

INFLUENCE OF THE GENOTYPE ON THE CLINICAL COURSE OF THE LONG-QT SYNDROME

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ABSTRACT

Background The congenital long-QT syndrome, caused by mutations in cardiac potassium-channel genes (*KVLQT1* at the LQT1 locus and *HERG* at the LQT2 locus) and the sodium-channel gene (*SCN5A* at the LQT3 locus), has distinct repolarization patterns on electrocardiography, but it is not known whether the genotype influences the clinical course of the disease.

Methods We determined the genotypes of 541 of 1378 members of 38 families enrolled in the International Long-QT Syndrome Registry: 112 had mutations at the LQT1 locus, 72 had mutations at the LQT2 locus, and 62 had mutations at the LQT3 locus. We determined the cumulative probability and lethality of cardiac events (syncope, aborted cardiac arrest, or sudden death) occurring from birth through the age of 40 years according to genotype in the 246 gene carriers and in all 1378 members of the families studied.

Results The frequency of cardiac events was higher among subjects with mutations at the LQT1 locus (63 percent) or the LQT2 locus (46 percent) than among subjects with mutations at the LQT3 locus (18 percent) ($P < 0.001$ for the comparison of all three groups). In a multivariate Cox analysis, the genotype and the QT interval corrected for heart rate were significant independent predictors of a first cardiac event. The cumulative mortality through the age of 40 among members of the three groups of families studied was similar; however, the likelihood of dying during a cardiac event was significantly higher ($P < 0.001$) among families with mutations at the LQT3 locus (20 percent) than among those with mutations at the LQT1 locus (4 percent) or the LQT2 locus (4 percent).

Conclusions The genotype of the long-QT syndrome influences the clinical course. The risk of cardiac events is significantly higher among subjects with mutations at the LQT1 or LQT2 locus than among those with mutations at the LQT3 locus. Although cumulative mortality is similar regardless of the genotype, the percentage of cardiac events that are lethal is significantly higher in families with mutations at the LQT3 locus. (N Engl J Med 1998;339:960-5.)

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THE hereditary long-QT syndrome is a familial disorder characterized by prolonged ventricular repolarization on the electrocardiogram and a propensity for syncope, polymorphic ventricular tachycardia (torsade de pointes), and sudden death.¹⁻⁶ Four specific mutations in cardiac ion-channel genes (*KVLQT1*, *HERG*, *SCN5A*, and *KCNE1*) have been identified.⁷⁻¹¹ The mutant *KVLQT1* gene at the LQT1 locus on chromosome 11 encodes an abnormal potassium-channel protein (α subunit) that, when expressed with a protein from the *minK* gene, reduces the current of the slowly activating, delayed inwardly rectifying (repolarizing) potassium channel.^{7,10} The mutant *HERG* gene at the LQT2 locus on chromosome 7 encodes an abnormal potassium-channel protein that reduces the current of the rapidly activating, delayed inwardly rectifying potassium channel.⁸ The mutant *SCN5A* gene at the LQT3 locus on chromosome 3 encodes an abnormal sodium-channel protein that does not allow the complete inactivation of sodium inflow, resulting in continued entry of sodium into the myocardial cell during repolarization.⁹ A fourth long-QT syndrome locus has been identified on chromosome 4 (locus LQT4), but the associated mutant gene has not yet been identified.¹² Recently, the mutant

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KCNE1 gene at the *LQT5* locus on chromosome 21 was identified, which encodes β subunits that assemble with *KVLQT1* α subunits to form slowly activating, delayed inwardly rectifying potassium channels.¹¹

The identification of three mutant genes at loci *LQT1*, *LQT2*, and *LQT3* associated with the long-QT syndrome was largely made possible by the study of patients enrolled in the International Long-QT Syndrome Registry.^{5,7-9} During the past 18 years, 728 families with clinically identified long-QT syndrome have been enrolled and followed as part of the registry. The broad spectrum of clinical manifestations among patients enrolled in the registry was an indication of the heterogeneity of the disease before the disease was linked to multiple loci. We have previously reported that the electrocardiographic phenotypes¹³ and factors triggering cardiac events^{14,15} differ in the three genetically distinct forms of long-QT syndrome. In the current study, we evaluated the clinical course of the long-QT syndrome on the basis of the genotype in members of the registry.

METHODS

Study Population

The study subjects were enrolled in the International Long-QT Syndrome Registry⁵ by four centers (in Rochester, N.Y.; Pavia, Italy; Salt Lake City; and Jerusalem, Israel). Genetic testing for the long-QT syndrome was performed in 541 members of 38 large families selected from the registry, since to be successful linkage analysis requires large families. There were 10 families with mutations at the *LQT1* locus in which 9 probands and 242 relatives were genetically tested, 22 families with mutations at the *LQT2* locus in which all probands and 127 relatives underwent genetic testing, and 6 families with mutations at the *LQT3* locus in which 5 probands and 136 relatives were tested. Most of the known mutations were originally identified in patients enrolled in the registry.^{7,9} Blood samples were obtained from the study subjects for the purpose of linkage and mutation analyses. The mutations were identified with the use of standard genetic tests.^{7,9} All subjects or their guardians provided informed consent for the genetic and clinical studies.

We also compared the phenotypic features of all 1378 enrolled members of the 38 families, on the basis of the assumption that the phenotype — and therefore the genotype — of affected members of a given family would be the same as that of the proband. This assumption was supported by our own data showing that 209 members of 38 families had the same mutation as their respective probands and that for the various genotypes, the proportions of carriers among genetically tested subjects were similar. Different intragenic mutations, including deletions, splice-donor mutations, and missense mutations, have been identified in some pedigrees.^{7,9,16} This study was intended to explore the clinical course of the long-QT syndrome not on the basis of specific intragenic mutations, but on the basis of the mutated gene locus (*LQT1*, *LQT2*, or *LQT3*), reflecting abnormalities in potassium-channel or sodium-channel function.

Phenotypic Characterization

Detailed pedigrees were constructed for each family. A clinical history and a 12-lead electrocardiogram were obtained at the time of enrollment of each family member in the registry. On these base-line electrocardiograms, the duration of the QT and RR intervals in lead II (or lead I or III if the QT interval was not

measurable in lead II) was determined, and the QT interval, corrected for heart rate (QTc) according to Bazett's formula, was determined.¹⁷ Clinical data were recorded on prospectively designed forms and included information on demographic characteristics, personal and family history of disease, electrocardiographic findings, therapy, follow-up, and end points.

End Points

The following cardiac events were included as end points: syncope events (fainting spells with transient loss of consciousness), aborted cardiac arrest (requiring defibrillation), and death. Only events occurring from birth through the age of 40 years were included in the analysis to limit possible confounding effects of coronary artery disease and other cardiovascular conditions on the outcome. Surviving family members were asked about the clinical circumstances surrounding the death of their relatives, the presence of preexisting medical problems, and the abruptness of the event. Unexpected, sudden death (i.e., death without warning) that occurred through the age of 40 without a known cause was categorized as related to the long-QT syndrome.

Since numerous patients with the long-QT syndrome had multiple cardiac events, we also evaluated the severity and lethality of cardiac events in the 38 families. We determined the percentage of subjects who had had multiple cardiac events, since this value is a reflection of the severity of the disease. We assessed the lethality of cardiac events by dividing the number of deaths related to the long-QT syndrome by the total number of cardiac events. To determine the natural course of the disease, we assessed cardiac events that occurred before treatment with beta-blockers was begun.

Statistical Analysis

The clinical features of the three groups identified on the basis of the genotype — *LQT1*, *LQT2*, or *LQT3* — were compared with use of analysis of variance, the Kruskal-Wallis rank test, and the chi-square test, as appropriate. The cumulative probability of a first cardiac event (syncope, aborted cardiac arrest, or death) in the first 40 years of life was determined for the three groups with use of the life-table method of Kaplan and Meier,¹⁸ and the results were compared with the log-rank test with the Bonferroni correction for multiplicity. Cox multivariate survivorship analyses¹⁹ were performed to evaluate the significance and independence of the genotype as a predictor of cardiac events through the age of 40 in carriers of mutations, after adjustment for sex, QTc, and heart rate.

RESULTS

Among the 541 subjects who underwent genotyping, 112 had mutations at the *LQT1* locus, 72 had mutations at the *LQT2* locus, and 62 had mutations at the *LQT3* locus. Their clinical characteristics are shown in Table 1. There was a higher percentage of female subjects in the *LQT2* group than in the other two groups. The mean heart rate and the incidence of bradycardia were not significantly different among the three groups. The mean QTc was significantly longer in the *LQT3* group than in the other groups ($P=0.03$): 48 percent of the subjects in the *LQT3* group had a QTc of more than 500 msec, as compared with 33 percent of subjects in the *LQT1* group and 28 percent of subjects in the *LQT2* group ($P=0.06$). The QTc was as low as 400 to 430 msec in some carriers of the long-QT syndrome. The treatments were similar in the three groups except that cardiac pacing was not used in the *LQT1* group.

TABLE 1. CHARACTERISTICS OF THE 246 SUBJECTS WITH A MUTANT LONG-QT SYNDROME GENE.*

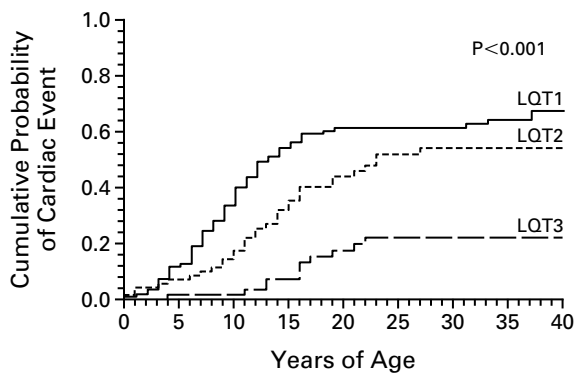
CHARACTERISTIC	LQT1 GROUP (N=112)	LQT2 GROUP (N=72)	LQT3 GROUP (N=62)
Median age at enrollment — yr	23	27	18
Age <15 yr at enrollment — no. (%)	37 (33)	21 (29)	25 (40)
Median no. of years for which clinical data were available	32	31	28
Female sex — no. (%)†	55 (49)	47 (65)	27 (44)
Base-line ECG findings‡			
No. of subjects analyzed	90	46	60
Heart rate			
Mean — beats/min	78±22	74±19	75±24
<60 beats/min — no. (%)	17 (19)	12 (26)	15 (25)
QTc			
Mean — msec†	490±43	495±43	510±48
Range — msec	400–620	410–640	430–630
≤440 msec — no. (%)	10 (11)	5 (11)	5 (8)
441–500 msec — no. (%)	50 (56)	28 (61)	26 (43)
>500 msec — no. (%)	30 (33)	13 (28)	29 (48)
Cardiac treatments through age of 40 — no. of subjects (%)			
Beta-blockers	56 (50)	42 (58)	24 (39)
Pacemaker†	0	12 (17)	5 (8)
Sympathectomy	2 (2)	5 (7)	3 (5)
Defibrillator	2 (2)	1 (1)	1 (2)
Cardiac events through age of 40			
≥1 cardiac event — no. (%)§	70 (62)	33 (46)	11 (18)
≥2 cardiac events — no. (%)§	41 (37)	26 (36)	3 (5)
Median age at first event — yr†	9	12	16
Aborted cardiac arrest — no. (%)	8 (7)	4 (6)	2 (3)
Death related to long-QT syndrome — no. (%)	2 (2)	0	2 (3)

*Plus-minus values are means ±SD.

†P<0.05 for the comparison of all three groups.

‡Electrocardiographic (ECG) data were obtained before treatment with beta-blockers was initiated.

§P<0.001 for the comparison of all three groups.



No. OF SUBJECTS				
LQT1 group	112	72	36	27
LQT2 group	72	56	29	16
LQT3 group	62	56	36	24

Figure 1. Kaplan–Meier Estimate of the Cumulative Probability of a Cardiac Event in the LQT1, LQT2, and LQT3 Groups.

The P value was computed with the log-rank test. The numbers of subjects at risk are given for each decade of age.

The LQT1 and LQT2 groups had a significantly higher frequency (Table 1) and cumulative probability (Fig. 1) of cardiac events than the LQT3 group. By the age of 15 years, 53 percent of subjects in the LQT1 group, 29 percent of those in the LQT2 group, and 6 percent of those in the LQT3 group had had a first cardiac event (Fig. 1). Thirty-seven percent of subjects in the LQT1 group and 36 percent of those in the LQT2 group had had multiple cardiac events, as compared with 5 percent of subjects in the LQT3 group ($P<0.001$). Multivariate Cox regression analysis of the 246 gene carriers indicated that after adjustment for base-line QTc, those with mutations at the LQT1 or LQT2 locus had a risk of a first cardiac event through the age of 40 years that was three to five times as high as that of subjects in the LQT3 group (Table 2). The risk of a first cardiac event was also higher in the LQT1 group than in the LQT2 group (hazard ratio, 1.58; $P=0.03$).

A longer QTc was associated with an increased risk of cardiac events (hazard ratio, 1.06 per 10-msec increase in QTc; $P=0.003$) (Table 2), and this association was independent of the genotype. Sex, heart rate, and interactions between sex and genotype and between QTc and genotype were not statistically significant prognostic factors. However, examination of the data indicated a higher-than-expected incidence of events among male subjects in the LQT1 group, and analysis of this particular interaction yielded a hazard ratio of 1.77 ($P=0.03$). Since the effect of sex in the LQT2 group was in the opposite direction (more cardiac events in female than in male subjects) and was not significant, no overall effect of sex was identified.

Cardiac events that occurred through the age of 40 years before beta-blocker therapy was instituted were assessed in all 1378 enrolled members of the 38 families, regardless of whether genotyping had been performed (Table 3). Members of families with mutations at the LQT1 locus had the highest frequency of cardiac events, and members of families with mutations at the LQT3 locus had the lowest frequency ($P=0.001$). Multiple cardiac events were also more frequent in members of families with mutations at the LQT1 or LQT2 locus than in members of families with mutations at the LQT3 locus ($P=0.002$). Multivariate Cox regression analysis (data not shown) of 851 family members for whom electrocardiographic data were available yielded similar results, confirming that the risk of cardiac events was higher in families with mutations at the LQT1 or LQT2 locus than in families with mutations at the LQT3 locus and that the QTc was an independent predictor of the likelihood of a first cardiac event. As shown in Figure 2, the likelihood of cardiac events could be predicted on the basis of both the QTc and the genotype.

TABLE 2. MULTIVARIATE ANALYSIS OF GENOTYPE AND QTc AS PREDICTORS OF A FIRST CARDIAC EVENT THROUGH THE AGE OF 40 IN 246 SUBJECTS WITH A MUTANT LONG-QT SYNDROME GENE.*

VARIABLE	HAZARD RATIO	95% CONFIDENCE INTERVAL	P VALUE
LQT1 (vs. LQT3)	5.49	2.88–10.46	<0.001
LQT2 (vs. LQT3)	3.43	1.73–6.83	<0.001
LQT1 (vs. LQT2)	1.58	1.04–2.43	0.03
QTc (per 10-msec increase)	1.06	1.02–1.10	0.003

*The LQT3 group was considered the reference group. Variables tested in the model included genotype, sex, base-line QTc, base-line heart rate, and sex–genotype and genotype–QTc interaction terms. P values for sex, base-line heart rate, and the interaction terms all exceeded 0.10.

Although there were significant differences in the frequency of cardiac events among the three groups, the overall frequency of death related to the long-QT syndrome was similar, 3 to 4 percent in each group (Table 3). The cumulative probability of death from the long-QT syndrome through the age of 40 was also similar among the groups (Fig. 3).

Since the patients with the long-QT syndrome have an increased risk of sudden death, we evaluated the lethality of cardiac events in families with known genotypes. Twenty percent of all cardiac events were

fatal in the LQT3 group, as compared with 4 percent in the LQT1 group and 4 percent in the LQT2 group (P<0.001).

DISCUSSION

We have previously shown that the three genotypes of the long-QT syndrome are associated with distinctive repolarization patterns.¹³ In the current study, we found evidence that the clinical course of disease in families with the three genotypes also differs. Subjects with mutations at the LQT1 or LQT2 locus, which lead to abnormalities of the delayed inwardly rectifying potassium channel, had a significantly higher likelihood of cardiac events than subjects with the *SCN5A* mutation at the LQT3 locus, which leads to sodium-channel abnormalities. Younger age at onset and a higher likelihood of recurrent cardiac events were also observed in the subjects in the LQT1 and LQT2 groups.

We found a wide range of QTc values (from 400 to 640 msec) among carriers of the gene for the long-QT syndrome, as has been reported in previous studies.^{13,20,21} Since previous studies of patients with the long-QT syndrome who had not undergone genotyping^{5,22} showed a significant association between the QTc and the probability of cardiac events, we evaluated the effect of the genotype and the QTc on the probability of cardiac events in 246 gene carriers. Multivariate Cox regression analysis showed that the genotype was an independent predictor of a first cardiac event. In other words, the

TABLE 3. INCIDENCE OF CARDIAC EVENTS THROUGH THE AGE OF 40 IN THE 38 FAMILIES STUDIED.*

VARIABLE	LQT1 GROUP	LQT2 GROUP	LQT3 GROUP
No. of families	10	22	6
No. of family members	629	394	355
Median no. of years for which clinical data were available	28	32	26
Cardiac events			
≥1 cardiac event — no. (%)†	118 (19)	62 (16)	34 (10)
≥2 cardiac events — no. (%)‡	55 (9)	35 (9)	11 (3)
Median age at first cardiac event — yr†	9	14	16
Total no. of events§	520	416	61
Lethality of cardiac events — no. of deaths/total no. of cardiac events (%)†	23/520 (4)	15/416 (4)	12/61 (20)
Death related to long-QT syndrome — no. (%)			
No. of deaths	23 (4)	15 (4)	12 (3)
As first cardiac event	14 (2)	5 (1)	9 (3)

*Only cardiac events that occurred before the initiation of treatment with beta-blockers were included in the analysis. All family members, regardless of whether they had undergone genotyping and whether their QTc was prolonged, were included in the analysis.

†P<0.001 for the comparison of all three groups.

‡P<0.005 for the comparison of all three groups.

§A subject could have had more than one cardiac event.

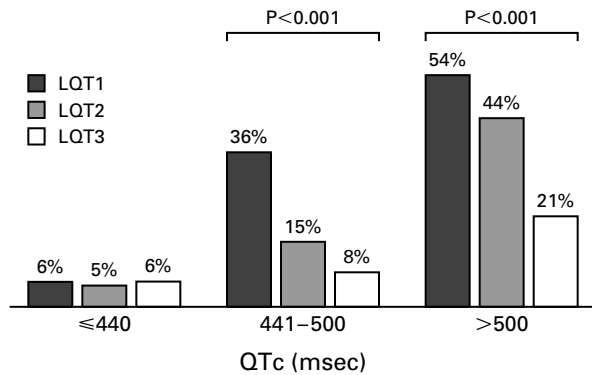


Figure 2. Percentage of Subjects with Cardiac Events According to the QTc in Family Members of Genotyped Families.

risk of cardiac events among patients with the long-QT syndrome who have similar QTc values differs depending on the genotype, and within each group, patients with a longer QTc have a higher risk of cardiac events than those with a shorter QTc. Therefore, in an evaluation of the risk of cardiac events in patients with the long-QT syndrome whose genotype is known, both the gene locus and the QTc need to be considered.

There was a significantly higher risk of cardiac events among male subjects in the LQT1 group, and a nonsignificantly higher risk was identified among female subjects in the LQT2 group. The small number of cardiac events in the LQT3 group precluded meaningful conclusions regarding sex. Although the mechanism underlying this finding is unclear, there is preliminary evidence that sex-hormone activity may modulate specific ion-channel kinetics and the response of beta-adrenergic receptors to triggering stimuli.^{23,24}

Further evidence of the genotype-related differences in the risk of cardiac events was provided by the multivariate Cox analysis of the risk of cardiac events before the initiation of beta-blocker treatment among 1378 enrolled members of the 38 families studied, rather than just those who underwent genotyping. This analysis provides insight into the natural course of the disease in families with a history of the long-QT syndrome without potential bias due to the selection of family members on the basis of genetic testing or electrocardiographic findings.

The frequency of death related to the long-QT syndrome in families with a history of the disease was similar regardless of the genotype (3 to 4 percent, with a cumulative mortality rate of 6 to 8 percent by the age of 40 years), despite the fact that there were significant differences in the frequency of cardiac events among the three groups. Since the analysis included all family members and since only

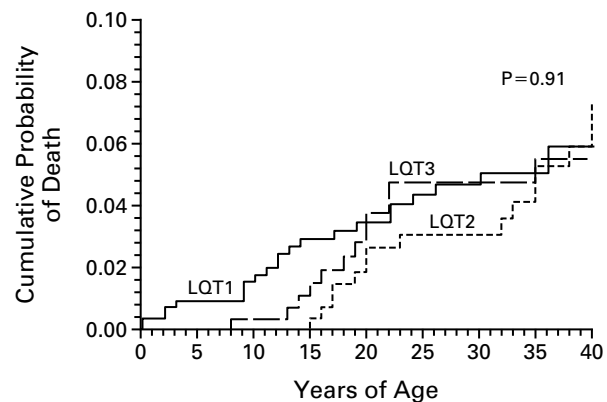


Figure 3. Kaplan-Meier Estimate of the Cumulative Probability of Death Related to the Long-QT Syndrome in the LQT1, LQT2, and LQT3 Groups.

There were no significant differences in cumulative mortality rates among the groups at the age of 40 ($P=0.91$). At the age of 15, the rates were 2.9 percent in the LQT1 group, 0.4 percent in the LQT2 group, and 1.5 percent in the LQT3 group ($P=0.006$ by the log-rank test).

approximately half of all family members are likely to be carriers of this autosomal dominant disorder, the actual mortality rate in affected patients was substantially underestimated.

The cumulative probability of cardiac events at the age of 40 differed significantly among the three groups, yet the cumulative mortality rate at the age of 40 was similar. This potential discrepancy suggests that the lethality of cardiac events — the risk of death during a cardiac event — differs in the three groups. It was significantly higher in the LQT3 group than in the LQT1 and LQT2 groups ($P<0.001$). The difference in the lethality of cardiac events between patients with potassium-channel abnormalities and those with sodium-channel abnormalities may relate to the electrophysiologic mechanisms of the onset and self-termination of torsade de pointes in these abnormalities.²⁵ Torsade de pointes in an experimental model of an LQT3-based sodium-channel abnormality (induced by the administration of the neurotoxin antopleurin) was associated with a significantly higher transmural dispersion of repolarization than in a model of an LQT2-based potassium-channel abnormality (induced by the administration of sotalol or almokalant).^{26,27} Our observation of increased lethality of cardiac events in patients with the *SCN5A* mutation may suggest the need for more aggressive treatment of these patients. Gene-specific therapy with class Ib sodium-channel blockers appears to be promising in these patients.²⁷⁻²⁹

We cannot draw any conclusions regarding the prevalence of specific mutations in patients with the long-QT syndrome, since the 38 families with a his-

tory of long-QT syndrome who were recruited for genetic screening were initially selected because of their large size, an advantage for linkage analysis. Systematic genetic screening is needed to establish the prevalence of specific mutations. The higher lethality of cardiac events in patients with mutations at the LQT3 locus may contribute to a potential underrepresentation of such patients among patients with a diagnosis of the long-QT syndrome. The frequency of cardiac events decreased after the initiation of beta-blocker therapy (data not shown), but the number of cardiac events in these patients was too small to allow a clinically relevant interpretation of the effectiveness of beta-blockers in the three groups.

The results of this study demonstrate that the genotype of the long-QT syndrome influences both the probability and the lethality of cardiac events, independently of the QTc.

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