The congenital long-QT syndrome (LQTS) is a familial heart disorder that is associated with a prolonged QT interval, T-wave abnormalities, and torsade de pointes (TdP) ventricular tachycardias that may cause syncope and occasionally sudden death. The diagnosis is based on clinical variables, including QT prolongation, a history of syncope, and/or documented TdP episodes. Molecular genetic studies have established that most congenital LQTS forms are caused by mutations in genes that encode cardiac ion channels. Among genotyped patients, mutations in KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) are the most prevalent by far. KCNQ1 and KCNH2 both encode components of the delayed rectifier potassium current (I_Ks and I_Kr, respectively), with I_Kr being the target of several antiarrhythmic and nonantiarrhythmic drugs with TdP potential. SCN5A encodes the cardiac sodium channel.

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The identification of these gene variants has sparked studies into possible genotype–phenotype correlations in LQTS with the aim of refining clinical management and providing genotype-tailored therapy. These studies have revealed that ECG patterns and symptom triggers are genotype specific, thus facilitating the establishment of a molecular genetic diagnosis using a candidate-gene approach. Similarly, therapy strategies may be refined because prognosis and the risk of cardiac events are genotype dependent. Moreover, the efficacy of β-blockers, long established as the mainstay of therapy in congenital LQTS, in preventing TdP episodes may be genotype dependent, being higher in LQT1 than in LQT2 or LQT3. This disparity in efficacy may be due to differences in arrhythmia mechanisms. Of note, TdP onset may or may not be pause dependent, ie, associated with pauses that immediately precede the first TdP beat. This distinction may reflect different electrophysiological mechanisms and affect the therapeutic efficacy of β-blockers. Identification of those patients who have pause-dependent TdP gains significance because these patients may benefit from ancillary treatment with pacemakers, which use algorithms to prevent bradycardias.
and pauses. Accordingly, we studied whether differences exist in pause dependence of TdP onset between LQT1, LQT2, and LQT3.

Methods

Patient Inclusion
We included all LQT1, LQT2, and LQT3 patients from research groups in the Netherlands (n=23), the International LQT Registry in the United States (n=12), Japan (n=9), and Germany (n=6) for whom ECGs of TdP onset were available that contained at least 3 RR intervals directly preceding TdP. Accordingly, we included 10 LQT1 patients from 10 families (7 whites, 3 Asians), 34 LQT2 patients from 30 families (26 whites, 8 Asians), and 6 LQT3 patients from 6 white families. ECGs were obtained from 12-lead ECGs (n=1/1005), telemetry (n=32, 64%), and stored intracardiac electrograms of implantable cardioverter-defibrillators (n=4, 8%). Patients were included only if TdP occurred in the absence of other potential causes, eg, drugs with TdP potential and metabolic imbalances.

ECG Analysis
TdP was defined as a polymorphic ventricular tachycardia of ≥3 beats with a QRS axis that revolved around the baseline (the latter was not required when only intracardiac electrograms of tachycardia were available). In 22 patients, multiple TdP episodes were available. For primary analysis, we studied only 1 episode per patient to avoid overrepresentation of patients for whom an excessive number of TdP episodes were available (in 1 LQT2 patient, 151 episodes during 1 admission were available); moreover, we elected to analyze only the first TdP episode to minimize the risk that any intervention instituted after the first TdP episode may have modified the mode of onset of subsequent TdP episodes. Being conscious of this latter possible confounder, we also analyzed subsequent TdP episodes in a secondary analysis to obtain an impression about the reproducibility of these findings. The mode of TdP onset was analyzed as shown in Figure 1. RR intervals were numbered with respect to the last supraventricular beat before TdP onset (designated 0). Thus, a short-long-short sequence15 initiating TdP involves intervals I(-2)-I(-1)-I(1). The last 3 consecutive RR intervals preceding TdP were measured, along with the TdP cycle length (from the first 3 TdP beats, ie, averaged from I,1, and I,3). In addition, we analyzed the rate of the preceding sinus rhythm. This analysis was thwarted by the facts that bigeminy often preceded TdP and that ECGs were not always recorded for sufficiently long periods surrounding TdP episodes. Thus, analysis of the rate of the sinus rhythm that preceded TdP was possible in only 32 of 50 patients (LQT1, 9; LQT2, 18; LQT3, 5). Sinus beats were analyzed if they occurred within 10 seconds before TdP onset. No generally accepted quantitative criteria to define TdP onset as pause dependent exist. Here, we considered TdP onset to be pause dependent when the duration of I,1 exceeded that of I,2 by ≥50% (arbitrary cutoff).

Statistical Analysis
Data are mean±SD. Group comparisons were made with the Fisher exact test (proportions) or the Mann-Whitney test (averages) when appropriate. Statistical significance was defined as P<0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics
Demographic variables were not significantly different between the LQTS groups (Tables 1 through 3). There was a marked preponderance of female patients (41 female, 9 male). The proportion of patients taking β-blockers (maximally tolerated doses) was similar among the LQTS groups: LQT1, 4 of 10 (40%); LQT2, 16 of 34 (47%); and LQT3, 1 of 6 (17%).

Pause Dependence of First TdP Episode
ECG analysis is summarized in Tables 1 through 3. When we analyzed the first TdP episode in each patient, we found that

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**Figure 1.** Method of ECG analysis. RR intervals I(-4) through I(3) are numbered with respect to last supraventricular beat (designated 0) before the TdP episode.

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**TABLE 1.** Demographic and ECG Variables in LQT1

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Mutation</th>
<th>β-Blocker</th>
<th>I₁₁₀₀ ms</th>
<th>I₂₁₀₀ ms</th>
<th>I₁₋₁₀₀ ms</th>
<th>I₁₋₀₀ ms</th>
<th>I₀₋₀₀ ms</th>
<th>I₁₋₀₀ ms</th>
<th>SR, ms</th>
<th>TdP, ms</th>
<th>Pause-Dependent First TdP</th>
<th>Pause-Dependent TdP, n</th>
<th>Non-Pause-Dependent TdP, n</th>
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<td>2</td>
<td>M</td>
<td>G269D</td>
<td>—</td>
<td>520</td>
<td>720</td>
<td>570</td>
<td>470</td>
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<td>300</td>
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<td>300</td>
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<td>0</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Del GGT (intron)</td>
<td>+</td>
<td>445</td>
<td>430</td>
<td>470</td>
<td>430</td>
<td>250</td>
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<td>450</td>
<td>230</td>
<td>...</td>
<td>0</td>
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</tr>
<tr>
<td>8</td>
<td>F</td>
<td>G269S</td>
<td>—</td>
<td>500</td>
<td>480</td>
<td>500</td>
<td>460</td>
<td>270</td>
<td>240</td>
<td>490</td>
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<td>...</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
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<td>A344V</td>
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<td>530</td>
<td>710</td>
<td>410</td>
<td>270</td>
<td>260</td>
<td>690</td>
<td>265</td>
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<td>12</td>
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<td>49</td>
<td>F</td>
<td>R259C</td>
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<td>770</td>
<td>580</td>
<td>740</td>
<td>600</td>
<td>400</td>
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<td>64</td>
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<td>810</td>
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<td>558</td>
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<td>473</td>
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<td>51</td>
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<td>52</td>
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</table>

SR indicates RR interval of sinus rhythm; NA, not available.
pause dependence of TdP onset was genotype dependent, being significantly more prevalent in LQT2 (23 of 34, 68%; Figure 2) than in LQT1 (0 of 10, 0%; Figure 3). Accordingly, analysis of average RR intervals revealed that the increase in cycle length between the I_{-3}, I_{-2}, and I_{-1} intervals was significantly larger in LQT2 than in LQT1 (479±364 versus 32±94 ms; $P<0.001$; Figure 6). TdP cycle length in LQT1 (276±52 ms) was significantly shorter than in LQT2 (353±59 ms; $P=0.001$), but sinus rhythm cycle length was not significantly different between groups (613±138 and 822±321 ms, respectively; $P=0.14$). In LQT3, the prevalence of pause dependence appeared to be intermediate (2 of 6, 33%), as were the duration of the I_{-1} intervals (859±279 ms) and the cycle length increase from I_{-2} to I_{-1} (153±290 ms; Figure 7). Because of the relatively small number of LQT3 patients, we did not conduct statistical comparisons between LQT3 and the 2 other LQT groups.
Influence of Gender and the Use of β-Blockers on First TdP Episode

Pause dependence was not sex dependent because it occurred in similar proportions in male patients (4 of 9, 44%) and female patients (20 of 41, 49%). The proportion of patients with pause-dependent TdP despite the use of β-blockers was lower in LQT1 (0 of 4, 0%) than in LQT2 (12 of 16, 75%; P=0.01). Nevertheless, the use of β-blockers did not modify whether pause dependence was present or absent because the proportion of pause dependence among LQT1 and LQT2 patients was similar among those who used β-blockers and those who did not, as follows: LQT1—pause dependence with β-blockers, 0 of 4 (0%), without β-blockers, 0 of 6 (0%); LQT2—pause dependence with β-blockers, 12 of 16 (75%), without β-blockers, 11 of 18 (61%).

Reproducibility of Pause Dependence

To study the reproducibility of pause dependence, we analyzed subsequent TdP episodes in the 22 patients with multiple TdP episodes. Results are summarized in Tables 1 through 3. Four LQT1 patients had multiple TdP episodes (range, 2 to 5); consistent with their first TdP episode, all subsequent TdP episodes were not pause dependent. In LQT2 patients, pause dependence was generally reproducible, as follows: All 17 LQT2 patients with multiple TdP episodes had pause-dependent TdP onset (2 to 91 episodes each). In 8 patients, all subsequent TdP episodes also were pause dependent. In 5 of the remaining 9 LQT2 patients with multiple episodes, subsequent TdP episodes were generally consistent with the first episode, being mostly pause dependent in 4 patients (3 to 151 episodes) and not pause dependent in 1 patient. However, in 4 LQT2 patients, subsequent TdP episodes were not generally consistent with the first. One LQT3 patient had 2 TdP episodes; both were not pause dependent.

Discussion

We found that pause dependence of TdP onset in congenital LQTS was genotype specific, being predominant in LQT2 but absent in LQT1. In contrast to previous studies,21 we did not find that the proportion of pause dependence was greater in female than male patients.

Proposed Arrhythmia Mechanisms and Therapy Implications

The disparity in pause dependence of TdP onset between LQT1 and LQT2 may point to different arrhythmia mechanisms. Clinical22 and experimental23 studies have provided evidence that pause-dependent TdP is triggered by

Table 3. Demographic and ECG Variables in LQT3

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Mutation</th>
<th>β-Blocker</th>
<th>l1-2, ms</th>
<th>l2-2, ms</th>
<th>l1-1, ms</th>
<th>l2-1, ms</th>
<th>l1-0, ms</th>
<th>l2-0, ms</th>
<th>SR, ms</th>
<th>TdP, ms</th>
<th>Pause-Dependent First TdP</th>
<th>Pause-Dependent TdP, n</th>
<th>Non-Pause Dependent TdP, n</th>
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<td>LQT3 Patients 1d F P1332L</td>
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<td>1010</td>
<td>1010</td>
<td>1010</td>
<td>875</td>
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<td>610</td>
<td>990</td>
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<tr>
<td>4y M R1623Q</td>
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<td>440</td>
<td>445</td>
<td>295</td>
<td>230</td>
<td>185</td>
<td>440</td>
<td>208</td>
<td>–</td>
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<td>1</td>
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<tr>
<td>17y F P701L</td>
<td>–</td>
<td>840</td>
<td>865</td>
<td>800</td>
<td>530</td>
<td>440</td>
<td>400</td>
<td>800</td>
<td>420</td>
<td>–</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>20y F I176V</td>
<td>–</td>
<td>960</td>
<td>760</td>
<td>760</td>
<td>600</td>
<td>340</td>
<td>260</td>
<td>830</td>
<td>300</td>
<td>–</td>
<td>0</td>
<td>2</td>
<td></td>
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<tr>
<td>57y F I1768V</td>
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<td>610</td>
<td>590</td>
<td>1180</td>
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<td>340</td>
<td>310</td>
<td>600</td>
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<td>76y F I1278N</td>
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<td>360</td>
<td>+</td>
<td>1</td>
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</table>

Mean 29y 795 707 859 548 363 314 732 339

SD 31y 233 166 279 139 79 83 214 81

SR indicates RR interval of sinus rhythm; NA, not available.

Figure 2. Typical example of TdP onset in an LQT2 patient (pause dependent).

Figure 3. Typical example of TdP onset in an LQT1 patient (not pause dependent).
early afterdepolarizations (EADs) carried by L-type Ca\(^{2+}\) channels. Numerical analysis has revealed that a pause (after a relatively fast heart rate) leads to enhanced Ca\(^{2+}\) release from intracellular Ca\(^{2+}\) stores.\(^{24}\) Subsequently, Ca\(^{2+}\)-dependent transmembrane currents (electrogenic Na\(^+\)/Ca\(^{2+}\) exchanger, \(I_{Na,Ca}\)) are altered in such a way as to allow L-type Ca\(^{2+}\) channels to recover more readily from inactivation and to reactivate before repolarization is complete, thus generating EADs. Of note, a critical duration of the pause is required for EADs to occur,\(^{24}\) comfortably supporting a beneficial role of pause-preventing pacemaker algorithms. At the same time, the absence of pause dependence in LQT1 suggests that EADs are not the predominant mechanism of TdP initiation here. Conversely, the relatively fast heart rate preceding TdP in LQT1 may be compatible with delayed afterdepolarizations (DADs) secondary to intracellular Ca\(^{2+}\) overload,\(^{25}\) although it does not fully exclude EADs.\(^{26}\) Accordingly, experimental studies have shown that \(I_{Na,Ca}\) blockade (LQT1) causes DADs but not EADs.\(^{27}\) Conversely, experimental \(I_{Na,Ca}\) blockade (LQT2) causes EADs, predominantly at slow heart rates.\(^{28}\) Either way, the proposed involvement of both DADs and pause-dependent EADs provides a rationale for the use of \(\beta\)-blockers in that these drugs counteract loading of intracellular Ca\(^{2+}\) stores by cAMP-dependent processes, notably Ca\(^{2+}\) influx through L-type Ca\(^{2+}\) channels.\(^{29}\) Ca\(^{2+}\) loading as a leitmotiv for TdP was further substantiated by experimental models of LQT2, which revealed the therapeutic efficacy of interventions to reduce intracellular Ca\(^{2+}\) loading through other pathways, eg, calmodulin-dependent pathways.\(^{30}\) Analysis of QT duration (as a measure of action potential duration) would have the potential of providing more mechanistic insights. Increased Ca\(^{2+}\) loading, occurring in parallel with QT prolongation, would facilitate DADs and DAD-dependent TdP. Unfortunately, we were unable to investigate a possible relationship between QT duration and pause dependence. In a large proportion of patients, analysis of QT duration was impossible because multiple ventricular premature beats preceded TdP onset and ECGs were not recorded for sufficiently long periods surrounding TdP episodes. Still, other mechanisms also may explain the therapeutic effects of...
By guest on May 2, 2017

β-blockers, in particular, β-adrenergic modulation of \( I_K \),\(^{31} \) and \( I_Kr \).\(^{32–35} \) Normally, β-adrenergic stimulation increases \( I_K \) and may mediate action potential shortening at fast heart rates. However, when physiological regulation of \( I_K \) by β-adrenergic signaling is disrupted, eg, by mutations in the \( I_K \) complex, action potential duration alternans at fast heart rates may occur, a phenomenon associated with susceptibility to reentrant tachyarrhythmias.\(^{31} \) β-Adrenergic regulation of \( I_Kr \) may be more complex (reviewed elsewhere\(^{12} \)). Some studies showed that acute\(^{33} \) and chronic\(^{34} \) β-adrenergic stimulation reduces \( I_Kr \). From these studies, β-adrenergic blockade would be expected to increase \( I_Kr \) and shorten action potential duration, which would explain its beneficial effects. However, other studies\(^{35} \) showed that β-adrenergic stimulation increases \( I_Kr \).

When these proposed electrophysiological mechanisms are considered for genotype-specific therapy, it is predicted that β-blockers alone have great efficacy in preventing non–pause-dependent TdP (LQT1), whereas β-blockers and pacemakers may work in a complementary fashion in pause-dependent TdP (LQT2). These predictions are supported by previous observations that β-blockers are less effective in preventing TdP in LQT2 than in LQT1.\(^{14} \) Thus, LQT2 patients not only are likely to respond the best to pacemaker therapy but also may require it the most. Still, it must be emphasized that β-blockers remain the cornerstone of congenital LQTS treatment (at least in LQT1 and LQT2) and that pacemaker therapy must be considered an ancillary treatment mode, particularly in LQT2.

Our findings also may provide further rationale for the management of acquired (drug-induced) LQTS. The predominant pause dependence of TdP onset in LQT2 found here corresponds with observations that drug-induced TdP in acquired LQTS is usually pause dependent\(^{20} \) because these drugs generally block \( I_Kr \).\(^{4} \) Accordingly, (temporary) pacing is also highly effective in acquired LQTS.

**Study Limitations**

We have defined pause dependence by a clear, yet arbitrary, \( \geq 50\% \) increase of \( I_{1.5} \), duration over \( I_{1.2} \), duration. Previous studies have used other arbitrary cutoff values, ie, any increment,\(^{15} \) a 20-ms increment,\(^{36} \) or a 40-ms increment\(^{21} \) over \( I_{1.2} \). To study whether the choice for any particular cutoff value may confound our primary analysis, we also analyzed the proportions of pause-dependent TdP onset in LQT1 and LQT2 when cutoff values other than 50% were used to define “pause dependence” (Figure 8). We found that the proportions of pause-dependent TdP onset remained significantly higher in LQT2 than in LQT1 when cutoff values of 0% \( (P=0.04) \), 20 ms \( (P=0.04) \), 40 ms \( (P=0.004) \), 10% \( (P=0.001) \), 25% \( (P=0.001) \), 75% \( (P=0.003) \), and 100% \( (P=0.007) \) were used. This analysis provided further support for our conclusion that pause-dependent TdP onset is far more common in LQT2 than in LQT1.

Although LQT1 and LQT2 are equally prevalent (each estimated to account for 40% to 45% of genotyped patients\(^{3} \)), we found that ECG documentation of TdP onset was far more prevalent in LQT2. The reasons are a matter of speculation. For instance, it may relate to the fact that TdP in LQT1 occurs mostly during exercise.\(^{8,9} \) Thus, TdP is less likely to recur and be documented during hospital admission. In contrast, TdP in LQT2 may be triggered by anxiety, which may continue during admission.\(^{37} \) Also, because β-blocker treatment is less effective in LQT2, TdP may still be readily observed during admission. Whatever the cause, the difficulty in obtaining ECG documentation of TdP onset in LQT1 may explain why the reported proportion of pause-dependent TdP onset in congenital LQTS is as high as 74% in some studies,\(^{21} \) although it should be only a little over 50%, given that TdP is rarely pause dependent in LQT1 and that LQT1 constitutes almost 50% of congenital LQTS. This discrepancy may be caused by underrepresentation of LQT1 patients because these patients are less easily included in such analyses. How the reported proportion of pause dependence could be confounded by overrepresentation or underrepresentation of LQT3 patients is unclear because it is unresolved whether TdP onset in LQT3 is pause dependent or not. Of note, the quantitative effect of possible confounding by LQT3 is likely to be small, given the low prevalence of LQT3 (8% among genotyped LQTS patients and 5% of all LQTS patients\(^{3} \)). In any case, these observations indicate that caution must be exercised when these studies and ours are interpreted because selection bias may result from the limited and disparate (between genotypes) availability of ECG documentation of TdP onset in congenital LQTS. Similarly, we cannot exclude that our findings apply mostly to severe LQTS patients who seek medical attention because of frequent TdP recurrences and that less severe cases may be underrepresented in this analysis.

**Conclusion**

Pause dependence of TdP onset is predominant in LQT2 but rare or absent in LQT1. This disparity may point to genotype-specific arrhythmia mechanisms and affect treatment strategies.
Acknowledgment
We thank Dr J.M. Ruijter for statistical advice.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

The onset of torsade de pointes ventricular tachycardia in long-QT syndrome (LQTS) is generally believed to be pause dependent, being initiated by a short-long-short sequence of preceding RR intervals. We studied whether this initiating sequence is present in the 3 most common types of inherited LQTS (LQT1, LQT2, and LQT3). This analysis may provide insight into the mechanism of and rationale for treatment strategies in the various forms of LQTS, in particular, the use of β-adrenergic blockers and the ancillary use of pacemakers programmed with pause-preventing algorithms. Fifty genotyped LQT1, LQT2, and LQT3 patients were studied. Pause dependence was predominant in LQT2 but absent in LQT1. In LQT1, torsade de pointes started without significant changes in the duration of the preceding RR intervals. These findings point to different arrhythmia mechanisms and may explain why β-adrenergic blockers as single treatment are more effective in LQT1 than in LQT2. Ancillary treatment with pause-preventing pacemakers may be required in LQT2.
Genotype-Specific Onset of Arrhythmias in Congenital Long-QT Syndrome: Possible Therapy Implications

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