The Common Long-QT Syndrome Mutation KCNQ1/A341V Causes Unusually Severe Clinical Manifestations in Patients With Different Ethnic Backgrounds

Toward a Mutation-Specific Risk Stratification

Lia Crotti, MD; Carla Spazzolini, DVM; Peter J. Schwartz, MD; Wataru Shimizu, MD; Isabelle Denjoy, MD; Eric Schulze-Bahr, MD; Elena V. Zaklyazminskaya, MD, PhD; Heikki Swan, MD; Michael J. Ackerman, MD, PhD; Arthur J. Moss, MD; Arthur A.M. Wilde, MD; Minoru Horie, MD; Paul A. Brink, MD, PhD; Roberto Insolia, PhD; Gaetano M. De Ferrari, MD; Gabriele Crimi, MD

**Background**—The impressive clinical heterogeneity of the long-QT syndrome (LQTS) remains partially unexplained. In a South African (SA) founder population, we identified a common LQTS type 1 (LQT1)—causing mutation (KCNQ1-A341V) associated with high clinical severity. We tested whether the arrhythmic risk was caused directly by A341V or by its presence in the specific ethnic setting of the SA families.

**Methods and Results**—Seventy-eight patients, all with a single KCNQ1-A341V mutation, from 21 families and 8 countries were compared with 166 SA patients with A341V and with 205 non-A341V LQT1 patients. In the 2 A341V populations (SA and non-SA), the probability of a first event through 40 years of age was similar (76% and 82%), and the QTc was 484±42 versus 485±45 ms (P=NS). Compared with the 205 non-A341V patients with the same median follow-up (30 versus 32 years), the 244 A341V patients were more likely to have cardiac events (75% versus 24%), were younger at first event (6 versus 11 years), and had a longer QTc (485±43 versus 465±38 ms) (all P<0.001). Arrhythmic risk remained higher (P<0.0001) even when the A341V patients were compared with non-A341V patients with mutations either localized to transmembrane domains or exhibiting a dominant-negative effect. A341V patients had more events despite β-blocker therapy.

**Conclusions**—The hot spot KCNQ1-A341V predicts high clinical severity independently of the ethnic origin of the families. This higher risk of cardiac events also persists when compared with LQT1 patients with either transmembrane or dominant-negative mutations. The identification of this high-risk mutation and possibly others may improve the risk stratification and management of LQTS. (Circulation. 2007;116:2366-2375.)

Key Words: arrhythmia ■ death, sudden ■ genetics ■ long-QT syndrome ■ risk factors

Heterogeneity of clinical manifestations is a well-known feature among patients affected by the long-QT syndrome (LQTS). The extent of this phenomenon became evident with the first large survey of LQTS as indicated by the presence within the same families of symptomatic and asymptomatic affected family members.1 It was, however, only in the molecular era that scientific attempts were initiated to explain this puzzling clinical observation that also carries implications for patient management.

**Clinical Perspective p 2375**

The identification of the 3 main genes for LQTS prompted, within a few years, a series of relevant observations. On the basis of a relatively small number of genotyped patients, it

© 2007 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.107.726950
was first suggested that LQTS type 3 (LQT3) was associated with less frequent but more lethal events.\(^5\) Subsequently, in a larger number of genotyped families, it was shown that patients with either LQT2 or LQT3 were more likely to develop cardiac symptoms, but largely because of the higher incidence of LQT1 patients having a normal resting QTc (ie, <440 ms).\(^3\) The shift of focus from the genes to the actual position of the various mutations within a given gene was the consequence of a study by Moss et al\(^4\) that called attention to the fact that LQT2 patients with mutations in the pore region had a higher risk for cardiac events. However, the possibility that a discrete mutation could be associated with significantly higher risk for life-threatening cardiac events has so far remained unexplored or unproven, in part because the vast majority of LQTS-causing mutations are private, family-specific mutations. In LQTS, relatively few so-called mutational hot spots exist.

In 2005, we reported an LQT1-causing mutation, **KCNQ1-A341V**, in a South African (SA) founder population that was associated with unusual clinical severity.\(^5\) Originated from a Dutchman who traveled to South Africa in 1670, this founder mutation comprises 22 **KCNQ1-A341V** genotype-positive SA families.\(^5\) Although we assumed that this unexpected clinical phenotype was caused directly by this particular missense mutation, we could not exclude the possibility that the clinical severity was mediated not by the **KCNQ1-A341V** mutation per se but by some other probably genetic or epigenetic factors present in these families all living in South Africa for >300 years.

To answer this question and to determine whether the high arrhythmic risk observed in the SA families was indeed due solely to the **KCNQ1-A341V** mutation, one of relatively few “hot spot” missense mutations, we performed the present study on non-SA patients with LQT1 secondary to A341V.

## Methods

### Study Population

The study population was obtained through an international collaborative project involving 10 centers from 8 countries worldwide (Finland, France, Germany, Italy, Japan, the Netherlands, Russia, and the United States). Genetic and clinical data, collected on prespecified forms, included genotype status, demographic information, personal and family history of disease, type and timing of symptoms, ECG measurements, treatment, and response to therapy.

Data were recorded for a total of 84 patients from 24 unrelated, non-SA families harboring the **KCNQ1-A341V** mutation. Among them, 6 individuals from 3 families were compound heterozygotes (A341V plus an additional mutation on LQTS-related genes) and were excluded from analysis because individuals with 2 independent mutations are more likely to be symptomatic.\(^6,7\) A341V genotype-positive patients were classified as either symptomatic or asymptomatic on the basis of a previous experience of cardiac events (syncope, cardiac arrest [CA], sudden cardiac death [SCD]) as defined previously.\(^5\) SCDs that occurred through 40 years of age in first-degree relatives and were judged to be LQTS-related according to an established policy\(^8\) were assumed to have occurred in A341V mutation carriers and consequently were included, even in the absence of direct genotyping and/or ECG documentation.

### Clinical Severity

The main objective of the study was to evaluate the clinical severity of LQTS among A341V genotype-positive patients with a heterogeneous ethnic background (non-SA-A341V) and to compare it with that of the SA founder population (SA-A341V) previously reported.\(^9\) In addition, we compared the clinical course of all A341V patients with that of an LQT1 population derived from the LQTS database maintained at our institution in Pavia, Italy. As markers of clinical severity, we considered the proportion of symptomatic mutation carriers, the incidence of life-threatening arrhythmias, age at first cardiac event, QTc interval duration, and event-free survival by Kaplan-Meier cumulative estimates. The cumulative probability of a first event was considered, both for any event and for CA/SCD, before the institution of \(\beta\)-blocker therapy and through 40 years of age.

Furthermore, we took into account the disparity in the extent of genetic testing and clinical evaluation among the family members of the 2 A341V populations under study (non-SA and SA) because the SA pedigrees underwent extensive genetic testing. The inclusion of small nuclear families could have biased the results toward an overestimate of the clinical severity, so we also performed 3 different sensitivity analyses according to a priori established exclusion criteria to limit this potential selection bias. Specifically, all the analyses were repeated by (1) limiting the study population to 54 non-SA mutation carriers from 9 unrelated families and to 146 SA mutation carriers from 14 families with at least 4 affected individuals each; (2) excluding all probands, regardless of the number of affected individuals per family; and (3) combining these 2 criteria.

On the basis of recent findings that both transmembrane mutations\(^9\) and dominant-negative functional mutations in **KCNQ1**\(^8\) were associated with increased disease severity, we also considered the possible effect of the mutation site (transmembrane-spanning or pore-forming domains versus C- and N-terminal domains) and the possibility that the clinical severity of A341V might be a consequence of its dominant-negative nature. Therefore, we compared all A341V genotype–positive patients with the LQT1 population stratified for mutation site and the LQT1 patients with dominant-negative mutations.

### Therapy

Data were collected on the administration and effectiveness of the treatment modalities applied to these LQTS patients: \(\beta\)-blockers, left cardiac sympathetic denervation, pacemaker, and implantable cardioverter-defibrillator. The assessment of the effectiveness of \(\beta\)-blockers was limited to those subjects with precise information on therapy and outcome and with at least 1 year of follow-up after initiation of treatment. To avoid the confounding role of possible comorbidities, we excluded from analysis those patients who started \(\beta\)-blocker therapy after 40 years of age. With the only exception of long-standing withdrawals (defined as a withdrawal of \(\beta\)-blocker therapy >1 week) or refusal of the prescribed \(\beta\)-blocker by the patient, all the events occurring during sporadic omission of the treatment were counted.

### Statistical Analysis

The clinical characteristics of the genotyped groups were compared by Student \(t\) test or the Mann-Whitney \(U\) test as appropriate for continuous variables, which were expressed as mean and SD or as median and interquartile range (IQR). Categorical variables were presented as absolute and relative frequencies and compared by \(\chi^2\) test with Yates continuity correction. Event-free survival was described by Kaplan-Meier cumulative estimates, with comparisons performed by the log-rank test. Time from birth to first event through 40 years of age was considered both for any event and for CA/SCD. Survival analyses also were performed by gender. To represent the natural history of the disease and to avoid the confounding role of \(\beta\)-blockers, observations were censored at initiation of \(\beta\)-blocker therapy in survival analyses. Multivariate Cox proportional-hazards model was used to evaluate the significant and independent contribution of clinical and genetic factors to the risk of a first cardiac event. SPSS version 13 (SPSS Inc, Chicago, Ill) was used for computation. Values of \(P<0.05\) (2 sided) were considered statistically significant.
We report data on 78 Clinical Severity manuscript as written.

Table 1. Clinical Characteristics of the Study Population and Comparison Between the 2 A341V Groups

<table>
<thead>
<tr>
<th></th>
<th>Non-SA-A341V Population</th>
<th>SA-A341V Population</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype-positive patients, n</td>
<td>78</td>
<td>166</td>
<td>...</td>
</tr>
<tr>
<td>Families, n</td>
<td>21</td>
<td>22</td>
<td>...</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>43 (55)</td>
<td>89 (54)</td>
<td>0.9</td>
</tr>
<tr>
<td>Symptomatic (any first event before 40 y of age), n (%)</td>
<td>53 (68)</td>
<td>131 (79)</td>
<td>0.09</td>
</tr>
<tr>
<td>Median age at onset, y (IQR)</td>
<td>6 (5–9)</td>
<td>6 (4–10)</td>
<td>0.82</td>
</tr>
<tr>
<td>CA/SCD, n (%)</td>
<td>19 (24)</td>
<td>55 (33)</td>
<td>0.21</td>
</tr>
<tr>
<td>SCD, n (%)</td>
<td>10 (13)</td>
<td>24 (14)</td>
<td>0.88</td>
</tr>
<tr>
<td>Asymptomatic, n (%)</td>
<td>25 (32)</td>
<td>35 (21)</td>
<td>...</td>
</tr>
<tr>
<td>≥15 y of age, n (%)</td>
<td>13 (17)</td>
<td>9 (5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ECG off β-blocker therapy, n</td>
<td>63</td>
<td>90</td>
<td>...</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>484±42</td>
<td>485±45</td>
<td>0.89</td>
</tr>
<tr>
<td>≥440 ms, n (%)</td>
<td>5 (8)</td>
<td>11 (12)</td>
<td>0.56</td>
</tr>
<tr>
<td>≥500 ms, n (%)</td>
<td>15 (24)</td>
<td>30 (33)</td>
<td>0.27</td>
</tr>
<tr>
<td>Median follow-up, y (IQR)</td>
<td>21.5 (11–40)</td>
<td>33 (17–56)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Clinical Severity

We report data on 78 KCNQ1-A341V genotype-positive patients originating from 21 worldwide families with a mean of 3.7±2.8 affected subjects per family.

Table 1 displays the clinical characteristics of this population. A slight but nonsignificant female gender predominance (55%) was present. During a median observation time of 21.5 years (IQR, 11 to 40 years) from birth to last contact, 53 patients (68%) became symptomatic before 40 years of age. Among these, 35 (45%) had syncope only, 9 (11.5%) had CA, and 10 (13%) suffered SCD. All the SCDs occurred while patients were off therapy; 7 occurred before 20 years of age. Exercise was the triggering factor for all (4 of 4) the episodes of witnessed SCD with available information on the circumstances associated with the terminal event. Overall, 19 patients (24%) suffered fatal or near-fatal events. Only 25 A341V patients (32%) were asymptomatic during the first 4 decades. Importantly, approximately half of these individuals are still ≤15 years of age and thus are too young to be considered truly asymptomatic with certainty because they are still at risk of a first cardiac event.

Table 1 also compares the occurrence of symptoms during follow-up from birth between the non-SA A341V patients and the SA-A341V population. The proportion of patients who experienced at least 1 cardiac event was not significantly different (68% in the non-SA population versus 79% in the SA population, P=0.09). However, the mean age at last contact was significantly different, with the non-SA population being younger (median, 21.5 years [IQR, 11 to 40 years] versus 33.5 years [IQR, 17 to 56 years]; P=0.001); furthermore, a higher number of asymptomatic subjects ≤15 years of age were in the non-SA population compared with the SA group (13 [17%] versus 9 [5%]; P<0.01). For this reason, the clinical status between the 2 groups also was compared following the exclusion of all A341V patients ≤15 years of age. The proportions of patients very likely to remain asymptomatic during comparable lengths of their clinical course remained small and very similar between the 2 A341V groups (25% and 19%, respectively, for non-SA versus SA group; P=0.5).

The median age at first event through 40 years of age was the same (6 years [IQR, 5 to 9 years] and 6 years [IQR, 4 to 10]; P=0.82), as was the incidence of LQTS-related fatal or near-fatal events (24% and 33%, respectively; P=0.21).

An ECG recorded in the absence of β-blocker therapy was available in 63 (81%) of the 78 non-SA A341V patients and in 90 (54%) of the 166 SA-A341V. Basal QTc was almost identical between the 2 groups (484±45 versus 485±45 ms, respectively; P=0.89). The QTc was ≤440 ms for 8% and 12% (P=0.56) of the 2 populations, respectively, whereas 24% and 33% had a QTc ≥500 ms (P=0.27).

Kaplan-Meier curves describing the cumulative survival to any first cardiac event (syncope, CA, SCD) before the institution of β-blocker therapy and through 40 years of age are shown for the entire non-SA population compared with the SA cohort in Figure 1. The median survival time (ie, the time by which at least 50% of the population has already had a first cardiac event) was 8 and 9 years, respectively (all together, 8 years; 95% confidence interval, 6.9 to 9.1). By 5 years of age, the cumulative event-free survival was 76% and 70%, respectively; by 10 years of age, it dropped to 38% and 35%. By the end of the observation period, no significant difference in survival was observed (24% versus 18%, P=0.25). However, because a slight trend toward a lower probability of a first cardiac event after 10 years of age was observed in the non-SA population, we also focused on those patients who had no cardiac events until 10 years of age and who were followed up through 40 years of age. Once again, no significant difference existed in event-free survival be-
between the 2 populations (data not shown; \textit{P}=0.11). Notably, by 20 years of age, regardless of ethnic subgrouping, all A341V patients destined to become symptomatic had already experienced a first cardiac event, with very few events occurring after 20 years of age. No significant difference was observed between male and female patients among both the non-SA (\textit{P}=0.61) and the SA A341V carriers (\textit{P}=0.19).

When the end point for the comparison of the cumulative survival was limited to CA/SCD (Figure 2), Kaplan-Meier curves described an almost identical pattern between the 2 A341V populations. By 40 years of age, the cumulative probability for combined fatal/near-fatal events was 35% and 31%, respectively (\textit{P}=0.93). The 3 sensitivity analyses confirmed the results reported above, and no significant differences were observed between the SA and non-SA populations.

Comparison Between A341V and Non-A341V LQT1 Populations

Because the SA and non-SA populations showed no significant difference in any of the markers of severity analyzed, all patients genotype positive for A341V were combined to compare the clinical expression of this specific mutation with that of a genetically heterogeneous non-A341V LQT1 group derived from our own LQTS database in Pavia (Table 2). The LQT1 A341V population (\textit{n}=244) had a significantly greater percentage of symptomatic patients, earlier age at first cardiac event, higher incidence of life-threatening arrhythmias, more prolonged mean QTc, lower frequency of silent mutation carriers, and twice the proportion of subjects with a QTc \textgreater;500 ms compared with the non-A341V LQT1 group (\textit{n}=205).

When the combined A341V population was plotted against the LQT1 non-A341V group, a significant difference in the cumulative event-free survival emerged in that by 40 years of age, 80% of the A341V population (SA and non-SA) but only 30% of the LQT1 non-A341V group had already experienced a first cardiac (\textit{P}<0.0001; Figure 3). A multivariate Cox model adjusted for gender and QTc showed that A341V patients were at higher risk of a first cardiac event compared with the LQT1 non-A341V group, with a hazard ratio of 4.
QTc was a significant and independent (\(P=0.004\)) predictor of cardiac events with a 6% increase in risk for each 10-ms increase in QTc. This pattern was confirmed when the comparison with the LQT1 population was performed according to the specific intragenic site of mutations and their functional effect. 

\(KCNQ1\)-A341V was associated with a much higher probability of experiencing a first cardiac event compared with the group comprising all other LQT1 non-A341V mutations, regardless of their being located in the transmembrane domain or in the C- and N-terminal regions of the protein (\(P<0.0001\); Figure 4).

We then compared our 2 A341V populations with the non-A341V group comprising only mutations with a dominant-negative effect functionally demonstrated (Figure 5). Even in this case, patients with the dominant-negative A341V mutation had a significantly higher probability of becoming symptomatic than patients with other dominant-negative LQT1-causing mutations (\(P<0.0001\)). We also wanted to compare the A341V mutation with another dominant-negative mutation (\(KCNQ1\)-G314S) producing a significantly greater (\(P<0.05\)) loss in repolarizing current (\(=55\%\) versus 70%) and found that the probability of experiencing a first cardiac event was still significantly higher for A341V (\(P=0.03\); Figure 6).

### 1) β-Blocker Therapy

For 67 of the 78 non-SA A341V patients (86%), adequate information on therapy and outcome was available. Of them, 34 (51%) received \(\beta\)-blocker therapy and fulfilled the pre-specified criteria for the evaluation of the response to treatment. Their median age at initiation of therapy was 7.5 years (IQR, 6 to 27 years).

During a median observation time on \(\beta\)-blocker therapy of 7.5 years (IQR, 5 to 11 years), 14 A341V genotype–positive patients (41%) suffered at least 1 cardiac event, including 3 CAs but no SCD. Six patients also received an implantable cardioverter-defibrillator, and 1 of them received appropriate shocks. Thus, life-threatening events on \(\beta\)-blocker therapy occurred in 4 of 34 LQT1 patients with A341V (12%).

When the same inclusion criteria for analysis were applied to the SA group, it was observed that 70 of 150 patients (47%) were on \(\beta\)-blocker therapy, with a median age at initiation of therapy of 10 years (IQR, 4 to 18 years). During a median follow-up on \(\beta\)-blocker therapy of 12.5 years (IQR, 6.5 to 22.5 years), 34 of 70 carriers (49%) suffered at least 1

### Table 2. Clinical Characteristics of the Entire A341V Population and Comparison With a LQT1 Non-A341V Group

<table>
<thead>
<tr>
<th>Genotype-positive patients, n</th>
<th>244</th>
<th>205</th>
<th>(\ldots)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>132 (54)</td>
<td>122 (59.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Symptomatic (any first event before 40 y of age), n (%)</td>
<td>184 (75)</td>
<td>49 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median age at onset, y (IQR)</td>
<td>6 (5–10)</td>
<td>11 (4–17)</td>
<td>0.001</td>
</tr>
<tr>
<td>CA/SCD, n (%)</td>
<td>74 (30)</td>
<td>14 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECG, n (%)</td>
<td>153 (63)</td>
<td>190 (93)</td>
<td>(\ldots)</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>485±43</td>
<td>465±38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\leq 440) ms, n (%)</td>
<td>16 (10.5)</td>
<td>45 (24)</td>
<td>0.002</td>
</tr>
<tr>
<td>(\leq 500) ms, n (%)</td>
<td>45 (29)</td>
<td>26 (14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median follow-up, y (IQR)</td>
<td>30 (15–51)</td>
<td>32 (14–46)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*2370 Circulation November 20, 2007*
cardiac event, including 15 CAs and 5 SCDs, for a total of 20 life-threatening events on therapy (29%).

Among the 104 patients with A341V who were on β-blocker therapy, 19 (18%) life-threatening events occurred (18 CA and 1 implantable cardioverter-defibrillator shock) and 5 SCDs (5%). In comparison, among the 76 non-A341V assessable patients, a 7% incidence was shown of any cardiac event while on β-blockers; of note, no CAs and only 1 SCD (1%) occurred.

Discussion

We previously reported that KCNQ1-A341V, a mutation with a mild dominant-negative effect, was associated with an unusually severe clinical phenotype in an SA founder population. To determine whether this clinical severity was specific to the SA families or was related directly to the A341V mutation per se, we have collected data on A341V mutation carriers from 21 unrelated families originating from different parts of the world and having a different ethnic background.

We assume that the A341V mutation arose independently in different and unrelated families for 2 main reasons. First, this mutation was found in families living for centuries in very different parts of the world. Second, this mutation occurs in the context of a CpG dinucleotide, a known molecular hot spot for transition mutations.

The major findings of the present study are that (1) the hot spot A341V on the KCNQ1 gene is indeed associated with an unusual clinical severity independently of the origin of the families, (2) patients with this mutation are at higher risk for cardiac events compared with a more general LQT1 population, and (3) this clinical phenotype is not fully explained by the biophysical properties of the mutation. This evidence should now be taken into account in the risk stratification.

![Figure 4](image-url) Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) in the entire A341V and in the LQT1 non-A341V groups according to specific mutation site. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy. Numbers at risk are indicated.

![Figure 5](image-url) Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) only in patients with LQT1 secondary to dominant-negative KCNQ1 mutations; the 2 A341V groups are plotted vs the LQT1 non-A341V group. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy. Numbers at risk are indicated.
process. We also unexpectedly found that recurrences of cardiac events despite β-blocker therapy were more frequent among KCNQ1-A341V patients than among LQT1 patients without this specific mutation. Accordingly, we recommend careful follow-up and management of the A341V patients.

**Mutation Site, Functional Effects, and Clinical Severity**

Risk stratification for LQTS is important for the therapeutic decision-making process, especially when dealing with young asymptomatic patients, but despite significant progress compared with 20 to 30 years ago,1,16 it is still in a developmental phase. In 2003, a risk stratification approach was proposed3 that was based on gender, genotype, and degree of QT prolongation. However, this approach could not take into account the by-then only initial evidence that within the same genetic subgroup, important differences in the phenotypic manifestations of the disease may reflect the specific site of the mutations.

The first reports in this area came in 1997 by Donger et al17 and in 2001 by Pippet et al18 who called attention to the fact that the KCNQ1-R555C and KCNQ1-G589D mutations, respectively, both located in the C-terminal region, were associated with a somewhat less severe clinical phenotype. In 2002, Moss et al4 in a relatively large collaborative study, indicated that LQT2 patients with a mutation in the pore region of KCNH2 were at higher risk for cardiac events compared with patients with a mutation on the same gene but in different regions of the protein. This was followed in 2003 and 2004 by 2 studies9,19 on the clinical impact of mutation site in LQT1 patients that reached opposite conclusions, thus complicating the attainment of a uniform interpretation.

Zareba et al19 reported on 294 LQT1 patients from the International LQTS Registry who had been classified into 3 groups according to their mutation site (pre-pore, pore, post-pore) and found no significant differences in clinical presentation, ECG parameters, and cardiac events. Relevant here is the fact that in this cohort, KCNQ1-A341V, considered a pore mutation, represented only 6% (6 of 101 cases) of the entire “pore-region” population.

Shimizu et al9 reported on 95 LQT1 Japanese patients from 37 different families who were classified according to the mutations being part of the transmembrane or of the C-terminal regions. Their main finding was a statistically significant greater risk of cardiac events for patients with mutations in the transmembrane region. Relevant here is the fact that in this investigation, at variance with the Zareba et al study, KCNQ1-A341V represented an impressive 29% (19 of 66 cases) of the entire “transmembrane” population.

We believe that an important contributing factor to the apparently very different results reported by Zareba et al and Shimizu et al lies in the large and significantly different representation of KCNQ1-A341V in their 2 reports (6% versus 29%; P<0.001). The striking clinical severity of this mutation, demonstrated in the present study, is probably sufficient to explain the more severe clinical picture associated with the Shimizu et al transmembrane mutations that included KCNQ1-A341V. Indeed, when following the same classification used by Shimizu et al, we divided our non-A341V LQT1 population according to the mutation site (transmembrane domain versus N and C terminal) and still observed a large difference between both these LQT1 genetic subgroups and the entire A341V population (P<0.0001).

Very recently, Moss et al8 demonstrated in 600 LQT1 patients that both the transmembrane location of the mutations and their dominant-negative effect are independent risk factors for cardiac events. Accordingly, we took into consideration the biophysical properties of KCNQ1-A341V to verify whether they could explain our findings.

Initially, A341V had been regarded as a simple loss-of-function mutation without dominant-negative effect.21,22 Later, Brink et al5 demonstrated that this mutation was associated with a mild dominant-negative effect with a loss in
Correlation.

Information necessary to make a complete genotype-phenotype assessments of the electrophysiological effects of LQTS-association (dominant-negative effect) fully explains the unusually (transmembrane) nor the functional consequence of the mutation. Indeed, in the A341V patients, neither the location of the mutation, G314S, that produced a loss of current of ≈70%,5 the pattern indicating a higher risk among patients with A341V was again documented.

Because our own non-A341V population appeared to be somewhat less symptomatic than other LQTS populations previously reported, for the sake of safety, we also made a comparison with the largest non-A341V population available to us, namely the 573 patients who were part of the recent study by Moss et al.8 Figure 7 shows Kaplan-Meier curves for these 573 patients, for the 19 A341V patients from the same study, and for our own 233 A341V patients. Two important points become apparent. The first is that the probability of arrhythmic symptoms is twice as large (80% versus 40%; P < 0.0001) among the A341V compared with the non-A341V patients. The second is the very impressive and practically identical Kaplan-Meier curves of the 19 A341V patients studied by Moss et al8 and of the 233 A341V patients from our study.

These data conclusively demonstrate the striking clinical severity associated with the A341V mutation and, at variance with a major recent publication,8 prove that cellular electrophysiological studies cannot always predict the clinical phenotype. Indeed, in the A341V patients, neither the location (transmembrane) nor the functional consequence of the mutation (dominant-negative effect) fully explains the unusually high clinical severity. We surmise that the current biophysical assessments of the electrophysiological effects of LQTS-causing mutations do not provide the whole gamut of information necessary to make a complete genotype-phenotype correlation.

Response to β-Blocker Therapy

In agreement with the evidence that among LQT1 patients, most cardiac events occur under conditions of increased sympathetic activity,12 treatment with β-blockers is extremely effective in these LQTS patients who represent the largest genetic subtype.11–15 Indeed, in LQT1 study populations with a percentage of symptomatic patients between 50% and 70%, the combined incidence of CA and SCD during rather long follow-up periods is only 1%.13,15

We were therefore surprised by observing what appears to be a rather incomplete protection for patients with A341V. A degree of caution is necessary in the interpretation of these data for which we do not have a ready explanation. It seems appropriate, however, to assess these patients very carefully with frequent follow-up visits to ensure that β-blockers are administered at full dose and to stress the importance of compliance. In addition, with QTc duration factored in as a known risk factor, the responsible physicians should be ready to consider the additional preventive steps represented by left cardiac sympathetic denervation23 and by implantable cardioverter-defibrillators.

A341V Patients

The present data on a uniquely large population of patients carrying the same genetic defect (KCNJ1-A341V) demonstrate that within LQTS patients, mutation-specific behaviors exist independently of different genetic backgrounds and ethnicities. When we compared the clinical severity present in the SA and in the non-SA A341V population, we found that it was very similar. The sensitivity analyses, performed by excluding the probands and by including only those families with at least 4 affected individuals, confirmed these findings. Therefore, all A341V genotype-positive patients (n = 244) were compared with a genetically heterogeneous LQT1 non-A341V population (n = 205) and were shown to be more likely to have longer QT intervals, to suffer more arrhythmic events, and to be somewhat less protected by β-blockers from life-threatening events. Clearly, they represent a group at much higher risk compared with other LQT1 patients.

Study Limitations

The study had 2 potential limitations that we tried to obviate. In general, the SA families are larger than the non-SA families. For this reason, we performed sensitivity analyses that confirmed the validity of the data. The study of the SA...
families goes back many more years and includes periods when the data collection cannot be accurately verified. Accordingly, we have excluded from the analysis of β-blocker therapy those older patients for whom precise information on dosage, compliance, and severity of the cardiac events could not be obtained with sufficient reliability.

Conclusions
The present study provides the largest data set on patients affected by LQTS who carry the exact same mutation. The data unequivocally show that KCNQ1-A341V is a mutation associated with unusual clinical severity. This finding, together with the recent evidence that genetically mediated neural control of heart rate may modulate arrhythmic risk in LQT1 patients, begins to unravel the old and puzzling neural control of heart rate may modulate arrhythmic risk in patients with this mutation from different parts of the world and to confirm the initial observation. The severity of other specific mutations has probably escaped notice so far because they are less common and therefore their clinical impact has been lost within the large series of patients with frequent mild mutations. The clinical message from our study is that in the future attention should be paid to families with a high percentage of symptomatic individuals and that, once the disease-causing mutations have been identified, collaborative studies similar to ours should be undertaken to test the possibility of identifying other clinically severe mutations. This will contribute to the development of a more accurate risk stratification grid for patients affected by LQTS.

Acknowledgments
We are grateful to Alessandro Vicentini, MD, Jennifer Robinson, MS, Maria Shkolnikova, MD, Svetlana N. Chuprova, MD, and Amiran S. Revishvili, MD, for contributing to data collection; to Matteo Pedrazzini, BSc, for contributing to molecular screening; to Alfred L. George, Jr, MD, for constructive criticism; and to Pinuccia De Tomasi, BS, for expert editorial support.

Sources of Funding
This work was supported by National Institutes of Health grants HL68880, HL33843, and HL51618; by the Italian Ministry of Foreign Affairs grant Basi genetiche della morte cardiaca improvvisa: identificazione dei geni modificatori della severità clinica della sindrome del QT lungo; by Leducq Foundation Alliance Against Sudden Cardiac Death grant; and by SBF 656-C1, DFG Schu1082/3-1 and 3-1 grants.

Disclosure
Dr Ackerman is a consultant for PGxHealth with respect to their FAMILION genetic test for cardiac channel mutations. The other authors report no conflicts.

References
The impressive clinical heterogeneity characteristic of the long-QT syndrome (LQTS) remains puzzling and hinders accurate risk stratification and targeted management. In a South African founder population, we identified a common LQTS type 1 (LQT1)–causing mutation (KCNQ1-A341V) associated with high clinical severity. We have now tested whether the arrhythmic risk was caused directly by A341V or by its presence in the specific ethnic setting of the South African families. We compared 78 patients from 10 countries, all with a single KCNQ1-A341V mutation, with 166 South African patients with A341V and 2 different populations of non-A341V LQT1 patients. In the 2 A341V populations, the probability of a first event before 40 years of age was similar (76% and 82%), and the QTc was similar. Compared with the LQT1 non-A341V patients, the A341V subjects were significantly more likely to have cardiac events, to be younger at first event, and to have a longer QTc. Arrhythmic risk remained higher even when the A341V group was compared with 573 LQT1 non-A341V patients. Thus, the hot spot KCNQ1-A341V predicts high clinical severity independently of the ethnic origin of the families. Neither the location (transmembrane) nor the functional consequence of the mutation (dominant-negative effect) fully explains the clinical phenotype. The identification of this high-risk mutation and possibly others may improve risk stratification and management of LQTS.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
The Common Long-QT Syndrome Mutation KCNQ1/A341V Causes Unusually Severe Clinical Manifestations in Patients With Different Ethnic Backgrounds: Toward a Mutation-Specific Risk Stratification

Lia Crotti, Carla Spazzolini, Peter J. Schwartz, Wataru Shimizu, Isabelle Denjoy, Eric Schulze-Bahr, Elena V. Zaklyazminskaya, Heikki Swan, Michael J. Ackerman, Arthur J. Moss, Arthur A.M. Wilde, Minoru Horie, Paul A. Brink, Roberto Insolia, Gaetano M. De Ferrari and Gabriele Crimi

_Circulation_. 2007;116:2366-2375; originally published online November 5, 2007; doi: 10.1161/CIRCULATIONAHA.107.726950

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2007 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/content/116/21/2366

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:

http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:

http://circ.ahajournals.org/subscriptions/