The long QT syndrome (LQTS) is a familial disease that predisposes to sudden death. The QT interval is measured on an electrocardiogram and is prolonged in individuals with LQTS. The gene responsible for LQTS, called KCNQ1, is located on chromosome 11 and encodes a potassium channel.

### Table 1: QT intervals

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean QT Interval (ms)</th>
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<tbody>
<tr>
<td>Children</td>
<td>390 ± 10</td>
</tr>
<tr>
<td>Adults</td>
<td>350 ± 10</td>
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</table>

The QT interval in children is significantly longer than in adults. A prolonged QT interval is a risk factor for torsades de pointes, a life-threatening arrhythmia.

The hypothesis that the KCNQ1 gene is responsible for LQTS is supported by several lines of evidence. For example, individuals with mutations in KCNQ1 have prolonged QT intervals. Additionally, animal models with mutations in KCNQ1 develop LQTS-like phenotypes.

In conclusion, the evidence presented strongly supports the hypothesis that KCNQ1 mutations are responsible for LQTS. Further research is needed to fully understand the pathophysiology of this disease.
genetic analysis were available for 74. Strict electrocardiographic criteria for QT interval prolongation, derived from a normal electrocardiographic database (5), were used to characterize the phenotype. Although the conventional upper limit for the corrected QT interval (QTc) is 0.44 s, this criterion has been shown to be inaccurate in separating normal individuals from those with LQT (6). To accommodate uncertainty in phenotypic classification at intermediate values of QTc, we characterized all family members in our study according to three phenotypic subsets: affected, unaffected, and equivocal (Table 1). To account for age and gender differences (5), we generated separate phenotypic definitions for three demographic subsets: children (<16 years old), adult (>16 years old) males, and adult females. Cytogenetic analysis of selected affected family members revealed no chromosomal aberrations.

We carried out genetic analyses using two methods. First, we used a complex segregation analysis that resulted in evidence for a single, completely dominant allele (7). We used this major locus and the H-ras-1 marker in a combined linkage and segregation analysis. This analysis (Fig. 2, bottom curve) shows that the major LQT locus is not tightly linked to H-ras-1 for the family in our study. The best estimate of the recombination fraction is 0.494, which is close to the value of 0.50 that corresponds to no linkage. Linkage can be excluded for θ < 0.13 by conventional exclusion criteria (lod score of −2.0, which corresponds to a P value of 0.0024) or for θ < 0.23 by chi-square with P = 0.05.

Second, for comparison with the results of Keating et al. (3), we performed conventional linkage analysis using their assumptions (dominant disease allele with a frequency of 0.001 and 0.9 penetrance) and their phenotypic definition. The use of their phenotypic definition, which is slightly different from the definition used by us (Table 1), resulted in a change in the status of 18 individuals from our studied pedigree, 17 from unaffected to equivocal, and one from affected to equivocal. Conventional linkage analysis (Fig. 2, top curve) also excludes linkage to H-ras-1 for θ < 0.095 according to the lod score criterion and yields an estimated recombination fraction of 0.500.

Our pedigree differs in several ways from the large Utah pedigree analyzed by Keating et al. (3). One difference is ethnicity, because different Jewish ethnic groups tend to live in relatively isolated populations until recent times, specific genetic defects might be expected in their gene pool that are different from those in other populations. Second, in the Israeli pedigree there are several consanguineous marriages. Although inbreeding creates a computational burden for linkage analysis, we were able to retain four of the five inbreeding loops in the pedigree. Only one inbreeding loop, in the third generation, has been broken. The major consequence of not accounting for inbreeding is overestimation of the frequency of the LQT allele; thus, inferences concerning linkage should not be affected.

This analysis, together with that of Keating et al., provides evidence for genetic heterogeneity in the determination of the LQT.

**Fig. 1.** LQT pedigree. Affected individuals (Table 1) are represented by solid circles (females) or solid squares (males); unaffected individuals by open circles and squares; individuals with equivocal LQT status by a central dot; those with unknown status by a short diagonal line from top left to bottom right; deceased individuals by a long diagonal line from top right to bottom left; and consanguineous marriages by two horizontal lines. Above and to the left of each genotyped individual, alleles of the DNA marker pUC EJ 6.6 (H-ras-1, American Type Culture Collection number 41028) are listed. At this locus, the restriction enzyme Bam HI revealed four distinct alleles: (A) 7.8 kb, (B) 6.5 kb, (C) 7.1 kb, and (D) 6.8 kb. Individuals with identical status and gender within the same nuclear family are represented by a single pedigree symbol, and their genotypes are presented separately above each symbol. The pedigree structure has been altered to protect confidentiality. Informed consent was obtained from all family members.

**Fig. 2.** Profile lod functions for linkage of H-ras-1 to LQT. Bottom curve shows lod scores from conventional linkage analysis (θ = 0.494). Top curve shows lod scores from conventional linkage analysis (θ = 0.500).

**REFERENCES AND NOTES**

Response: In our 1991 report (1), my colleagues and I described tight linkage between LQT and a polymorphism within the H-ras-1 gene on chromosome 11p15.5. Because the family used in our study was large and because the polymorphic marker was informative, the statistical support for linkage was strong, even though we used conservative phenotyping (2, 3). The LOD score for linkage between LQT and the H-ras-1 gene was more than 16, which indicated that the odds in favor of linkage were greater than \(10^{14}:1\). The maximum score of 16.44 was identified at a recombination fraction of 0, which indicated that the gene for LQT was likely to be close to H-ras-1. This discovery meant that genetic markers on chromosome 11p15.5 could be used for presymptomatic diagnosis of LQT in this family. We characterized six other families with autosomal dominant LQT (4) and found the LQT gene linked to markers on chromosome 11p15.5, which indicated that presymptomatic diagnosis was possible.

Evidence that a second locus might be involved in the pathogenesis of LQT has been presented by J. A. Tobin (5). His preliminary data, which used markers at the H-ras-1 locus, suggested that the disease phenotype in one large family in Iowa was not linked to chromosome 11p15.5. In their comment, Benhorin et al. present another example of locus heterogeneity for LQT. In a study that used a carefully characterized, large Israeli family, they found that the LQT phenotype was not linked to the H-ras-1 gene. Again, because of the large size of this family and because of the highly informative nature of the marker, the statistical support for this negative finding was strong.

Locus heterogeneity has been described for many inherited disorders including the myotonias, Charcot-Marie-Tooth, and familial hypertrophic cardiomyopathy. That LQT in the Israeli pedigree is not caused by a gene on chromosome 11p15.5 suggests that what we currently refer to as LQT consists of at least two distinct disorders.

It is not yet clear what percentage of familial LQT will be caused by mutations in a gene on chromosome 11p15.5, nor is the chromosomal location of a second LQT locus known. We recently found two families with LQT in which the phenotype was clearly not linked to chromosome 11p15.5 (6). A great deal of work needs to be done before we fully understand the molecular basis of these potentially deadly disorders. Locus heterogeneity has, in the short run, complicated genetic testing for LQT and disappointed many members of families with LQT. In the long run, however, the identification and characterization of two or more genetic mechanisms for this phenotype will teach us much about cardiac repolarization and arrhythmias.

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Evidence of genetic heterogeneity in the long QT syndrome

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