

sponding 95% confidence interval ranges from a 16.7% reduction to an 8.5% increase. Finally, within-level comparisons should be preceded by evidence of the heterogeneity of treatment effect based on an interaction test oriented to differences in absolute risk.

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Dual Inheritance of Sudden Death from Cardiovascular Causes

TO THE EDITOR: The long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia are the most common inherited cardiac channelopathies.¹ Although the disease mechanisms for these two disorders differ, the resulting arrhythmias are similar, and both are triggered by sympathetic stimulation.^{2,3} We identified the coexistence of the two diseases in one family.

A family with a history of recurrent sudden death was studied. During the past 30 years, nine members have died suddenly between 7 and 40 years of age. A borderline QT interval corrected for heart rate (QTc) of 450 msec in one asymptomatic relative (identified as V-1 in Fig. 1) was noted. Genetic testing revealed a heterozygous mutation in *KCNQ1* (1343delC, p.P448fsX465), confirming the diagnosis of the long-QT syndrome type 1.⁴ A diagnostic molecular test for this muta-

tion was therefore performed in all consenting family members.

Subsequently, one girl (identified as V-13 in Fig. 1) who did not inherit the *KCNQ1* mutation died suddenly at 13 years of age. In addition, several other noncarriers had symptoms such as syncope. Resting electrocardiograms (ECGs) from these family members did not show any abnormalities. During exercise stress testing, premature ventricular beats were detected. A second familial disorder was suspected. Therefore, family members were evaluated to identify members meeting the following criteria: symptoms or sudden death during sympathetic stimulation, normal findings on a resting ECG, the absence of structural cardiac abnormalities, and premature ventricular beats during exercise.

A pedigree analysis indicated that the second

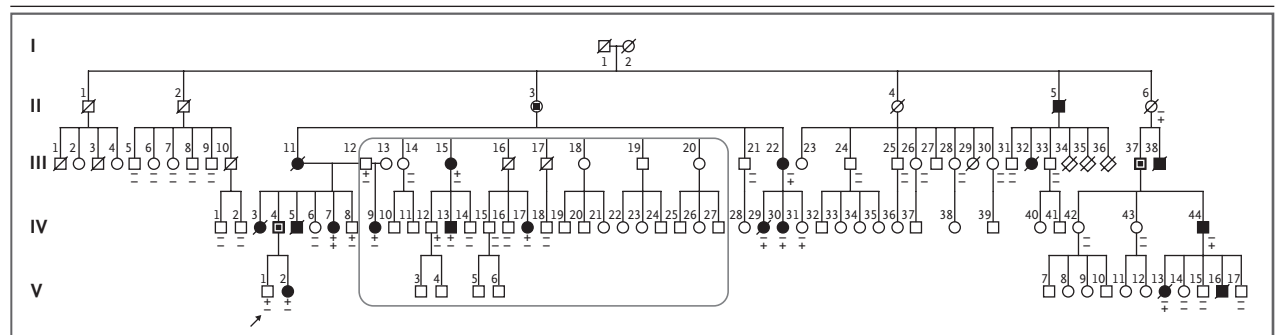


Figure 1. Key Extract of the Pedigree of Five Generations of a Family with the Long-QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia.

Circles indicate female family members, squares male family members, solid symbols clinically affected family members, and open symbols clinically unaffected family members. Deceased family members are indicated by slashes through the symbols. Symbols with squares within squares and squares within circles indicate obligate carriers. Diamonds indicate persons for whom sex was unknown. The upper symbol below a circle or square indicates the presence (+) or absence (-) of the *KCNQ1* mutation, and the lower symbol indicates the presence (+) or absence (-) of the *RYR2* mutation in persons who underwent DNA testing. The boxed area is the part of the family in which the *KCNQ1* mutation was introduced by marriage.

disorder was characterized by autosomal dominant inheritance. Given the propensity for sudden death during sympathetic stimulation in the absence of structural heart disease, catecholaminergic polymorphic ventricular tachycardia was considered to be the likely diagnosis. Sequencing of the cardiac ryanodine receptor 2 (RYR2) gene⁵ (the locus affected in catecholaminergic polymorphic ventricular tachycardia) revealed a novel heterozygous mutation affecting the FKBP12.6-binding domain (c.7210C→A, p.P2404T) that cosegregated with the phenotype. This mutation was absent in 200 healthy controls.

One living family member is a carrier of both mutations. She has clinical characteristics that are consistent with both disorders (i.e., a borderline QTc of 447 msec and premature ventricular beats at a heart rate of 100 beats per minute). Despite therapy with beta-blockers, she had a sudden cardiac arrest at 17 years of age from which she was successfully resuscitated.

Our findings underscore the fact that even when a known genetic disorder is present in a family, other clinically significant conditions may coexist. When there is doubt, the willingness to reevaluate and explore alternative genetic diseases might be the key to putting together the pieces of a complex puzzle.

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Augmentation of J Waves and Electrical Storms in Patients with Early Repolarization

TO THE EDITOR: Early repolarization, consisting of an elevation of the QRS–ST junction (J point), QRS notching or slurring (J wave), and a tall, symmetric T wave, is generally considered to be benign.¹ On the basis of preclinical experimental evidence, it has been suggested that some forms of early repolarization seen in the clinic may not be benign, especially when associated with the occasional appearance of J waves or ST-segment elevation.² Sporadic case reports and basic electrophysiological research have suggested a critical role of the J wave in the pathogenesis of idiopathic ventricular fibrillation.^{3,4} Clinical evidence in support of an association between early repolarization and idiopathic ventricular fibrillation was previously reported in preliminary form by Haïssaguerre et al. and is fully disclosed by these researchers in this issue of the *Journal*.⁵ However,

direct evidence of a relation between early repolarization and the appearance of accentuated J waves in idiopathic ventricular fibrillation has been scarce.

We evaluated the incidence of early repolarization among 1395 controls who were representative of the general population and 15 patients classified as having idiopathic ventricular fibrillation, excluding patients with long- and short-QT syndromes, the Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia. Among the 15 patients with idiopathic ventricular fibrillation, 4 presented with electrical storm (four or more episodes of ventricular fibrillation in 1 day). Continuous electrocardiographic monitoring of the patients with electrical storm was performed in the coronary care unit.

The incidence of early repolarization among