Flecainide Provocation Reveals Concealed Brugada Syndrome in a Long QT Syndrome Family With a Novel L1786Q Mutation in SCN5A

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Background: Mutations in SCN5A can result in both long QT type 3 (LQT3) and Brugada syndrome (BrS), and a few mutations have been found to have an overlapping phenotype. Long QT syndrome is characterized by prolonged QT interval, and a prerequisite for a BrS diagnosis is ST elevation in the right precordial leads of the electrocardiogram.

Methods and Results: In a Danish family suffering from long QT syndrome, a novel missense mutation in SCN5A, changing a leucine residue into a glutamine residue at position 1786 (L1786Q), was found to be present in heterozygous form co-segregating with prolonged QT interval. The proband presented with an aborted cardiac arrest, and his mother died suddenly and unexpectedly at the age of 65. Flecainide treatment revealed coved ST elevation in all mutation carriers. Electrophysiological investigations of the mutant in HEK293 cells indicated a reduced peak current, a negative shift in inactivation properties and a positive shift in activation properties, compatible with BrS. Furthermore, the sustained (hva,un) tetrodotoxin-sensitive sodium current was found to be drastically increased, explaining the association between the mutation and LQT3 syndrome.

Conclusions: The L1786Q mutation is associated with a combined LQT3 and concealed BrS phenotype explained by gating characteristics of the mutated ion channel protein. Hence, sodium channel blockade should be considered in clinical evaluation of apparent LQT3 patients. (Circ J 2014; 78: 1136–1143)

Key Words: Ion channel kinetics; Repolarization; Sodium channel blockade; T-wave morphology
variants without association with sudden cardiac death. LQTS in patients with an SCN5A mutation is due to gain of function of the late sodium current, categorized as LQT3, leading to an increased persisting depolarizing late sodium current prolonging the cardiac action potential. In contrast, BrS caused by SCN5A mutations is due to a loss of function of the sodium channel. This can be caused either by reduced I Na peak amplitudes, negative sodium current in SCN5A L1786Q, or any combination of these changes in gating. Given that the reduction in the transient sodium current in SCN5A BrS patients occurs in the initial part of the action potential (phase 1), whereas the persistent late sodium current in SCN5A LQTS patients is active throughout the whole action potential, coexistence of the 2 apparent opposing sodium channel phenotypes is possible.

**Methods**

**Ethics**

All clinical information was collected, and genetic testing performed, for clinical reasons. No examinations were done that were not indicated by standard care. Hence ethics approval is not relevant according to Danish law and regulations.

**Flecainide Test**

Flecainide 2 mg/kg bodyweight (maximum 150 mg) was injected over 10 min into a cubital vein with simultaneous ECG recordings during flecainide injection and 30 min afterwards.

**Conservation Score**

The conservation score was calculated as described by Jons et al10 using the 10 sodium channels (SCN1A-SCN11A) in Table 1 as reference values. A score of 1 indicates maximum conservation and 0, no conservation.

**Genetic Testing**

Mutation screening of SCN5A was performed with capillary array electrophoresis (CAE) single-strand conformation polymorphism analysis (SSCP)17,18 on genomic DNA isolated from blood, followed by direct DNA sequencing of aberrant conformers. The primers used have been described previously in detail.16 The proband was also screened for mutations in KCNQ1, KCNH2 (HERG), KCNE1 (MinK), and KCNE2 (MiRP1). Primer sequences and conditions are available upon request (mic@ssi.dk). The mutation was denoted based on the full-length 2,016-amino acid splice variant (Genebank NM_198056.2/ NP_932173.1).

**DNA Constructs**

Human SCN5A (hH1) in pcDNA3 was a gift from Dr H. Abriel (Lausanne University). The L1786Q mutation was introduced into pcDNA3-hSCN5A using overlapping oligonucleotides followed by full plasmid polymerase chain reaction. The integrity of the sub-cloned construct was verified on sequencing.
sodium aspartate, 70; CaCl₂, 1; MgCl₂, 1; Hepes, 10; EGTA, 11; external pipette solution (mmol/L) was as follows: CsCl, 60; cation, which were done at room temperature. The inner membrane potential, Vₜ₀, was activated or inactivated, and K the slope factor. EP data were compensated (80%). No leak subtraction was performed. In all experiments the seal resistance was >1.5 GΩ and were 2–4 MΩ and were compensated (80%). No leak subtraction was performed. In all experiments the seal resistance was >1.5 GΩ and, for the sustained current measurements, >2 GΩ. Is was blocked with 50 μmol/L tetrodotoxin (TTX, Alomone labs, Jerusalem, Israel). The sustained current data used in the Figures are given as an average of the last 50 ms (450–500 ms) of the voltage steps. Series resistance was <10 MΩ during the entire experiment. Update was performed between each sweep.

Data Analysis
Peak current densities were measured during an activation protocol and Is densities (pA/pF) were obtained by dividing the peak Is by the cell capacitance. For the activation and steady-state inactivation curves, data from individual cells were fitted with a Boltzmann equation, y(Vₘ)="1/(1+exp((Vₘ-Vₜ₀)/K)), in which y is the normalized current or conductance, Vₘ the membrane potential, Vₜ₀ the voltage at which half of the channels are activated or inactivated, and K the slope factor. EP data were analyzed using Excel (Microsoft), Igor Pro (Wavemetrics, Lake Oswego, OR, USA), and GraphPad Prism (GraphPad Software, San Diego, CA, USA).

Statistical Analysis
Data are represented as mean±SEM. Two-tailed Student’s t-test was used to compare means; P≤0.05 was considered as statistically significant.

Results

Genetics
Genetic analysis was performed in all family members with the exception of the proband’s mother (Figure 1, I-2), for whom the carrier status was assumed given the fact that she died suddenly and unexpectedly at age 65 and that her husband did not carry the mutation, making her an obligate carrier. All clinically affected subjects (black circles/squares) were heterozygous carriers of a novel missense mutation in SCN5A, L1786Q. The mutated residue is highly conserved in voltage-gated Na⁺-channels with a conservation score of 1.0, given that the original leucine is present in all known human SCN-proteins and, additionally, cross-species alignment of Nav1.5 shows this leucine to be conserved beyond the mammalian kingdom (Table 1). All clinically unaffected family members were found to have the WT with lysine at codon 1786.

Clinical Presentation
The proband (Figure 1, II-1) was resuscitated after a cardiac arrest at the age of 48 without any neurological deficits. The ECG showed a clearly prolonged corrected QT interval of 0.48 s, but without signs of an ST segment elevation pattern on resting ECG (Figure 2A). After flecainide challenge, coved-type 1 ST elevation was seen (Figure 2B). It was not possible to induce ventricular tachycardia/fibrillation during EP study using a standard protocol with up to 3 extra stimuli (minimum of 200 ms) and 2 basic drive cycle lengths (600 and 400 ms) from the right ventricular apex and outflow tract. Due to the cardiac arrest an ICD was implanted. Afterwards the proband received 3 appropriate shocks. During flecainide testing a coved ST segment elevation pattern was induced in lead V1. The brother (Figure 1, II-3) and a niece of the proband (Figure 1, III-3) also had clear QT prolongation without significant BrS pattern, but after flecainide provocations a clear BrS type 1 pattern was seen (Figures 2E, F). The brother was asymptomatic but his daughter (the proband’s niece) had experienced a single syncopeal event at home following a tooth extraction with infection. Both were treated with a prophylactic ICD. The proband’s niece did not experience any shocks during follow-up, whereas the brother has received 2 inappropriate shocks due to episodes of rapidly conducted atrial flutter. The clinical EP characteristics are listed in Table 2.

Figures 2C,D shows the recorded ICD electrogram strips with 2 induction modes of arrhythmia: LQTS mode with short-long-short coupling sequence (Figure 2D) and BrS mode with a sudden premature beat eliciting the ventricular tachycardia (Figure 2C).

Whole-Cell Patch-Clamping
In order to investigate whether altered biophysical properties of the L1786Q Nav1.5 mutation can explain the observed patient phenotype, voltage-clamp patch-clamping was performed. Transient expression in HEK293 cells, followed by whole-cell patch-clamping of the cells superfused with 37±1°C in an extracellular solution containing 130 mmol/L sodium, revealed

Patch-Clamping
For electrophysiological (EP) studies, HEK293 cells were transiently co-transfected with 0.3 μg wild-type (WT) or L1786Q Nav1.5 encoding constructs together with 0.2 μg of pcDNA3-EGFP as a reporter gene, using Lipofectamine (Invitrogen, USA) according to the manufacturer instructions. Measurements were performed 1–3 days after transfection. Whole-cell currents were measured at 37±1°C, except for the measurements of the sustained current, which were done at room temperature. The internal pipette solution (mmol/L) was as follows: CsCl, 60; cesium aspartate, 70; CaCl₂, 1; MgCl₂, 1; Hepes, 10; EGTA, 11; Na₂ATP, 5; pH, 7.2, with CsOH; external solution (mmol/L): NaCl, 130; CsCl, 5; CaCl₂, 2; MgCl₂, 1.2; Hepes, 10; glucose, 5; pH, 7.4, with CsOH. Measurements were controlled with Pulse software (HEKA Elektronik, Lambrecht, Germany), using an EPC-9 amplifier (HEKA Elektronik). Borosilicate glass pipettes were pulled on a DPZ-Universal puller (Zeit Instrumente, Munich, Germany). The pipettes had a resistance of 1.5–2.5 MΩ when filled with intracellular solution. The series resistances recorded in the whole-cell configuration were 2–4 MΩ and were compensated (80%). No leak subtraction was performed. In all experiments the seal resistance was >1.5 GΩ, and, for the sustained current measurements, >2 GΩ. Is was blocked with 50 μmol/L tetrodotoxin (TTX, Alomone labs, Jerusalem, Israel). The sustained current data used in the Figures are given as an average of the last 50 ms (450–500 ms) of the voltage steps. Series resistance was <10 MΩ during the entire experiment. Update was performed between each sweep.
Figure 2. Electrocardiogram (ECG) and electrogram (EGM) traces: (A) ECG trace from the proband with QT prolongation but without any signs of ST elevation. (B) ECG trace from the proband during flecainide test with coved pattern. (C) Brugada syndrome pattern with ST elevation and a premature beat with a short coupling interval eliciting arrhythmia. (D) Long QT syndrome pattern of induction without ST elevation in EGM and a short-long-short coupling sequence. (E) ECG trace from the proband’s niece (Figure 1, III-3) before flecainide testing. (F) ECG trace from the proband’s niece (Figure 1, III-3) during flecainide testing. Note that lifted leads were used. (V1 and V2 lifted to the 3rd intercostal space. Lifted V1½ is placed on sternum in the same height as lifted V1 and V2.)

Table 2. Clinical Characteristics of L1786Q Mutation Carriers

<table>
<thead>
<tr>
<th></th>
<th>QTc (s)</th>
<th>HR (beats/min)</th>
<th>QRS (ms)</th>
<th>Syncope</th>
<th>ICD</th>
<th>Sudden death (65 years)</th>
<th>Appropriate shock</th>
<th>Aborted cardiac arrest</th>
<th>Inducibility at EP study</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>II-1</td>
<td>0.48</td>
<td>50</td>
<td>114</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>II-3</td>
<td>0.47</td>
<td>61</td>
<td>152</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>III-3</td>
<td>0.48</td>
<td>69</td>
<td>118</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (VFib)</td>
</tr>
</tbody>
</table>

EP, electrophysiology; HR, heart rate; ICD, implantable cardioverter defibrillator; VFib, ventricular fibrillation; NA, not available.
which could explain the BrS phenotype. The half steady-state activation potential was shifted from $-28.5\text{ mV}$ to $-13.3\text{ mV}$ (Figure 3E; Table 3), while the half steady-state inactivation potential was shifted from $-67.0\text{ mV}$ to $-88.3\text{ mV}$ for WT and L1786Q, respectively (Figure 3C; Table 3). A positive shift in activation potential and a negative shift in inactivation potential will lead to a reduced availability of the channels, which will be consistent with a loss-of-function phenotype as observed in BrS.

A biophysical explanation for the observed LQTS phenotype

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**Figure 3.** Biophysical properties of wt vs. L1786Q Na$\text{v}$1.5 channels. (A) Voltage clamping of either WT or mutant (L1786Q) SCN5A transfected HEK293 cells at 37°C. Representative traces. Increasing depolarizing voltages increasingly activate the Nav1.5 channels, but, because the reversal potential of sodium is approximately 50 mV, the peak current decreases at potentials higher than approximately $-20\text{ mV}$. (B) Current voltage (I–V) relationship. (C) Normalized peak current at the maximum current recorded (wt, $-20\text{ mV}$; L1786Q, $-5\text{ mV}$). (D) Steady-state inactivation as a function of voltage. (E) Steady-state activation as a function of voltage. The Boltzmann curves were obtained as described. The applied voltage protocols are shown in inserts. Arrows indicate were the current values are recorded. The leftward shift in inactivation and the rightward shift in activation of L1786Q compared to WT are both parameters that will reduce peak sodium current. (F) Sustained current at different potentials recorded from wt- and L1786Q-expressing cells at 37°C. Normalized for cell size. *$P<0.05$; **$P<0.01$; ***$P<0.001$.
was addressed by analyzing the late sodium current before and after addition of the sodium channel blocker TTX (Figure 4A). Fifty µmol/L TTX enforces an 80–90% block of both WT and L1786Q Na+ current. These experiments were conducted at 20±1°C to maintain a stable recording over the time course of TTX application. The TTX block produced a 3-fold increase in the sustained (I_sust, late) L1786Q current as compared to WT current when holding the potential at ~20 mV (Figure 4B) despite the fact that L1786Q peak current was reduced drastically (Figure 4C). Further, because the membrane potential in a cardiomyocyte changes throughout the action potential, the voltage dependence of the sustained current was investigated at different voltages (Figure 3F). The sustained current was recorded in sodium channel expressing cells at 37±1°C without TTX block. Mock transfected HEK293 cells show only a very low sustained current (data not shown). Both WT and L1786Q channels have voltage-dependent sustained currents, with the highest current at the most negative values. The L1786Q sustained current (normalized to cell size) is significantly larger at −15 mV to −30 mV. Thus, the data show an increased sustained current for the L1786Q mutant channel, which would be compatible with the observed LQT3 phenotype.

The EP investigations of the L1786Q Na+-1.5 sodium channel therefore provide evidence for the observed mixed phenotype of LQT and BrS.

Discussion

The main finding of the study is that the SCN5A L1786Q mutation leads to an overlap syndrome with combined LQTS and BrS, without any signs of ST elevation in the resting ECG.

Today almost 100 mutations in SCN5A leading to BrS have been identified,25 some of them with overlap syndromes between LQTS, CCD and sick sinus node syndromes.26 As shown in Table 4, only 6 other mutations have been clinically documented with comorbid BrS and LQTS. These 6 mutations span from the DII–III linker to the C-terminus.

The SCN5A L1786Q mutation is located in the C-terminal end of SCN5A, in proximity to the E1784K and 1795insD mutations.27 The C-terminus is thought to have a role in stabilizing the inactivated channel, where it interacts with the intracellular linker between the DIII and DIV domain of SCN5A.28 As shown in Figure 3, the L1786Q mutation leads to a reduced peak sodium current, a leftwards shift in the inactivation curve, and a rightwards shift in the activation curve, which would result in a reduced availability of functional sodium channels, and thereby to a loss-of-function phenotype. Whereas most WT channels are released from inactivation at the resting membrane potential, the leftwards shift in voltage-dependent inactivation makes a large fraction of L1786Q channels inactivated at the resting potential, hence, not available for activation during the depolarizing process. The rightwards shift in activation kinetics causes the sodium channels to activate at more positive potentials, which would also result in reduced peak sodium current.

For the overlap mutations, encompassing a dual BrS and LQTS phenotype (Table 4), where EP analyses have been performed, a ubiquitous increase in late sodium current causes the LQTS phenotype, and a reduction of early sodium current causes the BrS phenotype. All but delK1500 had reduced peak sodium current, but the characterization of delK150023 was performed at a resting potential of −100 mV instead of at a more physiological value of −85 mV, masking the real effect on the peak sodium current difficult to quantify. The large negative shift in the steady-state inactivation of delK1500, however, would lead to a net reduction of peak sodium current compatible with BrS.

L1786Q provides a significant increase in the late sodium current. Interestingly, the present analyses show a voltage dependency of this late current. The L1786Q late current is more pronounced at more negative voltages. These data thereby indicate that the sustained current has the largest impact in the late part of the phase II of the action potential, which gradually shows a declining potential, and may also have an impact on phase III repolarization. Such a relative increase in a depolarizing current in the later part of the action potential will lead to a prolongation of the action potential duration and thereby prolonged QT interval.

The clinical history of the proband indicates a malignant mutation with a course of aborted cardiac arrest and several occurrences of appropriate ICD shocks. According to the proposed diagnostic criteria, coved-type ST segment elevation should be present in 2 right precordial leads (>2 mm),29,30 which was not fulfilled in the proband. But recently it has been shown that patients with only single-lead coved ST elevation in lead V1 or V2 have a similar prognosis to that of the classical pattern with elevation in 2 leads.31

From the ICD print-outs (Figures 2C.D), it is clear that there are 2 modes of initiating events. In Figure 2D a premature ventricular beat is followed by a post-ectopic pause, giving rise to the short-long-short sequence typical of LQTS, but in Figure 2C an early premature ventricular beat with a short coupling interval suggests a phase 2 reentry arrhythmia,32 a classic pattern for BrS.

Table 3. Biophysical Properties of Na+1

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>L1786Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak current (µA/µF)</td>
<td>–604±113**</td>
<td>–190±55**</td>
</tr>
<tr>
<td>(pre-pulse: –120 mV)</td>
<td>(n=7, at –20 mV)</td>
<td>(n=8, at –5 mV)</td>
</tr>
<tr>
<td>Steady-state activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1/2 (mV)</td>
<td>–28.5±1.9</td>
<td>–13.3±1.1</td>
</tr>
<tr>
<td>(n=7)</td>
<td></td>
<td>(n=8)****</td>
</tr>
<tr>
<td>Slope, k value</td>
<td>5.0±0.4</td>
<td>9.3±0.9</td>
</tr>
<tr>
<td>mV/e-fold</td>
<td></td>
<td>mV/e-fold**</td>
</tr>
<tr>
<td>Steady-state inactivation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1/2 (mV)</td>
<td>–67.0±1.4 mV</td>
<td>–88.3±2.2 mV</td>
</tr>
<tr>
<td>(n=11)</td>
<td></td>
<td>(n=8)****</td>
</tr>
<tr>
<td>Slope, k value</td>
<td>4.7±0.3</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>mV/e-fold</td>
<td></td>
<td>mV/e-fold**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.05, ***P<0.001. †Recorded in HEK293 cells expressing WT Na+1.5 and L1786Q Na+1.5. WT, wild type.

Treatment of overlap syndrome patients with combined LQTS + BrS imposes a clinical problem. Beta-blockers are effective in LQTS, but are known to increase ST elevation in BrS.33 Sodium blocker may worsen BrS, although quinidine has been suggested to be useful in BrS due to the beneficial β-blocking effect, but its β-blocking abilities could induce further QT prolongation and torsades. Mexiletine has been shown not to unmask BrS in the overlap mutation SCN5A E1784K, but there are no reports of its continued use in these overlap syndrome patients. A new alternative could be ranolazine, a late sodium current blocker, which may shorten the QT interval without affecting the peak current,34 hence should be beneficial for LQTS, with no negative effect on the BrS. In the present family we decided to implant ICD in all affected subjects, even the asymptomatic subject, because of the possible need for β-blocker treatment for the LQTS, which may be harmful in BrS. Due to the limited evidence in overlap syndrome, it is unknown whether this will be justified in the future or reflect an
The baseline T-wave morphology in the 3 patients is similar to late onset of a normal T-wave pattern as described by Zhang et al. This pattern is seen in <10% of all LQTS patients with SCN5A mutations, where late onset peaked/biphasic (53%) and asymmetrical peaked T-waves (12%) are more commonly seen. Interestingly, the similar late onset of a normal T-wave pattern was also seen in 2 of the other combined BrS/LQTS mutations (E1784K, L1795insD8), whereas in the other published mutations the baseline full 12-lead ECG without flecainide overtreatment.

Given that the presence of LQT3 and BrS phenotypes in the same patients is extremely infrequent, it is very difficult to investigate the relationship between the 2 syndromes. When BrS is caused by a mutated SCN5A gene it is due to a loss of function in the transient sodium current, while LQT3 syndrome is caused by an increased sustained (or late) sodium current. The present EP investigations do not indicate that the sustained sodium current somehow facilitates a reduced transient sodium current, and it is still unknown whether LQT3 unmasks or masks BrS.

The baseline T-wave morphology in the 3 patients is similar to late onset of a normal T-wave pattern as described by Zhang et al. This pattern is seen in <10% of all LQTS patients with SCN5A mutations, where late onset peaked/biphasic (53%) and asymmetrical peaked T-waves (12%) are more commonly seen. Interestingly, the similar late onset of a normal T-wave pattern was also seen in 2 of the other combined BrS/LQTS mutations (E1784K, L1795insD8), whereas in the other published mutations the baseline full 12-lead ECG without flecainide

Table 4. EP Characteristics of Mutations Associated With LQTS+BrS Phenotype

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Late sodium current</th>
<th>Activation shift</th>
<th>Inactivation shift</th>
<th>Peak sodium current</th>
<th>Clinical phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1114N</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>BrS+LQTS</td>
</tr>
<tr>
<td>W1191X</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>BrS+LQTS</td>
</tr>
<tr>
<td>delK1500</td>
<td>+23</td>
<td>+23</td>
<td>–23</td>
<td>–23</td>
<td>BrS+LQTS</td>
</tr>
<tr>
<td>Del KPO</td>
<td>+19</td>
<td>019</td>
<td>(–)19</td>
<td>NA</td>
<td>BrS+LQTS, LQTS</td>
</tr>
<tr>
<td>Del F1617</td>
<td>+/–126</td>
<td>026</td>
<td>–26</td>
<td>026</td>
<td>BrS, LQTS</td>
</tr>
<tr>
<td>E1784K</td>
<td>+27</td>
<td>+27</td>
<td>–27</td>
<td>–27</td>
<td>LQTS+BrS</td>
</tr>
<tr>
<td>L1786Q</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Present study</td>
</tr>
<tr>
<td>1795 insD</td>
<td>+8</td>
<td>+8</td>
<td>–8</td>
<td>–8</td>
<td>LQTS+BrS</td>
</tr>
</tbody>
</table>

*Late sodium current reduced at negative voltage potentials and increased at positive voltage potentials. BrS, Brugada syndrome; EP, electrophysiology; LQTS, long QT syndrome; NA, not available.
were not included for evaluation. In the case of E1784K the ECG was also normal in some subjects and only after sodium channel blockade with either pilsicainide or ajmaline, the Brugada pattern was seen.\textsuperscript{27} It is also noticeable that these 3 mutations with late-onset normal pattern were C-terminal mutations in SCN5A.

**Conclusion**

We have described a case of combined BrS and LQTS in a patient with SCN5A L1786Q mutation, in whom the typical BrS type-1 ST segment elevation was unmasked by flecainide provocation. The present results thereby confirm that a proportion of LQTS patients with a mutation in SCN5A may harbor a type-1 ECG Brugada ECG pattern when exposed to a class 1C antiarrhythmic. Given that the pharmacological treatment of BrS is different from that of LQTS, great care should be taken in defining the phenotype. We suggest that all LQTS patients with SCN5A mutations undergo sodium blocker provocation test to exclude BrS.

**Acknowledgments**

Jette Rasmussen is thanked for excellent technical assistance. Funding was obtained from the Fraenkel Foundation and the Danish Council for Strategic Research. Funding was also received from the Danish National Research Foundation, the Fraenkel Foundation, and the Danish Agency for Science and Innovation. On behalf of all authors, the corresponding author states that there is no conflict of interest.

**References**