QT interval is a heritable quantitative trait with evidence of linkage to chromosome 3 in a genome-wide linkage analysis: The Framingham Heart Study

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OBJECTIVES To identify genomic regions linked to QT interval duration in an unselected population.
BACKGROUND QT interval prolongation is associated with increased risk of sudden cardiac death and coronary heart disease and may result from acquired conditions or inherited ion channel defects. The influence of genetic variants on QT interval length in apparently healthy individuals is uncertain.
METHODS We studied subjects from the Framingham Heart Study in whom 12-lead ECGs were available from regular clinic examinations. QT, QT-peak, and RR intervals were measured using digital calipers. A 10-centiMorgan (cM) density genome-wide scan was performed in a subset of the largest families having at least two members with ECG phenotypes (326 families). Variance components methods (Genehunter) were used.
RESULTS Evidence was observed for significant heritability of the QT interval (h^2 0.35; 95% CI, 0.29–0.41), QT-peak interval (h^2 0.37; 95% CI, 0.29–0.45), and calculated JT interval (h^2 0.25; 95% CI, 0.19–0.31). In the genome-wide linkage analysis, we found suggestive evidence for linkage of the QT interval 19 to 48 cM from the tip of the short arm of chromosome 3 (maximum two-point LOD score 3.00, maximum multipoint LOD score 2.71). After fine-mapping with seven microsatellite markers, the peak multipoint LOD score rose to 2.84 at 24.4 cM. The region of linkage contains potassium and sodium channel genes, including the *SCN5A* gene, which has been implicated in one form of the long QT syndrome and in the Brugada syndrome.
CONCLUSIONS QT and related ECG intervals are heritable traits in a large unselected population. We provide suggestive evidence for a quantitative trait locus on chromosome 3 influencing QT interval duration. Further studies are warranted to identify genes that influence QT interval variation and to determine the role of heritable factors in life-threatening QT prolongation.

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Introduction

QT interval length is a complex and dynamic trait. Prolonged QT interval duration is found in the clinical presentation of rare mendelian disorders of Long QT Syndrome (LQTS) and as a consequence of medications or electrolyte disturbances. In both congenital LQTS and medication-induced QT prolongation, a prolonged QT interval is clearly associated with an increased risk of ventricular arrhythmia or arrhythmic death. Isolated QT interval prolongation also is associated with an increased risk of sudden cardiac death in men and women in some but not all populations.[1–6] Moreover, data from the Atherosclerosis Risk in Communities (ARIC) Study show that QT interval prolongation predicts coronary heart disease risk.[7] Because sudden cardiac death may cause 250,000 deaths annually in the United States,[8] QT interval prolongation may have a significant impact on the risk of sudden cardiac death. Several twin studies indicate the QT interval is a heritable trait.[9–18] The National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study found evidence that 34% of the variation in QT interval duration is heritable.[19] However, the influence of genetic variants on QT interval length in apparently healthy individuals is uncertain.

Linkage analysis traditionally has been used in positional cloning strategies to identify gene mutations causing highly penetrant monogenic diseases. To date, such studies of families with congenital LQTS have led to the identification of mutations in six ion channels and one structural protein that result in syndromes with variable penetrance and expression.[20,21] Genome-wide linkage analyses in unselected populations have been used to identify chromosomal regions containing loci affecting complex traits, such as QT interval variation. This approach is unbiased and uses anonymous markers to locate genes, the function of which may not be known. Thus, novel targets may be identified for research and therapy.

We sought to estimate the heritability of the QT interval and related measures and to conduct a genome-wide linkage analysis among subjects in the Framingham Heart Study. Understanding the genetic determinants of the QT interval may help to elucidate the pathophysiology of sudden cardiac death, identify populations at risk, and suggest targets for prevention and therapy.

Methods

Study sample

The Framingham Heart Study is a prospective epidemiologic study established in 1948 to evaluate potential risk factors for coronary heart disease.[22,23] The original cohort included 5,209 men and women who were 28 to 62 years old at study entry. Subjects underwent repeat examinations every 2 years. In 1971, another 5,124 subjects were entered into the Framingham Offspring Study, including children or spouses of the children of the original cohort. Offspring subjects underwent examinations every 4 years. Study design and selection criteria have been reported.[24,25] The original and offspring cohorts are predominantly Caucasian (of European ancestry).

Subjects for the current study were derived from Framingham Heart Study participants who had resting ECGs obtained during routine scheduled visits to the Framingham Heart Study: original cohort subjects from 1968 to 1971 (examination cycle 11) and offspring study subjects from 1971 to 1975 (examination cycle 1). Of the 8,079 examinees, the subjects considered for heritability assessment included all original and offspring cohort subjects who were members of families with at least one other phenotyped individual. The following subjects were excluded: 245 who were younger than 20 years, 386 for prevalent coronary heart disease, 20 for use of antiarrhythmic medications, 33 for atrial fibrillation, and 39 for missing or technically poor ECGs. After exclusions, 1,962 original cohort participants and 3,071 offspring cohort participants in 1,141 families (family size range 2–46) were available for heritability assessment. A subset of the heritability cohort was utilized for linkage analysis, including all biologic members of genotyped families. Thus, linkage analysis consisted of 1,492 genotyped subjects from 326 families with a total of 2,246 phenotyped individuals. The genotyped sample included the following relative pairs: parent–offspring pairs (n = 1,677), sibling pairs (n = 2,024), cousin pairs (n = 1398), and avuncular pairs (n = 1,264). All subjects provided written informed consent.

Determination of ECG intervals

Standard 12-lead ECGs were obtained at 25 mm/s and 0.1 mV/mm on strips of lined paper (Hewlett Packard), as previously described.[26] Digital ECG measurements were made by eResearchTechnology, Inc., Philadelphia, PA (previously known as Premier Worldwide Diagnostics, Ltd.). Using digital calipers, QT, QT-peak, RR, and QRS intervals were measured. The *QT interval* was defined as the onset of the QRS to the return of the T wave to baseline, taking care to exclude U waves, if present, in leads II, V_2, and V_5. If a TU complex was present, the T-wave offset was taken to be the nadir of the curve between the T and U waves. To examine potentially distinct and clinically important physiologic components of repolarization, we defined the related phenotypes of QT-peak and JT interval.[27,28] The *QT-peak* interval was measured in lead II from the beginning of the QRS to the peak of the T wave. The *QRS duration* was measured in lead II from the