defective processing to the cell surface.

Cell surface expression of both M1766L and G1743R has been reported to be rescued by mexiletine, a \( Na^+ \) channel blocker sometimes used in the treatment of LQT3. Peak \( I_{\text{Kr}} \) of M1766L and G1743R were increased 12- and 93-fold, respectively, when cultured with a very high concentration (500 \( \mu \text{mol/L} \)) of mexiletine, well above the therapeutic range of 2.8 to 11 \( \mu \text{mol/L} \). Similarly, we have found that high concentrations of quinidine and lidocaine can rescue L1825P (data not shown). Indeed, a common emerging theme is rescue of misprocessed mutant cell surface molecules by pharmacological agents known to bind to these molecules. The initial studies on \( KCNH2 \) mutant N470D illustrated that blockers including E-4031, astemizole, and cisapride can restore the trafficking of the mutant proteins, possibly by acting as chemical chaperones to promote proper protein folding or assembly, thereby permitting the channel to exit the ER. Our study shows for the first time that surface expression of a trafficking defect LQT3 mutation can be rescued by the \( I_{\text{Kr}} \) blocker cisapride at close to its therapeutic concentration of 0.17 \( \mu \text{mol/L} \). The mechanism underlying the cisapride effect is uncertain; although it may behave as a chaperone, this effect could also reflect nonspecific actions on the general ER quality control apparatus.

This study, like previous work in the field, examined membrane proteins in heterologous expression systems. A limitation of this approach is that cardiac myocytes could include regulatory mechanisms absent in CHO or tsA-201 cells and thus exhibit a different phenotype. A challenge to the field is to develop systems to study mutant membrane
proteins in more physiological contexts, ie, with normal numbers, under normal transcriptional control, in native cells.

In conclusion, our study demonstrates SCN5A L1825P to be an ER-retained LQT3 mutation, and its cell surface expression can be partially restored by cisapride close to the therapeutic concentration. However, by augmenting late inward sodium current, this rescue probably exacerbated the LQT3 phenotype. These data not only identify a new mechanism contributing to the acquired LQTS phenotype but also strongly support the concept that the well-recognized phenotypic variability in LQTS and other diseases of cell surface molecules may be determined in part by variable delivery of channels to the cell surface.

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References


**CLINICAL PERSPECTIVE**

The major mechanism whereby drugs prolong the QT interval and cause torsade de pointes is block of the cardiac potassium current, \( I_{Kr} \). In a minority of cases, drug-induced torsade is the first clue to previously unrecognized congenital long-QT syndrome. The starting point for this study was a report that identified the cardiac sodium channel mutation L1825P in a patient with torsade after exposure to the potent \( I_{Kr} \) blocker cisapride. The described electrophysiological properties of the mutant channel were quite typical of the sodium channel–linked form of the long-QT syndrome, with a maintained late inward current that should prolong the QT interval; despite this, the patient had a normal QT interval. This study identifies failure of cell surface expression as a mechanism for the normal QT; this is consistent with an emerging concept that mutations in channels and other membrane proteins can cause misfolding, which is recognized by an intracellular quality assurance process that then prevents trafficking to the cell surface. This study also describes unexpected rescue of L1825P cell surface expression by cisapride. There are 2 important conclusions. The first is that the index patient probably developed torsades not only because cisapride blocks \( I_{Kr} \) but also because it allowed more mutant sodium channels to get to the cell surface, further prolonging QT. More generally, the data support the idea that the well-recognized variability in the extent to which the QT interval is prolonged in patients with long-QT syndrome mutations may reflect variable cell surface expression of mutant channels.
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