


8. H. C. Bazett, Heart 7, 353 (1920).

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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^{16}. 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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REFERENCES AND NOTES


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