THE SPECTRUM OF SYMPTOMS AND QT INTERVALS IN CARRIERS OF THE GENE FOR THE LONG-QT SYNDROME

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Abstract *Background.* The familial long-QT syndrome is characterized by a prolonged QT interval on the electrocardiogram, ventricular arrhythmias, and sudden death. It is not certain, however, that the length of the QT interval is a sensitive or a specific diagnostic criterion. Recently, we identified genetic markers on chromosome 11 that distinguished between carriers and noncarriers of the gene for the long-QT syndrome in three families. In this study, we compared the clinical features of carriers and noncarriers and assessed the diagnostic accuracy of the QT interval.

Methods. We obtained medical histories and electrocardiograms from 199 family members. QT intervals corrected for heart rate (QT_c) were determined independently by two blinded investigators. Carriers of the long-QT gene (83 subjects) and noncarriers (116 subjects) were distinguished by genetic-linkage analysis.

Results. Fifty-two of the carriers of the long-QT gene (63 percent) had a history of syncope, whereas four (5 percent) had a history of aborted sudden death. The QT_c intervals of the gene carriers ranged from 0.41 to 0.59 second (mean, 0.49). By contrast, the QT_c intervals of the noncarriers ranged from 0.38 to 0.47 second (mean, 0.42). On average, carriers of the gene for the long-QT syndrome had longer QT_c intervals than noncarriers, but there was substantial overlap (in 126 of the 199 subjects, or 63 percent). The use of a QT_c interval above 0.44 second as a diagnostic criterion resulted in 22 misclassifications among the 199 family members (11 percent). QT_c intervals of 0.47 second or longer in males and 0.48 second or longer in females were completely predictive but resulted in false negative diagnoses in 40 percent of the males and 20 percent of the females.

Conclusions. In families affected by the long-QT syndrome, measurement of the QT_c interval may not permit an accurate diagnosis. DNA markers make it possible to make a genetic diagnosis in some families, but not all gene carriers have symptoms. (N Engl J Med 1992; 327:846-52.)

THE long-QT syndrome[1-5] is an inherited disorder associated with recurrent syncope and sudden death from ventricular arrhythmias. We recently identified genetic markers on the short arm of chromosome 11 (11p) that are closely linked to the locus of the long-QT gene in seven families.[6-8] These families have been classified as having the Romano–Ward form of the long-QT syndrome, which is characterized by autosomal dominant inheritance without familial deafness.[1-5] A second form of the disorder, called the Jervell and Lange-Nielsen syndrome, has an autosomal recessive pattern of inheritance and is associated with deafness.[3-5] It is not clear, however, whether all families currently classified as having the Romano–Ward form will prove to be genetically homogeneous.

The diagnosis of the long-QT syndrome has been based on a family history of the disorder and on the prolongation of the QT interval on the electrocardiogram, often defined as a QT interval corrected for heart rate (QT_c) of more than 0.44 second.[9-11] The syndrome has been difficult to diagnose for a number of reasons. First, the family history may be unremarkable, even in patients with symptoms that subsequently prove to be familial. Second, the QT interval is inherently variable, changing in a given person in relation to heart rate, autonomic tone, age, use of medications, and the presence of other disorders. Finally, it has not been possible to determine the range of QT intervals in carriers of the long-QT gene, making the development of specific electrocardiographic criteria difficult. Since the genetic markers that we have identified are very informative and are closely linked to the clinical features of the disease in all persons studied, they can be used to identify carriers and noncarriers of the gene unambiguously. In this study of three kindreds, we describe the clinical characteristics of carriers of the long-QT gene, as well as those of noncarriers and spouses. We also evaluate the diagnostic usefulness of the QT interval and show that using the QT interval alone for the phenotypic classification of family members will lead to misclassifications.

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Supported in part by the LDS Hospital–Deseret Foundation, the National Institutes of Health (NIH), the American Heart Association, and the Howard Hughes Medical Institute, and by a Technology Access Grant from the NIH Genome Center, a Syntex Scholars Award, and a research grant (MO1-RR00064) from the National Center for Research Resources of the Public Health Service.

METHODS

Clinical Characterization of the Families

We have previously described the three long-QT pedigrees used in this study.[3,6,7,12,13] We evaluated 254 members, including 46 spouses, of three families with the long-QT syndrome. The largest family, Family 1, is of Danish descent. Family 2 (Fig. 1) is of Irish descent, whereas Family 3 is of mixed Danish and English descent. Genealogic records, which date back to the early 19th century, show no relationship among the three families. Genotypic data confirm that they are not closely related, since disease-marker haplotypes were different in all three.[6,7]

Informed consent was obtained from all subjects before their enrollment in the study. Probands from each family were identified on the basis of a history of syncope and a prolonged QT interval. Family members were identified through genealogic records and were evaluated on the basis of history and electrocardiographic screening. Electrocardiograms were not available for 12 persons (6 family members and 6 spouses), so these people were excluded from the study. Subjects with electrocardiographic abnormalities

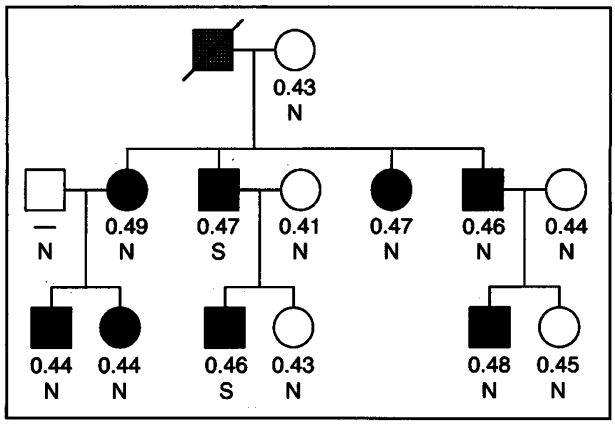

Figure 1. Pedigree of Family 2 with the Long-QT Syndrome.
Persons identified by genotype analysis as carrying the long-QT gene are indicated by solid circles (females) or squares (males), whereas noncarriers are indicated by open symbols. The hatched symbol with a slash represents a deceased family member for whom no DNA could be obtained; the phenotypes of such persons were not included in this study. The QT_c interval, expressed in seconds, is shown below each symbol. N denotes no symptoms, S one or more syncopal episodes, and a dash that no data were available.

unrelated to the long-QT syndrome, such as bundle-branch block, myocardial infarction, organic heart disease, or drug-induced QT prolongation, were excluded. One carrier of the gene, 2 noncarriers, and 6 spouses were excluded on the basis of these criteria, leaving 199 family members and 34 spouses. The earliest electrocardiographic record available was the one used, and it was obtained before the institution of beta-blocker or other drug therapy. Serial electrocardiograms, obtained over a period of more than 18 years, were available for 53 of 83 gene carriers and 68 of 116 noncarriers. For a given person, these electrocardiograms frequently revealed differences in the QT_c interval, ranging from a change of 0.01 second in 38 subjects to a change of 0.09 second in 1 subject. However, the mean QT_c intervals in both carriers and noncarriers when serial electrocardiograms were used were identical to the values calculated when only the initial electrocardiograms were used. The mean (±SD) QT_c interval calculated from serial electrocardiograms for gene carriers was 0.49±0.03 second, and the value calculated from the initial electrocardiogram was identical; the mean value for noncarriers was 0.42±0.02 second, as compared with 0.43±0.02 second when only the initial electrocardiogram was used.

The QT interval was measured blindly by two investigators in Lead II, or in Lead V_5 when the reading from Lead II was technically unsatisfactory. Correlation analysis showed a coefficient of 0.95 between these two sets of measurements. The termination of the T wave was taken to be the point of maximal change in the slope as the T wave merges with the base line.[14,15] Three consecutive cycles that had as constant a cycle length as possible were measured, and the values were averaged. In the presence of sinus arrhythmia, measurements were made at the most common and constant cycle length or, when no cycle length predominated, at the longest cycle that remained consistent for at least several beats. We did not include U waves in the measurement. The QT_c was calculated by Bazett's formula, which adjusts the QT interval for the heart rate.[16] The distribution of QT_c intervals in the carriers and noncarriers of the long-QT gene among the 199 family members (excluding the spouses) was examined, and the sensitivity and specificity over a range of QT_c intervals were determined.

The history of symptoms reported by each subject was studied by investigators unaware of the results of the genetic analysis. We evaluated the presence of syncope, the number of syncopal episodes, the subject's age at the onset of symptoms, and the number of morbid events, defined as syncopal episodes requiring cardioversion or resuscitation (aborted sudden death) or those resulting in serious complications, such as neurologic damage. Symptoms such as palpitations and lightheadedness were not assessed.

Identification of Carriers of the Long-QT Gene

Genotyping of individual subjects was performed as described elsewhere,[6,7] with DNA markers that detect polymorphisms at the loci for H-*ras*-1, insulin, tyrosine hydroxylase, and insulin-like growth factor 2 on chromosome 11p. Because these markers were completely linked with the long-QT gene in these families, gene-carrier status was determined for each person by direct analysis of haplotypes.[6,7] When these markers were used in combination, the degree of informativeness was complete for all persons at risk.

Statistical Analysis

Age at the onset of symptoms and mean QT_c interval were evaluated for statistical difference by analysis of variance.[17] In this analysis, carriers of the long-QT gene were compared with noncarriers (with the sexes studied both in combination and separately), and symptomatic gene carriers were compared with asymptomatic gene carriers. The frequency of symptoms and morbid events was compared between family members by chi-square analysis.[17] P values were calculated by two-tailed tests. The sensitivity, specificity, and overall diagnostic accuracy of a range of QT_c intervals were calculated.[18] Values are given as means ±SD.

Results

Identification of Gene Carriers

The genetic status of each family member was determined by haplotype analysis using markers on chromosome 11p. There were 83 gene carriers, or 42 percent of the 199 family members studied. They included 40 females (48 percent) and 43 males (52 percent), indicating that there was no significant sex difference among the gene carriers in this study.

Symptoms in Carriers of the Long-QT Gene

Sixty-three percent of the gene carriers (52 of 83) had had at least one syncopal episode, whereas 37 percent had never had syncope. Seven percent of the noncarriers reported a history of fainting or syncope ($P<0.001$). The incidence of symptoms in carriers of the long-QT gene was identical for both sexes (63 percent). The age at the onset of symptoms in all carriers of the gene ranged from 1.5 to 39 years (mean [±SD], 10.7±7.6). The mean age at onset was earlier in males (7.9±3.1 years; range, 3 to 14) than in females (14±9.7 years; range, 1.5 to 39; $P = 0.02$). Among the gene carriers with symptoms, the majority of both sexes (76 percent of symptomatic females and 70 percent of symptomatic males) had recurrent syncope. Among the carriers of the long-QT gene, the mean ages of the symptomatic and asymptomatic groups were similar (22.3 and 19.9 years, respectively). The mean follow-up in the symptomatic group was longer than that in the asymptomatic group (11 vs. 7 years), but the ranges were similar (1 to 18 years vs. 1 to 17 years).

Four of the 83 gene carriers (5 percent) had a history of aborted sudden death, and 2 had neurologic se-

Table 1. Morbid Events in Subjects with the Long-QT Syndrome.

Subject No./Sex	QT_c Interval (seconds)*	Age (yr) at First Symptom	No. of Syncopal Events	Age (yr) at Time of Event	Activity or Mental State at Time of Event	Outcome
Gene carriers						
1/M	0.48	4	8	13	Running, frightened	Aborted sudden death, neurologic damage
2/M	0.53	5	25	12	Exercise electrocardiography	Torsade, cardioversion, no sequelae
3/F	0.49	16	3	31	Speaking in meeting, anxiety	Aborted sudden death, mild neurologic damage
4/F	0.52	19	3	19	Cocaine use	Torsades de pointes, cardioversion, no sequelae
Historical subjects						
5/M	0.49	2½	1	2½	Overly tired	Sudden death
6/M	0.45	6	3	14	Running, frightened	Sudden death
7/M	—	9	2	12	Swimming	Sudden death
8/M	—	3	1	3	Swimming	Sudden death
9/F	0.51	12	7	26	Tennis	Sudden death
10/F	0.56	12	25	36	Teaching class, anxiety	Sudden death
11/F	—	12	12	22	In meeting, anxiety	Sudden death
12/F	—	12	1	12	Swimming	Sudden death
13/F	—	22	1	22	Swimming	Sudden death

*A dash indicates that no measurement of the subject's QT interval was available.

quelae (Table 1). By contrast, no such events occurred among the 116 noncarriers ($P = 0.016$). All the gene carriers who had aborted sudden death were in Family 1, which contained 68 carriers; none of the members of the smaller families, which contained a total of 15 carriers, had a history of aborted sudden death.

Sudden death had occurred in an additional nine members of Family 1, representing five generations, over a 30-year period (Table 1). The mean age at death for these persons was 16.6±11.0 years. Among the males, the mean age at death was 7.9±6.0 years (ages at death, 2.5, 3, 12, and 14 years), and among the females it was 23.6±8.6 years (ages at death, 12, 22, 22, 26, and 36 years). Four of these nine deaths (44 percent) occurred at the time of the first episode of syncope: those of the 2½-year-old boy, the 3-year-old boy, the 12-year-old girl, and the 22-year-old woman. The genotypes of these subjects are unknown, because they all died before genetic analysis. The diagnosis of the long-QT syndrome in these nine subjects was based on prolongation of the QT_c interval visible on electrocardiograms made before death (in four patients), a typical history of recurrent syncope induced by stress, exercise, or both or sudden death

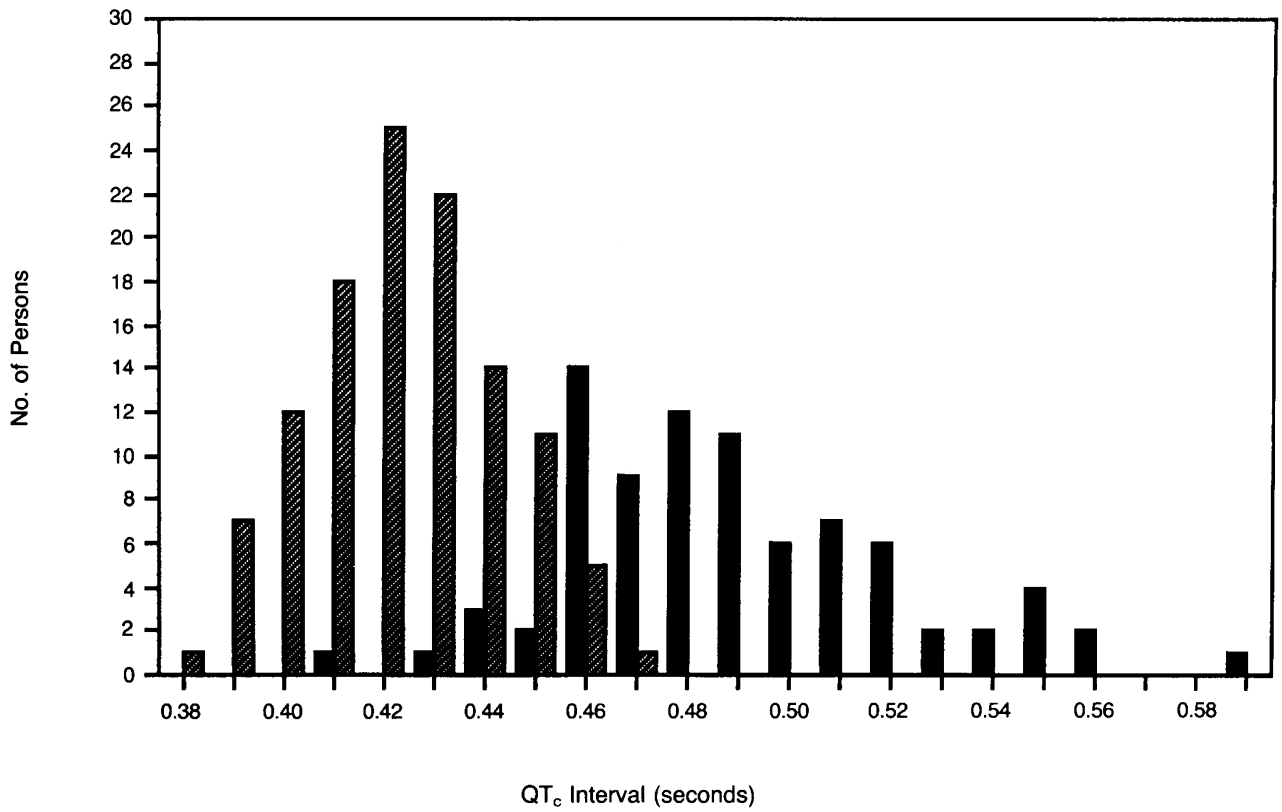

Figure 2. Distribution of QT_c Intervals among Carriers (Solid Bars) and Noncarriers (Hatched Bars) of the Long-QT Gene in All Three Kindreds Studied.

The number of persons of either sex who had a given QT_c interval is shown. Spouses are not included.

at a young age (four patients), or obligate-carrier status determined on the basis of transmission to children (two patients). We cannot calculate the risk of sudden death for living gene carriers accurately from these historical data, because the total number of carriers in ancestral generations cannot be determined.

Distribution of QT_c Intervals

To determine whether the electrocardiogram is a reliable diagnostic tool for the long-QT syndrome, the QT_c values of the gene carriers were compared with those of the noncarriers. The distribution of QT_c values among carriers and noncarriers in all three families is shown in Figure 2, and the distribution of values among the spouses in Figure 3. The QT_c intervals among carriers of the long-QT gene ranged from 0.41 to 0.59 second (mean, 0.49±0.03), as compared with 0.38 to 0.47 second (mean, 0.42±0.02) among noncarriers ($P<0.001$). The distribution of the QT_c values among the spouses was similar to that among the noncarriers (range, 0.39 to 0.45 second; mean, 0.42±0.02) (Fig. 3). Thus, a substantial overlap of values was observed between carriers and noncarriers in these families; the region of overlap was from 0.41 to 0.47 second (Fig. 2). The majority of the family members (126 of 199, or 63 percent) had QT_c values in this region. For these persons, gene-carrier status could not be determined on the basis of the electrocardiogram alone.

Because a QT_c interval of more than 0.44 second has often been used as a diagnostic criterion for QT prolongation, we evaluated the usefulness of this criterion in these families. Among the family members (with the spouses excluded), a QT_c of 0.44 second or less was present in 5 of the 83 carriers (6 percent), 4 of whom were male (4 of 43, or 9 percent; QT_c intervals, 0.41, 0.43, 0.44, and 0.44 second) and 1 of whom was female (1 of 40, or 2 percent; QT_c interval, 0.44 second). A QT_c above 0.44 second was present in 17 of the 116 noncarriers (15 percent), 4 of whom were male (4 of 47, or 9 percent) and 13 of whom were female (13 of 69, or 19 percent). The use of the QT_c value of 0.44 second as a cutoff therefore leads to misclassifications.

The distribution of QT_c intervals was evaluated separately for male and female family members. For male gene carriers, the intervals ranged from 0.41 to 0.55 second (mean, 0.48±0.03), and for female carriers, the intervals ranged from 0.44 to 0.59 second (mean, 0.50±0.03) (Fig. 4). Among noncarriers, the mean QT_c intervals were similar in male and female subjects (0.42±0.02 second and 0.43±0.02 second, respectively).

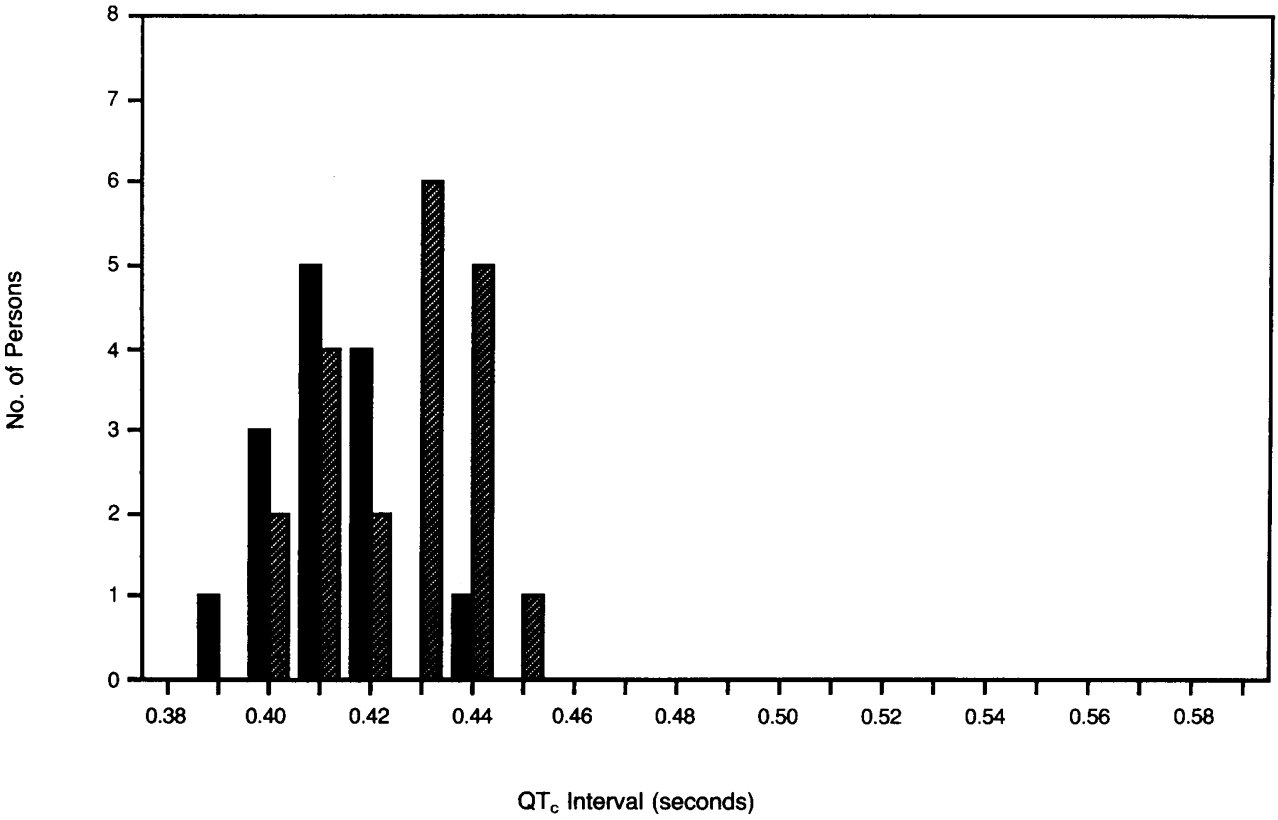

Figure 3. Distribution of QT_c Intervals among Spouses.
Solid bars denote males, and hatched bars females.

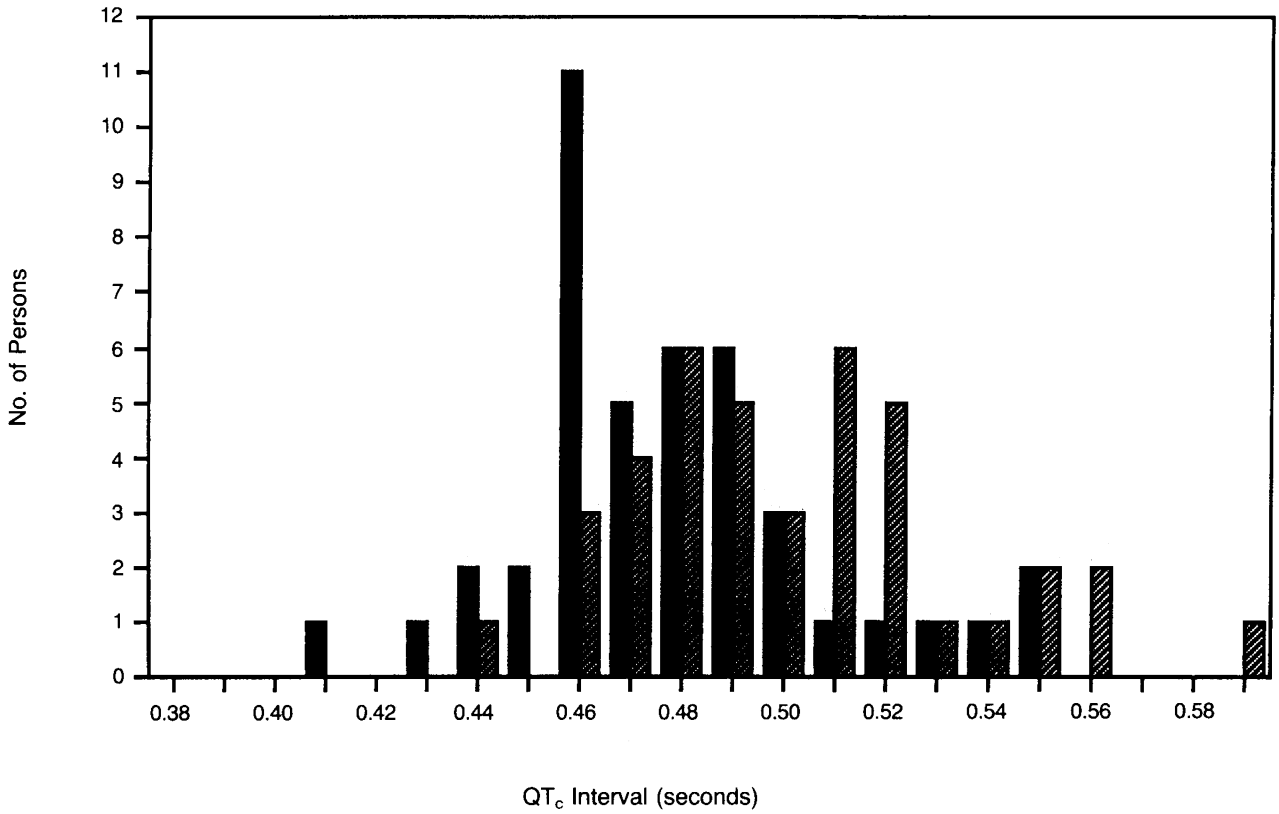

Figure 4. Distribution of QT_c Intervals among Carriers of the Long-QT Gene, According to Sex. Solid bars denote males, and hatched bars females.

There was no significant difference in mean QT_c intervals between symptomatic and asymptomatic gene carriers (0.49±0.03 second and 0.48±0.03 second, respectively; P = 0.4). The mean QT_c interval for eight family members with a history of morbid events, including four historical subjects for whom electrocardiographic records were available and four living carriers of the long-QT gene, was 0.50±0.03 second, not significantly different from the mean value for symptomatic subjects without such serious sequelae (0.48±0.04 second, P = 0.2).

To determine the usefulness of the electrocardiogram in the diagnosis of the long-QT syndrome, the sensitivity, specificity, positive and negative predictive values, and overall accuracy were calculated for a range of QT_c intervals with the spouses excluded (Table 2). In males, a QT_c of 0.47 second or longer had a positive predictive value of 100 percent, and a value of 0.41 second or less had a negative predictive value of 100 percent. In females, a QT_c of 0.48 second or longer yielded a positive predictive value of 100 percent, and a value of 0.44 second or less a negative predictive value of 100 percent. The highest overall accuracy for the diagnosis of gene-carrier status occurred at a QT_c of 0.46 second or above, at which value the accuracy was 96 percent for females and 91 percent for males. Thus, the electrocardiogram is helpful in the diagnosis of the long-QT syndrome, but in subjects with a wide range of QT_c intervals the test is neither completely sensitive nor specific.

Discussion

Because the distributions of QT_c intervals for carriers and noncarriers of the long-QT gene overlap substantially, the diagnosis of the long-QT syndrome on the basis of an arbitrary cutoff point in the QT_c interval leads to misclassifications. In our three kindreds, the use of a cutoff point of 0.44 second would have led to the misclassification of 5 gene carriers (6 percent) and 17 noncarriers (15 percent). False classification of a gene carrier as normal is a serious problem, because such persons are at risk of sudden death. Conversely, misclassifying noncarriers as affected may lead to substantial anxiety and inappropriate treatment.

Currently, analysis using tightly linked DNA markers is available for clinical diagnosis in some families with the long-QT gene. To date, no such families have been described in which the mutation is not linked to genetic loci near the H-*ras*-1 gene on the short arm of chromosome 11.[6,7] It is possible, however, that families will be identified whose mutation is not linked to chromosome 11p; in that event, these markers would not be useful. Furthermore, the genetic diagnosis of the syndrome in isolated cases or in very small families is not currently feasible. Genetic analysis of such persons must wait until the specific mutations in the

Table 2. Sensitivity and Specificity of QT_c Intervals for the Diagnosis of the Long-QT Syndrome in the Study Population.*

QT_c	Males		Females	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
≥0.40	100.0 (43/43)	8.5 (4/47)	100.0 (40/40)	5.8 (4/69)
≥0.41	100.0 (43/43)	23.5 (11/47)	100.0 (40/40)	13.0 (9/69)
≥0.42	97.7 (42/43)	46.8 (22/47)	100.0 (40/40)	23.1 (16/69)
≥0.43	97.7 (42/43)	63.8 (30/47)	100.0 (40/40)	47.7 (33/69)
≥0.44	95.4 (41/43)	87.2 (41/47)	100.0 (40/40)	63.6 (44/69)
≥0.45	90.7 (39/43)	90.7 (43/47)	97.5 (39/40)	81.0 (56/69)
≥0.46	86.0 (37/43)	94.9 (45/47)	97.5 (39/40)	94.0 (65/69)
≥0.47	60.4 (26/43)	100.0 (47/47)	90.0 (36/40)	98.3 (68/69)
≥0.48	48.8 (21/43)	100.0 (47/47)	80.0 (32/40)	100.0 (69/69)
≥0.49	34.8 (15/43)	100.0 (47/47)	65.0 (26/40)	100.0 (69/69)

*Values for sensitivity were calculated by dividing the number of true positive results (the first number in parentheses) by the number of true positive and false negative results (the second number in parentheses). Values for specificity were calculated by dividing the number of true negative results (the first number in parentheses) by the number of true negative and false positive results (the second number in parentheses).

gene for long-QT disease have been characterized.

In the meantime, the QT_c interval and the patient's medical and family history will continue to be used for diagnosis. In the families we studied, the electrocardiogram permitted a definite diagnosis to be made when the QT_c interval was 0.48 second or longer in female family members and 0.47 second or longer in male family members. Whether these values will be useful for other families with the long-QT syndrome remains to be determined. The diagnosis of the syndrome may be clarified by exercise testing, since preliminary data suggest that QT intervals in patients with the syndrome fail to shorten appropriately and the ratios of the QT interval to the QS2 interval lengthen excessively as compared with those of control subjects.[15] The positive and negative predictive values and the overall accuracy of the QT_c values described here may not be useful for the diagnosis of the long-QT syndrome in other populations, because the prevalence of the abnormal gene in those populations may differ.

The extent or existence of QT_c prolongation was not useful for predicting morbid events in carriers of the gene. For example, one person who died suddenly had a QT_c of 0.45 second. An observation that may have therapeutic implications is that 44 percent of victims of sudden death (four of nine members of Family 1) reportedly died during the first syncopal episode, and another died during the second such episode. There has been no consensus about the treatment of young asymptomatic subjects with the long-QT syndrome. Although these observations are preliminary, they may support the suggestion that treatment should be started at the time of diagnosis, even if the patient is asymptomatic.

We found that 63 percent of gene carriers reported a history of symptoms. There were no significant sex differences among this symptomatic group, a finding that contrasts with previous studies showing that females were more likely to be symptomatic than males.[9,19,20] We did find that among gene carriers symptoms appeared at an older age in women than in men, as reported previously.[20]

In the present study, 52 percent of the gene carriers were male and 48 percent were female, as would be expected with autosomal inheritance. These findings differ from previous reports in which a preponderance of affected persons were female. Moss et al.[9] reported that 64 percent of those enrolled in an international registry of subjects with long QT intervals were female. Hashiba reviewed 28 families with the long-QT syndrome and reported that 76 percent of the affected family members were female,[19] and in a study of 13 families he and his colleagues found that 68 percent of females screened by electrocardiography had prolonged QT intervals, as compared with 49 percent of males.[20] In a recent report from the international registry, Moss et al.[21] reported that 69 percent of the probands and 60 percent of other affected family members listed in the prospective registry were female. Our findings and the results of others may be discrepant because we examined carriers of the long-QT gene, whereas previous studies looked only at the phenotype. In our study, if we used a QT_c interval above 0.44 second for the diagnosis of the long-QT syndrome, 19 percent of normal females would have been misclassified as having the syndrome, whereas only 9 percent of males would have been similarly misclassified. With the use of the same electrocardiographic criterion, 9 percent of the male gene carriers as compared with 2 percent of the female gene carriers would have been misclassified as normal. Thus, our observations support previous studies showing that the distribution of QT_c in normal females tends to be skewed toward longer intervals than are found in males,[22] leading to a potential sex bias in classification of the long-QT syndrome. Alternatively, the discrepancy between our findings and the results of others may be due to differences between the populations studied. The expression of the long-QT phenotype is likely to be affected by many genetic and environmental factors, among which sex may be one. It is also possible that the primary genetic factor (in this case, a gene located on chromosome 11p) may differ in different populations.

Unfortunately, our results do not indicate which gene carriers are at risk for syncope or sudden death. Although 63 percent of the carriers had reported symptoms, only 5 percent had experienced aborted sudden death, and 37 percent had never had syncope. Because the follow-up with these families is ongoing, this number probably underestimates the size of the final symptomatic group. The extent of QT_c prolongation did not predict the risk of either syncope or morbid events in gene carriers. The mean QT_c intervals were similar in those who were symptomatic, those who had morbid events, and those who were asymptomatic. Further studies will be necessary to identify which gene carriers are at risk for ventricular arrhythmias, syncope, and sudden death.

We are indebted to Ronald Menlove, Ph.D., for the statistical evaluations; to Donald Atkinson for technical support; to Jenny Haase for assistance in the preparation of the manuscript; and in particular to the many members of the families with the long-QT syndrome who have spent countless hours assisting with this project.

References

1. Romano C, Gemme G, Pongiglione R. Aritmie cardiache rare dell'eta' pediatrica. II. Accessi sincopali per fibrillazione ventricolare parossistica. Clin Pediatr (Bologna) 1963;45:656-83.
2. Ward OC. A new familial cardiac syndrome in children. J Ir Med Assoc 1964;54:103-6.
3. Vincent GM, Abildskov JA, Burgess MJ. Q-T interval syndromes. Prog Cardiovasc Dis 1974;16:523-30.
4. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. Am Heart J 1975;89:378-90.
5. Schwartz PJ. Idiopathic long QT syndrome: progress and questions. Am Heart J 1985;109:399-411.
6. Keating M, Atkinson D, Dunn C, Timothy K, Vincent GM, Leppert M. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene. Science 1991;252:704-6.
7. *Idem*. Consistent linkage of the long-QT syndrome to the Harvey *ras*-1 locus on chromosome 11. Am J Hum Genet 1991;49:1335-9.
8. Keating M. Linkage analysis and long QT syndrome: using genetics to study cardiovascular disease. Circulation 1992;85:1973-86.
9. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: a prospective international study. Circulation 1985;71:17-21.
10. Moss AJ. Prolonged QT-interval syndrome. JAMA 1986;256:2985-7. [Erratum, JAMA 1987;257:487.]
11. Weintraub RG, Gow RM, Wilkinson JL. The congenital long QT syndromes in childhood. J Am Coll Cardiol 1990;16:674-80.
12. Vincent GM, Timothy KW, Jaiswal D. Seventeen year study of a Romano-Ward Long QT family. Circulation 1989;80:Suppl II:II-654. abstract.
13. Vincent GM. Long term follow-up of a family with Romano-Ward prolonged QT interval syndrome. In: Butrous GS, Schwartz PJ, eds. Clinical aspects of ventricular repolarization. London: Farrand Press, 1989:411-3.
14. *Idem*. The heart rate of Romano-Ward syndrome patients. Am Heart J 1986; 112:61-4.
15. Vincent GM, Jaiswal D, Timothy KW. Effects of exercise on heart rate, QT, QT_c and QT/QS2 in the Romano-Ward inherited long QT syndrome. Am J Cardiol 1991;68:498-503.
16. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353-70.
17. Zar JH. Biostatistical analysis. 2nd ed. Englewood Cliffs, N.J.: Prentice-Hall, 1984.
18. Weinstein MC, Fineberg HV. Clinical decision analysis. Philadelphia: W.B. Saunders, 1980:79-92.
19. Hashiba K. Hereditary QT prolongation syndrome in Japan: genetic analysis and pathological findings of the conducting system. Jpn Circ J 1978;42: 1133-50.
20. Hashiba K, Mitsuoka T, Mori M, Kiya F. The QT prolongation syndrome: long-term follow-up study of 13 families with Romano-Ward syndrome. Heart Vessels Suppl 1987;2:47-55.
21. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. Circulation 1991;84:1136-44.
22. Lipman BS, Massie E, Kleiger RE. Clinical scalar electrocardiography. 6th ed. Chicago: Year Book Medical, 1973:670.