Contribution of Sodium Channel Mutations to Bradycardia and Sinus Node Dysfunction in LQT3 Families

Marieke W. Veldkamp,* Ronald Wilders,* Antonius Baartscheer, Jan G. Zegers, Connie R. Bezzina, Arthur A.M. Wilde

Abstract—One variant of the long-QT syndrome (LQT3) is caused by mutations in the human cardiac sodium channel gene. In addition to the characteristic QT prolongation, LQT3 carriers regularly present with bradycardia and sinus pauses. Therefore, we studied the effect of the 1795insD Na+ channel mutation on sinoatrial (SA) pacemaking. The 1795insD channel was previously characterized by the presence of a persistent inward current (I_{pst}) at −20 mV and a negative shift in voltage dependence of inactivation. In the present study, we first additionally characterized I_{pst} over the complete voltage range of the SA node action potential (AP) by measuring whole-cell Na+ currents (I_{Na}) in HEK-293 cells expressing either wild-type or 1795insD channels. I_{pst} for 1795insD channels varied between 0.8±0.2% and 1.9±0.8% of peak I_{Na}. Activity of 1795insD channels during SA node pacemaking was confirmed by AP clamp experiments. Next, I_{pst} and the negative shift were implemented into SA node AP models. The −10-mV shift decreased sinus rate by decreasing diastolic depolarization rate, whereas I_{pst} decreased sinus rate by AP prolongation, despite a concomitant increase in diastolic depolarization rate. In combination, moderate I_{pst} (1% to 2%) and the shift reduced sinus rate by ∼10%. An additional increase in I_{pst} could result in plateau oscillations and failure to repolarize completely. Thus, Na+ channel mutations displaying an I_{pst} or a negative shift in inactivation may account for the bradycardia seen in LQT3 patients, whereas SA node pauses or arrest may result from failure of SA node cells to repolarize under conditions of extra net inward current. (Circ Res. 2003;92:976-983.)

Key Words: long-QT syndrome ■ ion channels ■ sinoatrial node ■ electrophysiology ■ sudden death

The inherited long-QT syndrome is a familial rhythm disorder typically characterized by prolongation of the QT-interval on the ECG and life-threatening cardiac arrhythmias.1,2 One form of the familial long-QT syndrome (LQT3) is caused by mutations in the gene encoding the cardiac sodium channel (SCN5A).3 To date, the biophysical properties of the mutant sodium channels have been assessed for at least 21 of the distinct genetic mutations in SCN5A that have been linked to LQT3 (see online Table 1, available in the online data supplement at http://www.circresaha.org). In most of these mutations, incomplete or slowed channel inactivation induces a small persistent sodium inward current (I_{pst}) during prolonged depolarization (see online Table 1). This small I_{pst} at plateau potentials is sufficient to delay repolarization of the action potential and underlies the QT-prolongation on the ECG.

Previous research has focused on the correlation between altered Na+ channel kinetics and ventricular action potential prolongation, because the latter renders the heart vulnerable to tachyarrhythmias, especially Torsade de Pointes. In addition to the characteristic QT-prolongation, however, bradycardia and sinus pauses have also been associated with the LQT3 phenotype, indicating a role for the sodium channel in sinoatrial pacemaking in humans.4 This was at least reported for carriers of the ΔKPQ,5 D1790G,6 E1784K,7 1795insD,8,9 and ΔK150010 mutations. Because QT-prolongation is most pronounced at lower heart rates, whereas virtually absent at high heart rates,11 bradycardia represents an important indirect factor in predisposition to lethal arrhythmias in LQT3 families. However, bradycardia may also be the direct cause of sudden death, as was diagnosed for 1 member of the D1790G family who died of sinus arrest (J. Benhorin, MD, written communication, 2001)12 and, as we suspected, for members of the 1795insD family.9 The latter family with a high incidence of nocturnal sudden death was previously characterized by bradycardia-dependent QT-prolongation, intrinsic sinus node dysfunction, and generalized conduction abnormalities.9 The mechanism underlying LQT3-associated bradycardia has not been unraveled yet. Thus, the aim of the present study was to investigate whether each of the altered biophysical properties of the mutant 1795insD Na+ channel (and other mutant channels; see the online data supplement).
ie, incomplete inactivation and a negative shift in voltage-dependence of inactivation, can give rise to bradycardia and sinus pauses.

Materials and Methods

Transfection

Mutant (1795insD) SCN5A cDNA was prepared in the pCGI vector for bicistronic expression of mutant channel and green fluorescent protein, as described previously.13 To express mutant or wild-type hH1, HEK-293 cells were cotransfected with 2 μg of Na-channel α-subunit cDNA and 2 μg hβ1-subunit cDNA (kindly provided by J.R. Balser, Vanderbilt University, Nashville, Tenn) using lipofectamine (Gibco BRL, Life Technologies). Transfected HEK-293 cells were cultured in MEM (Earle’s salts and L-glutamine) supplemented with nonessential amino acid solution, 10% FBS, 100 IU/mL penicillin, and 100 μg/mL streptomycin in a 5% CO2 incubator at 37°C for 1 to 2 days. Only cells exhibiting green fluorescence were selected for electrophysiological experiments.

Electrophysiology

Sodium currents were measured in the whole-cell configuration of the patch-clamp technique using an Axopatch 200B amplifier (Axon Instruments) and the following solutions (in mmol/L): bath (external) solution: NaCl 140, KCl 4.7, MgCl2 2.0, NaHCO3 4.3, Na2HPO4 1.4, glucose 11, and HEPES 16.8, pH adjusted to 7.4 (NaOH); and pipette (internal) solution: CsF 100, CsCl 40, EGTA 10, NaCl 10, MgCl2 1.2, and HEPES 10, pH adjusted to 7.3 (NaOH). Patch electrodes were pulled from borosilicate glass and had a tip resistance of 2 to 3 MΩ when filled with pipette solution. Series resistance was compensated for 75% to 80%. Sodium currents were recorded at room temperature (21°C). Persistent inward Na+ current was determined from the tetrodotoxin (TTX)-sensitive current by taking the average current amplitude over the last 50 ms of the current trace. This fraction was 0% in control and 1% to 3% in the mutant case. We carried out similar simulations with the peripheral SA nodal cell model by Zhang et al.,17 which allows modulation of intrinsic rate by simulated application of acetylcholine.18 All simulations were run for a sufficiently long time to reach steady-state behavior.

Results

1795insD Persistent Inward Current

Recently, we reported that the persistent inward current (I_{ps}) through 1795insD Na+ channels was 1.4% of the peak current at a potential of −20 mV.13 In the present study, we measured TTX-sensitive currents during 300-ms depolarizations to various potentials between −120 and 0 mV (Figure 1) to establish their amplitudes also at other voltages within the range of the sinus node action potential. Figure 1A shows whole-cell currents recorded during depolarizations to −40 mV from HEK-293 cells cotransfected with hβ1 plus wild-type (left) or 1795insD (right) cDNA during control and in presence of 30 μmol/L TTX. Examination of the TTX-sensitive currents at high gain (insets) revealed a small residual current in cells expressing 1795insD Na+ channels but not in cells expressing wild-type channels. At −40 mV, the magnitude of this I_{ps} was 0.04±0.14% (mean±SEM, n=7) and 1.05±0.26% (n=6) of the peak current (I_{peak}) for wild-type and 1795insD channels, respectively, whereas I_{peak} was −5.9±0.6 and −6.8±1.2 nA, respectively. Figure 1B shows the average current-voltage (I-V) relation of I_{ps} for both channel types. The shape of the 1795insD persistent I-V relation was similar to that of 1795insD peak I_{ps} (not shown), with an activation threshold of −60 mV and a maximum amplitude near −25 mV. At voltages between −60 and 0 mV, I_{ps} varied between 0.8±0.2% and 1.9±0.8% of I_{peak} (Figure 1C).

Figure 1. Late inward currents in wild-type and 1795insD mutant channels. A, Whole-cell currents obtained from HEK-293 cells expressing wild-type (WT; left) or 1795insD mutant (right) sodium channels. Representative current traces recorded during 300-ms steps to −40 mV from a holding potential of −120 mV before and after application of 30 μmol/L TTX. Insets: TTX-sensitive currents obtained by subtraction. Dashed lines indicate zero-current level. Note persistent inward component for 1795insD mutant channel. B, Mean I-V relationships of I_{ps} for wild-type (n=7) and 1795insD (n=6) Na+ channels. Bars indicate SEM. C, I_{ps} for wild-type (n=7) and 1795insD mutant (n=6) expressed as percentage of I_{peak} vs V_{m}.
shift in steady-state inactivation\textsuperscript{8,13} were implemented in a rabbit SA node action potential model.\textsuperscript{14} The shift in steady-state inactivation was set at −10 mV, and \( I_{\text{pot}} \) was varied between 0\% and 2\%.

Figure 3 shows the computed effects of the altered channel properties on SA nodal pacemaking. Because of the moderately negative maximal diastolic potential (MDP) of the SA node model cell (Figure 3A, top), the far majority of \( \text{Na}^+ \) channels is normally inactivated. Only during the diastolic depolarization phase between −60 and −40 mV (Figure 3A, middle), the voltage range where activation and inactivation relationships overlap, some minor \( \text{Na}^+ \) channel activity is present. During this phase, \( \text{Na}^+ \) channels generate a small inward current, thus contributing to diastolic depolarization. A −10-mV shift in steady-state inactivation per se, which reduces the overlap, renders the AP shape unaltered (Figure 3A, top, dashed line) but decreases diastolic depolarization rate (DDR), thereby increasing cycle length (CL). This effect results from a reduced \( \text{Na}^+ \) current during diastolic depolarization (Figure 3A, middle) and the consequent reduction in net inward membrane current (Figure 3A, bottom).

Figure 3B shows the effects of 1\% to 2\% \( I_{\text{pot}} \) per se. The presence of 1\% \( I_{\text{pot}} \) (Figure 3B, dashed lines) becomes manifest as an extra inward sodium current during the AP and during the (final phase of) diastolic depolarization (Figure 3B, middle). Consequently, the net outward membrane current during the AP is reduced, whereas the net inward membrane current during the (final phase of) diastolic depolarization and the upstroke of the AP is slightly increased (Figure 3B, bottom). These changes result in a prolongation of the AP and a slight increase in DDR, respectively (Figure 3B, top). The latter can be appreciated from Figure 3C, where the same data are plotted on an expanded time scale and are aligned at the beginning of the diastolic depolarization phase at −60 mV. Because the AP prolongation dominates, the overall effect is an increase in CL. With 2\% \( I_{\text{pot}} \), these effects were similar but more pronounced (Figures 3B and 3C, dotted lines).

Figure 3D shows the aggregate effect of the shift in inactivation and \( I_{\text{pot}} \). The main difference between the aggregate effect compared with \( I_{\text{pot}} \) alone is a decreased instead of increased sodium inward current during diastolic depolarization (Figure 3D, middle). Consequently, the increase in DDR as observed for \( I_{\text{pot}} \) alone is no longer present, so that the increase in CL is more pronounced (Figure 3D, top).

Figure 4 summarizes the above results. For convenience, CL was transposed to sinus rate (SR). The main conclusion is that the −10-mV shift and \( I_{\text{pot}} \) both induce a slowing of SR, both individually and in combination. The negative shift alone gave rise to a 3\% decrease in SR from 158 to 153 bpm (Figure 4A). The presence of 1\% or 2\% \( I_{\text{pot}} \) alone reduced SR by 3\% and 9\% to 153 and 144 bpm, respectively (Figure 4B). In combination with the shift in inactivation, SR decreased by 6\% and 11\%, respectively (Figure 4C). The mechanism underlying this change in SR is different for both conditions, as can be appreciated from the changes in action potential parameters. In case of the −10-mV shift, the decrease in SR is entirely attributable to a decrease in DDR, which is reduced from 92 to 84 mV/seg (Figure 4A). The effect of the 1\% or
2% $I_{pst}$ is less straightforward (Figure 4B). On the one hand, there is an increase in action potential duration (APD$_{100}$), eg, from 168 to 225 ms at 2% $I_{pst}$, which tends to decrease SR. On the other hand, there is an increase in DDR, eg, from 92 to 97 mV/sec at 2% $I_{pst}$, which tends to increase SR. However, the increasing effect of increased DDR on SR is by far outweighed by the decreasing effect of increased APD$_{100}$.

Because several studies report $I_{pst}$ values of 4% to 6% (see online Table 1), we extended our experiments by examining the effects of $I_{pst}/H_11022$ both alone and in combination with the $H_11002$-mV shift. Increasing $I_{pst}$ to 3% (Figure 5A) critically disturbed the balance between inward and outward currents, resulting in oscillations at plateau potentials and failure to repolarize to MDP.

Taking into consideration that 1795insD carriers have 1 normal and 1 mutant allele, we repeated the above computations under conditions of 50% wild-type and 50% 1795insD channels. In case of 1% to 2% $I_{pst}$, the effects on SA node AP parameters were similar but less pronounced compared with 100% mutant channels (not shown). At 3% $I_{pst}$, the plateau oscillations were no longer observed (Figure 5B). These oscillations and failure to repolarize occurred on increasing $I_{pst}$ to 5% to 6% (not shown).

Next, to investigate to what extent our simulation results depend on the particular $I_{Na}$ equations or AP model used, we carried out additional simulations with the peripheral SA nodal cell model by Zhang and colleagues (50% mutant and 50% wild-type channels). This model allows for physiological control of intrinsic rate by application of acetylcholine (ACh), which, in a concentration-dependent manner, depresses the L-type calcium current, shifts the activation curve of the hyperpolarization-activated current $I_f$, and activates the ACh-induced potassium current $I_{K,ACh}$. Figure 7 shows the computed effects of $I_{pst}$ and the $H_11002$-mV shift on SA nodal pacemaking in the Zhang et al model in the absence (left) and presence (right) of 100 nmol/L ACh. Application of ACh slightly shortened APD and markedly decreased DDR, resulting in an increase in intrinsic cycle length (Figure 7A). As in our previous simulations, the negative shift affects DDR by reducing net inward current during the final phase of repolarization. Because this net inward...
current is already small in the presence of ACh, as apparent from the reduced DDR (Figure 7A, right), the net effect on CL is larger than in the absence of ACh (Figure 7B). As before, $I_{\text{pst}}$ modulates CL by reducing net outward current during the action potential plateau. In the presence of ACh, the increase in CL is slightly smaller than in the absence of ACh (Figures 7C through 7E). In combination, the effects of the negative shift and $I_{\text{pst}}$ are again almost additive (Figures 7F through 7H). When normalized to intrinsic cycle length, the effects of the shift on CL are more prominent in presence of ACh than in absence thereof, whereas the effects of $I_{\text{pst}}$ are less prominent (Figure 6B, solid bars, and Figure 6C). Because intrinsic cycle length increases with increasing concentrations of ACh,$^{18}$ Figure 6C also shows that the combined effect of the negative shift and $I_{\text{pst}}$ on the percent decrease in sinus rate (or percent increase in CL) is more pronounced at lower intrinsic sinus rate. In other words, our simulations predict that the bradycardic effect of the 1795insD mutation is more pronounced at low sinus rate, which is in agreement with clinical observations (see Table 2 of Reference 9).

**Discussion**

**Mechanism of Sinus Rate Reduction**

In the present study, we describe the effects of the biophysical properties of 1795insD mutant Na$^+$ channels on sinoatrial node electrical activity using rabbit SA node action potential models (and action potential clamp experiments). Our main finding is that the most prominent characteristics of 1795insD mutant Na$^+$ channels—the presence of a persistent inward current and a negative shift in voltage-dependence of inactivation—cause a reduction in sinus rate, both separately and in combination. Our study provides insight into the mechanism by which slowing of sinus rate is being effected.

In the computational model, the contribution of wild-type Na$^+$ channels to SA node automaticity is limited to the diastolic depolarization phase. Because of the moderately negative MDP (near −60 mV) of central SA node cells, most Na$^+$ channels reside in the inactivated state and are not available for activation. In fact, Na$^+$ channel activity is only...
remains available for activation, and consequently, Na\(^+\) channel openings are present and persist at a very low probability over the entire voltage range of activation. First, this results in extra inward Na\(^+\) current during the final phase of diastolic depolarization, increasing diastolic depolarization rate. Second, this results in extra inward Na\(^+\) current during the upstroke of the AP, slightly increasing upstroke velocity. Finally and most importantly, this results in extra inward Na\(^+\) current during the plateau phase, thereby increasing APD. The overall effect is a slowing of sinus rate, indicating that the effect of increased APD by far outweighs the effect of increased DDR.

When persistent current and a shift in inactivation are combined, the extra net inward Na\(^+\) currents during the upstroke and the plateau of the AP are maintained but inward Na\(^+\) current during diastolic depolarization is reduced. In effect, this produces an extra reduction in sinus rate, because the negative shift in inactivation cancels out the increase in DDR induced by \(I_{\text{rest}}\) without affecting the \(I_{\text{rest}}\)-induced increase in APD. In line with the model calculations of Figure 3D, mutant channels in action potential clamp experiments indeed displayed a small, but substantial, inward sodium current during the upstroke and the plateau phase of the SA node AP.

During the plateau and diastolic depolarization phase, membrane resistance is relatively high. Therefore, small changes in current are sufficient to induce considerable changes in the time course of these phases of the action potential. The computational model predicts that the delicate balance of inward and outward currents during the plateau phase gets seriously disturbed when persistent current is increased to >2% (in case of 100% mutant channels). Beyond this critical level, extra net inward current results in oscillating behavior and failure to repolarize. With 50% mutant and 50% wild-type channels, all of the above described effects were qualitatively the same but less pronounced. For example, oscillating behavior and failure to repolarize occurred at 5% to 6% \(I_{\text{rest}}\).

**Sodium Current in Mammalian Sinoatrial Node**

In the last 2 decades, a large body of information on the ionic mechanism underlying mammalian cardiac pacemaker activity has been obtained from animal experiments.\(^{16,21}\) The importance of Na\(^+\) channels in SA nodal pacemaking used to be debated, because \(I_{\text{Na}}\) was assumed to be small or absent in SA nodal cells.\(^{19,21}\) However, an increasing number of studies now report the presence of \(I_{\text{Na}}\) in adult SA nodal cells, up to densities of 100 pA/pF in the more peripheral cells.\(^{16}\) Moreover, experiments with the specific Na\(^+\) channel blocker TTX in rabbit SA node preparations clearly show a reduction in beating rate in the presence of the drug, providing evidence that \(I_{\text{Na}}\) actually contributes to SA node electrical activity.\(^{19,20,22–25}\) Also, the recent observations that mice heterozygous for knock-in KPQ-deletion (SCN5A\(^{\text{K+}}\)) frequently exhibit sinus pauses and bradycardia\(^{26}\) additionally support a role for \(I_{\text{Na}}\) in SA node pacemaking in mammalian species.

The goal of this study was to unravel the mechanism by which sodium channel mutations, in particular the 1795insD

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**Figure 6.** Changes in CL for 3 different sinoatrial node action potential models as a result of a −10-mV shift in inactivation and the presence of 1% to 3% \(I_{\text{Na}}\). Simulations carried out with 100% mutant channels (A) and 50% mutant and 50% wild-type Na\(^+\) channels (B and C). Plateau oscillations and failure to repolarize completely. Note differences in ordinate scales.

Present in the voltage range of the Na\(^+\) window current, where activation and inactivation relationships overlap. Consequently, Na\(^+\) channels generate a small inward current at voltages between −60 and −40 mV, thus normally contributing only to diastolic depolarization. Action potential clamp experiments in HEK-293 cells expressing wild-type channels confirmed that little inward current was present during the entire SA nodal AP. Unfortunately, technical limitations (current noise, possible minor offset in zero-current level) prevent detection of current as small as the wild-type sodium current that would flow during diastolic depolarization, as predicted by the SA node AP model (≈0.06 pA/pF; Figure 3A, middle, solid line).

The negative shift in voltage dependence of inactivation of the 1795insD mutant Na\(^+\) channel narrows the voltage range of Na\(^+\) window current and thus reduces Na\(^+\) inward current during the diastolic depolarization phase. This results in a slowing of diastolic depolarization, thereby increasing the duration of this phase and reducing sinus rate.

A different mechanism underlies the reduction in sinus rate resulting from the presence of persistent inward current. Because of the incomplete channel inactivation at prolonged depolarizations, a small number of (noninactivated) channels

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**A**

![Graph A](http://example.com/graph-a.png)

**B**

![Graph B](http://example.com/graph-b.png)

**C**

![Graph C](http://example.com/graph-c.png)
mutation, may cause sinus bradycardia and the occurrence of sinus pauses in LQT3 patients. The relevance of the results presented here strongly depends on whether Na+ channels are actually present in human SA node cells. Because human SA node preparations are not available for in vitro experiments, little is known on the various ionic currents present and their relative contribution to pacemaking. However, there are strong indications that Na+ channels also play a role in sinus node automaticity in humans. Several descriptions of plant poisoning involve toxins (grayanotoxins, veratrum alkaloids, and aconitine) that affect the cardiac sodium channel and have an effect on heart rate.25,27 Interestingly, these toxins all induce a persistent inward current by inhibition of inactivation and cause significant bradycardia, among other symptoms. Also, the observation that flecainide, a sodium channel blocker that preferentially inhibits Na+ persistent inward current,28 increased heart rate in D1790G mutation carriers6 may provide additional evidence in favor of a role of Na+ channels in human SA node automaticity.

Comparison With Clinical Features
Apart from the 3 mutations for which sinus bradycardia was observed in presence of drugs (see Table 1 in the online data supplement), there are 5 LQT3 families for which sinus bradycardia and the occurrence of sinus pauses or arrest were explicitly described. In carriers of the ΔKPQ5 and the ΔK150010 mutation, mean heart rate (HR) was reduced by 17% to 19%5 and sinus pauses and arrest were observed.10 In carriers of the 1795insD mutation, mean HR was reduced by 9% and lowest mean HR by 13%.9 In one patient, long asystolic episodes up to 9 seconds were monitored. In carriers of the D1790G mutation, mean HR was also reduced by 9%, and 3 cases with sinus arrest were reported.6 In the E1784K family, sinus bradycardia was present in 3 carriers and occasional sinus pauses in 1 of them.7 Notably, all mutant Na+ channels associated with the above families displayed both a persistent inward current and a negative shift in inactivation.7,10,13,29–31 The various computer simulations performed all predict—indepenent of the particular SA node

Figure 7. A, Control action potentials of the Zhang et al27,28 peripheral SA nodal cell model in the absence of ACh (left) and in the presence of 100 nmol/L ACh (right). B through H, Simulated effects of 1795insD mutant biophysical properties (50% mutant and 50% wild-type channels). Dashed lines represent wild-type control. Arrows indicate increase in cycle length.
model, \( I_{Na} \) equations, and intrinsic cycle length—that this combination reduces sinus rate by increasing APD and slowing DDR. There are, however, quantitative differences. For example, with a shift of \(-10 \text{ mV} \) and a \( \Delta v_{Na} \) of \(2\%\), the reduction in SR varied between 4.4% and 22% in case of 50% mutant and 50% wild-type channels (Figures 6B and 6C). The model values for SR reduction compare well with those reported for the respective families. The computer simulations also predict that SA node cells start to oscillate at plateau potentials and fail to repolarize if \( I_{Na} \) is increased above a critical level. This phenomenon may represent the cellular correlate to sinus pauses or arrest. It suggests that intrinsic or extrinsic factors generating little additional net inward current during the plateau phase, either by decreasing outward current or increasing inward current, can induce the transition from relative bradycardia into sinus node dysfunction.

**Summary**

In summary, bradycardia presents an important factor in the genesis of lethal arrhythmias in LQT3 families. The majority of LQT3 sodium channel mutations cause a persistent inward current. In about half of these mutations, this persistent current is accompanied by a negative shift in steady-state inactivation. We show that both a persistent inward current and a negative shift in inactivation slow sinus rate and do so through different mechanisms. In combination, the persistent current and the shift reduce sinus rate to a greater extent than each separately, their effects being almost additive. We conclude that LQT3 sodium channel mutations giving rise to a persistent inward current not only underlie QT-prolongation but also sinus bradycardia and sinus pauses. Moreover, in families with LQT3 sodium channel mutations in which the persistent current is accompanied by a negative shift in inactivation, sinus bradycardia is aggravated.

**Acknowledgments**

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Contribution of Sodium Channel Mutations to Bradycardia and Sinus Node Dysfunction in LQT3 Families

Online Data Supplement

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One form of the familial long-QT syndrome (LQT3) is caused by mutations in the gene encoding the cardiac sodium channel (SCN5A; see Ref. 1 for review). To date, the biophysical properties of the mutant sodium channels have been assessed for at least 21 of the distinct genetic mutations in SCN5A that have been linked to LQT3. In Table 1 of this Online Data Supplement we summarize the data on channel properties that are of particular importance to our study, i.e., the presence of a persistent sodium inward current (I_{pst}) during prolonged depolarization and the presence of a negative shift in the steady-state inactivation curve. Thus, this table does not list mutations in SCN5A that have been linked to LQT3, but for which no data on channel properties are available, e.g., the T1645M and T1304M mutations identified by Wattanasirichaigoon et al.,\(^2\) and the D1114N, L1501V, ΔF1617, R1623L, and S1787N mutations that were identified by Splawski et al.\(^3\)
### Table 1  Electrophysiological characteristics of mutant sodium channels associated with long-QT syndrome type 3

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Domain</th>
<th>Syndrome</th>
<th>Sinus node dysfunction</th>
<th>Shift in inactivation</th>
<th>Persistent $I_{Na}$</th>
<th>Ref.</th>
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<td>DI-DII linker</td>
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<td>—</td>
<td>n.s.</td>
<td>n.s.</td>
<td>4</td>
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<tr>
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<td>drug-induced LQT</td>
<td>—</td>
<td>n.s.</td>
<td>n.s.</td>
<td>4</td>
</tr>
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<tr>
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<td>DII-DIII linker</td>
<td>LQT-SIDS</td>
<td>—</td>
<td>—</td>
<td>2–4%</td>
<td>6</td>
</tr>
<tr>
<td>F1250L</td>
<td>DIII-S2</td>
<td>drug-induced LQT</td>
<td>—</td>
<td>n.s.</td>
<td>n.s.</td>
<td>4</td>
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<td>LQT</td>
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<td>LQT-SIDS</td>
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<td>—</td>
<td>2.5–5%</td>
<td>9</td>
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<td>DIII-DIV linker</td>
<td>LQT, Brugada, PCCD</td>
<td>sinus pauses, sinus arrest</td>
<td>−13.4 mV</td>
<td>1.5%</td>
<td>11</td>
</tr>
<tr>
<td>Δ1505-1507 (ΔKPQ)</td>
<td>DIII-DIV linker</td>
<td>LQT</td>
<td>relative bradycardia</td>
<td>−5.8 mV</td>
<td>&lt;5.0%</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
<td>0.6–0.8%</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
<td>1–4%</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
<td>2–4%</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
<td>1.7%</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
<td>2–5%</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0%</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>R1623Q</td>
<td>DIV-S4</td>
<td>LQT</td>
<td>—</td>
<td>n.s.</td>
<td>&lt;5%</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>&lt;3%</td>
<td>18</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>−7.2 mV</td>
<td>—</td>
<td>19</td>
</tr>
</tbody>
</table>

*Table 1 continues on next page*
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Domain</th>
<th>Syndrome</th>
<th>Sinus node dysfunction</th>
<th>Shift in inactivation</th>
<th>Persistent $I_{\text{Na}}$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1644H</td>
<td>DIV-S4</td>
<td>LQT</td>
<td>—</td>
<td>—</td>
<td>0.5%</td>
<td>8</td>
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<tr>
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<td></td>
<td></td>
<td>n.s.</td>
<td>9</td>
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<tr>
<td>M1766L</td>
<td>DIV-S6</td>
<td>LQT-SIDS</td>
<td>sinus bradycardia with lidocaine, propanolol, and mexiletine</td>
<td>+11 mV</td>
<td>11%</td>
<td>20</td>
</tr>
<tr>
<td>I1768V</td>
<td>DIV-S6</td>
<td>LQT</td>
<td>—</td>
<td>+7.6 mV</td>
<td>n.s.</td>
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<td>V1777M</td>
<td>C-terminal</td>
<td>LQT</td>
<td>—</td>
<td>−12.4 mV</td>
<td>4.0%</td>
<td>22</td>
</tr>
<tr>
<td>E1784K</td>
<td>C-terminal</td>
<td>LQT</td>
<td>sinus bradycardia, sinus pauses</td>
<td>−12.1 mV</td>
<td>2–4%</td>
<td>23</td>
</tr>
<tr>
<td>D1790G</td>
<td>C-terminal</td>
<td>LQT</td>
<td>relative bradycardia, sinus arrest</td>
<td>−16.3 mV</td>
<td>n.s.</td>
<td>15</td>
</tr>
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<td></td>
<td>−15.0 mV</td>
<td>n.s.</td>
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</tr>
<tr>
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<td></td>
<td>−14.6 mV</td>
<td>6.0%</td>
<td>26</td>
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<tr>
<td></td>
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<td>−15.6 mV</td>
<td>—</td>
<td>27</td>
</tr>
<tr>
<td>1795insD</td>
<td>C-terminal</td>
<td>LQT, Brugada</td>
<td>relative bradycardia, sinus pauses</td>
<td>−7.3 mV</td>
<td>n.s.</td>
<td>28</td>
</tr>
<tr>
<td>Y1795C</td>
<td>C-terminal</td>
<td>LQT</td>
<td>—</td>
<td>n.s.</td>
<td>2.1%</td>
<td>30</td>
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<tr>
<td>L1825P</td>
<td>C-terminal</td>
<td>drug-induced LQT</td>
<td>severe bradycardia with cisapride</td>
<td>−11.0 mV</td>
<td>2.6%</td>
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</tr>
<tr>
<td>R1826H</td>
<td>C-terminal</td>
<td>LQT-SIDS</td>
<td>—</td>
<td>—</td>
<td>2.0%</td>
<td>6</td>
</tr>
</tbody>
</table>

Shift in steady-state inactivation is relative to the wild-type channel. Persistent $I_{\text{Na}}$ is expressed as percent of peak sodium current. —, no experimental data available; n.s., no statistically significant effect; LQT-SIDS: LQT3 mutation identified in sudden infant death syndrome; PCCD: progressive cardiac conduction system disease.
References


