

Brief Report

MOLECULAR BASIS OF THE LONG-QT SYNDROME ASSOCIATED WITH DEAFNESS

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IN 1957, Jervell and Lange-Nielsen reported a syndrome of congenital sensory deafness associated with a prolonged QT interval in four children of a Norwegian family.¹ The affected children had multiple syncopal episodes, and three died suddenly at the ages of four, five, and nine years. Since 1957, other examples of the long-QT syndrome associated with deafness (the Jervell and Lange-Nielsen syndrome) have been described.²⁻⁴ In all cases, the apparent mode of inheritance was autosomal recessive. This syndrome is rare (estimated incidence, 1.6 to 6 cases per million).² Affected persons are susceptible to recurrent syncope, and they have a high incidence of sudden death and short life expectancy. Syncope results from torsade de pointes ventricular tachycardia and ventricular fibrillation.^{5,6}

The Romano-Ward syndrome is an autosomal dominant form of the long-QT syndrome and is not associated with deafness or other phenotypic abnormalities.^{7,8} The incidence of the Romano-Ward syndrome is higher than that of the Jervell and Lange-Nielsen syndrome, but affected persons generally have milder symptoms.^{9,10}

In previous studies, we mapped the genes for the autosomal dominant long-QT syndrome to chromosomes 11p15.5 (*LQT1*), 7q35-36 (*LQT2*), and 3p21-24 (*LQT3*).¹¹⁻¹³ A fourth gene (*LQT4*) was mapped to chromosome 4q25-27.¹⁴ We subsequently identified genes for *LQT1* (*KVLQT1*), *LQT2* (*HERG*), and *LQT3* (*SCN5A*).¹⁵⁻¹⁸ These genes encode cardiac ion channels and support the hypothesis that the long-QT syndrome results from delayed myocellular repolarization. Functional expression of *KVLQT1* in xenopus oocytes and mammalian cells induces a potassium current unlike any known cardiac current. In

recent experiments, we and others demonstrated that the *KVLQT1* protein joins with another protein known as minimal potassium-channel subunit (minK) to form a cardiac potassium channel expressing the cardiac slow delayed rectifier potassium current (I_{Ks}), a channel that contributes to myocellular repolarization.^{19,20}

In this study, we hypothesized that the Jervell and Lange-Nielsen syndrome results from mutations that affect both alleles of an autosomal dominant gene for the long-QT syndrome. We discovered that a patient with the Jervell and Lange-Nielsen syndrome had a homozygous mutation of *KVLQT1*. Other family members also had prolongation of the QT interval corrected for heart rate (QTc) with an autosomal dominant pattern of inheritance, but they had normal hearing and were heterozygotes. These data indicate that homozygous mutation of *KVLQT1* causes the Jervell and Lange-Nielsen syndrome.

METHODS

Ascertainment and Phenotyping of the Kindred

A patient with the Jervell and Lange-Nielsen syndrome was referred to us. A team of researchers attended a large family gathering organized by the patient's paternal aunt and grandmother. Information on the pedigree and the patient's history was collected at the gathering, and electrocardiograms and blood samples were obtained.

The members of the family ranged in age from 13 months to 82 years. Each subject was characterized phenotypically on the basis of the QTc and the presence of symptoms as described.^{11,13,21} Subjects were classified as phenotypically affected by the long-QT syndrome if they had symptoms (syncope, seizures, or aborted sudden death) and QTc intervals of 0.45 sec^{1/2} or more or were asymptomatic with QTc intervals of 0.47 sec^{1/2} or more. Subjects were classified as unaffected if they were asymptomatic and had QTc intervals of 0.41 sec^{1/2} or less. The status of asymptomatic persons with QTc intervals of between 0.42 and 0.46 sec^{1/2} and symptomatic persons with QTc intervals of less than 0.45 sec^{1/2} was classified as uncertain. The criteria for the assignment of phenotypes were not age-dependent. Informed consent was obtained from all the subjects or their guardians. The research protocol was reviewed and approved by the appropriate institutional review boards. Phenotypic data were interpreted by investigators who did not know the patients' genotypes.

Linkage Analysis

Linkage analysis is a technique that can be used to determine whether a gene responsible for a phenotype is located on the same chromosomal segment as a genetic marker. With this technique, an investigator examines a family to determine whether a phenotype is inherited with a specific DNA-sequence variant (allele) of known chromosomal location. Genes or segments of DNA that have two or more forms are known as polymorphic markers and can be detected with the polymerase chain reaction (PCR).²²

In this study, we used linkage analysis to determine whether the phenotype of the long-QT syndrome was inherited with the polymorphic markers *TH* and *D11S1318*, which are located near *KVLQT1*.¹⁷ Small, synthetic DNA primers (oligonucleotides) were used to amplify DNA from each subject by PCR. The reactions were completed with 75 ng of DNA in a final volume of 10 μ l with a thermocycler (model 9600, Perkin-Elmer Cetus). The amplification conditions were as follows: 94°C for 3 minutes, followed by 30 cycles of 94°C for 10 seconds, 58°C for 20 seconds, and 72°C for 20 seconds. Ten microliters of 95 percent forma-

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mid loading dye was added to each reaction, and the samples were denatured at 94°C for 5 minutes and placed on ice. Three microliters of each sample was separated on 6 percent denaturing polyacrylamide gels. The gels were dried on 3MM filter paper (Whatman, Clifton, N.J.) and exposed to film for 12 hours at -70°C. The pattern of the alleles in each subject (the genotype), which appears as bands of variable size on the film, was determined by inspection.

The genotypes were scored without knowledge of the phenotypic data and were entered into a computerized relational data base. The likelihood of odds (lod score) for linkage was determined with the Linkage version 5.1 software package.²³ Penetrance was assumed to be 95 percent, and the frequency of the gene for the long-QT syndrome (0.001) was assumed to be the same in male and female subjects. The allelic frequencies were set to 1/n, where n equals the number of alleles for each marker in this family (*TH*, 5 alleles; *KVLQTL*, 2 alleles; *D11S1318*, 10 alleles).

Mutation Analysis

Single-strand conformation polymorphism (SSCP) analysis was used to screen for mutations in *KVLQTL*.¹⁵ With this technique a small (approximately 200-bp) section of a patient's genomic DNA is amplified by PCR. If the patient has a mutation, both the normal and the mutant alleles are amplified. The two products can then be separated on nondenaturing gels and distinguished. The principle underlying SSCP analysis is that a single strand of DNA migrates through a nondenaturing gel at a rate dependent on the size and the specific sequence of the strand.²⁴ Another strand identical in size that contains a substitution of a single nucleotide will travel through the same gel at a slightly different rate. The difference in mobility results from an altered conformation in the DNA molecule that has the nucleotide substitution, and an abnormal SSCP band is produced.

PCR was completed with 75 ng of DNA in a volume of 10 μ l with a thermocycler (model 9600, Perkin-Elmer Cetus). The amplification conditions were as follows: 94°C for 3 minutes, followed by 5 cycles of 94°C for 10 seconds, 64°C for 20 seconds, and 72°C for 20 seconds and 30 cycles of 94°C for 10 seconds, 60°C for 20 seconds, and 72°C for 20 seconds. The reaction mixtures were diluted with 40 μ l of 0.1 percent sodium dodecyl sulfate and 10 mM EDTA and with 30 μ l of 95 percent formamide loading dye. The mixture was denatured at 94°C for 5 minutes and placed on ice. Three microliters of each sample was separated on 5 percent and 10 percent nondenaturing polyacrylamide gels (acrylamide:bisacrylamide, 49:1) at 4°C and on 0.5 \times and 1 \times Mutation Detection Enhancement gels (MDE, FMC BioProducts, Rockland, Me.) at room temperature. Electrophoresis of the 5 percent and 10 percent gels was completed at 40 W for three to five hours; electrophoresis of the 0.5 \times and 1 \times MDE gels was completed overnight at 350 V and 600 V, respectively. The gels were dried on 3MM filter paper and exposed to film for 18 hours at -70°C.

DNA-Sequence Analysis

SSCP bands were cut out of the gel and eluted in 100 μ l of double-distilled water at 65°C for 30 minutes. Ten microliters of eluted DNA was used as a template in a second PCR reaction with the original primer pair. The products were separated on 1 percent low-melting-temperature agarose gels (FMC BioProducts), extracted with phenol-chloroform, and precipitated in ethanol. DNA was sequenced in both directions by the dideoxy chain-termination method with a DNA sequencer (model 373A, Applied Biosystems).

RESULTS

Phenotypic Characteristics

We studied a family of Scottish descent in which one child had the Jervell and Lange-Nielsen syndrome. This female infant (Patient V-5, Fig. 1) was

born to a consanguineous marriage of second cousins. At 35 weeks' gestation, the obstetrician informed the 25-year-old mother that the fetal heart rate had dropped to 70 to 80 beats per minute. An ultrasound study showed normal growth and development, with a heart rate of 80 and a regular rhythm. At 38 weeks the heart rate continued to be slow. A second ultrasound study confirmed normal development, bradycardia, and regular rhythm. The infant was born without complications by normal vaginal delivery.

The slow heart rate persisted after birth. One hour after delivery, at the time of the first bottle feeding, the infant had cyanosis and hypotonia. She was rushed to the pediatric intensive care unit. Her serum electrolytes and a hematologic evaluation were normal. Blood cultures, urinalysis, urine cultures, and a chest film were negative. An electrocardiogram showed sinus bradycardia with a rate of 82 beats per minute and prolongation of the QT interval, with a QTc of 0.61 sec^{1/2}. On the third hospital day, a pediatric cardiologist made the diagnosis of the long-QT syndrome and treatment with propranolol was started. On the eighth day, audiograms indicated bilateral sensory deafness. A neurologic evaluation was otherwise unremarkable, and no evidence of brain-stem dysfunction was found. There was no evidence of dysmorphism.

On day 10, the infant was sent home with an apnea monitor. At the age of four weeks, serial audiograms revealed no responses to auditory stimuli in a soundproof room or through earphones. Trials with battery-powered behind-the-ear hearing aids also indicated no responses. There was no evidence of infection, meningitis, or temporal bone fractures and no history of treatment with ototoxic drugs. At 26 months the proband continued to be treated with propranolol and had no documented syncope, seizures, or tachyarrhythmia.

The family members were not evaluated further. Seven months after the delivery of the proband, her mother had a cardiac arrest and died when her alarm clock sounded. She was exhausted and extremely anxious at the time.

After the mother's death, the family was referred to our laboratory for genetic evaluation. Phenotypic analysis revealed that 14 family members had prolonged QTc intervals ranging from 0.47 to 0.53 sec^{1/2} (Fig. 1). Thirty-two family members had borderline QTc intervals, ranging from 0.42 to 0.46 sec^{1/2}. Six family members reported a history of syncope. Three had had one syncopal episode each: Subject II-13 (QTc, 0.46 sec^{1/2}; precipitating cause of syncope unknown), Subject III-29 (QTc, 0.49 sec^{1/2}; syncope while smoking marijuana), and Subject IV-4 (QTc, 0.51 sec^{1/2}; syncope while exercising). Three other family members had multiple episodes of syncope: Subject III-27 (QTc, 0.53 sec^{1/2}; syncope while exer-

cising), Subject III-33 (QTc, 0.46 sec^{1/2}; precipitating cause of syncope unknown), and Subject IV-14 (QTc, 0.41 sec^{1/2}; syncope while exercising or at rest). None of the family members reported hearing deficits. Formal audiometric analyses of Subjects IV-4, V-1, and V-3 showed normal hearing.

On the basis of this inspection, it is apparent that

the phenotype of the long-QT syndrome is inherited as an autosomal dominant trait in this kindred (Fig. 1). This pattern of inheritance is characterized by transmission of the disease phenotype from parent to child, the presence of the phenotype in each generation, and the involvement of both sexes. Father-to-son transmission is observed in this family, a fact that rules out X-linked inheritance.

Linkage Analysis

We used linkage analysis to determine whether the gene responsible for the long-QT syndrome in this kindred was located on the same chromosome as one of the known autosomal dominant genes for the long-QT syndrome. The polymorphic markers *TH* and *DIIS1318*, which map to the *KVLQT1* region of chromosome 11, were completely linked to the long-QT syndrome phenotype.¹⁷ The lod scores for linkage were 4.70 and 5.46 at a recombination fraction of 0.00 for *TH* and *DIIS1318*, respectively (P<0.001 for both markers) (Table 1). These data indicate that *KVLQT1* is an excellent candidate for the gene that causes the long-QT syndrome in this family.

Mutation Analysis

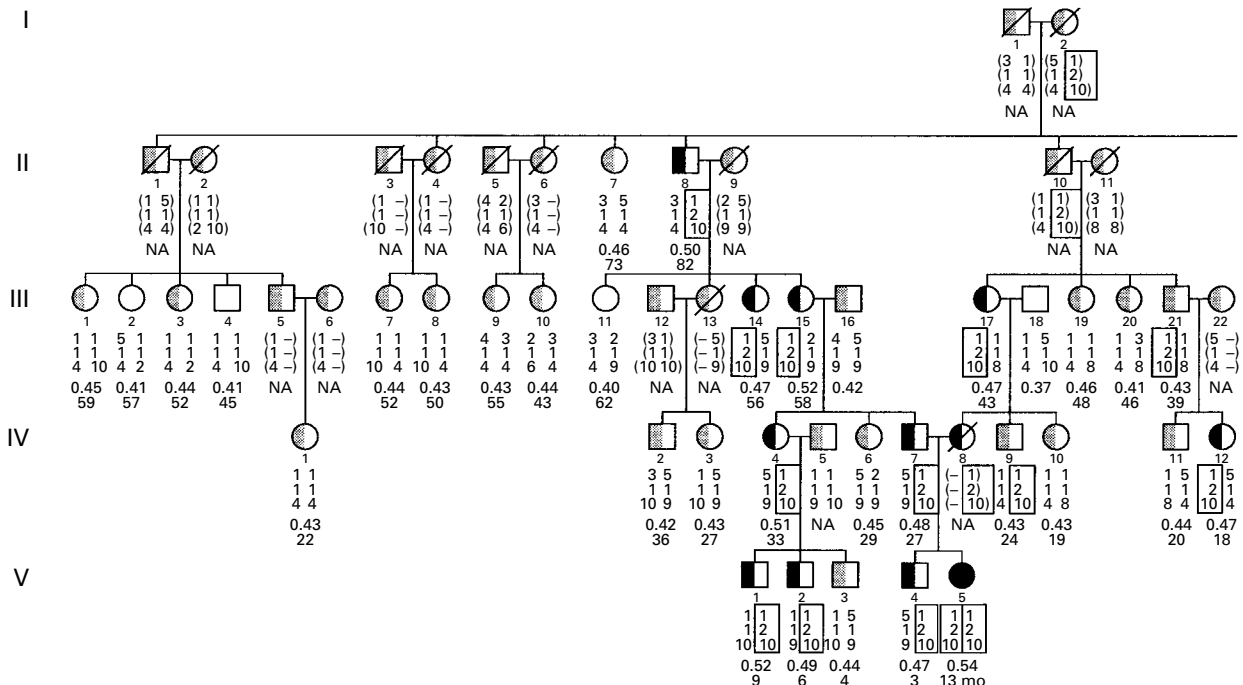
We screened DNA samples from affected subjects for functional mutations in *KVLQT1*, using SSCP to detect mutations. An abnormal band was observed

TABLE 1. PAIRWISE LOD SCORES FOR THE KINDRED STUDIED, RELATING THE PHENOTYPE OF THE LONG-QT SYNDROME TO MARKERS AT CHROMOSOME 11p15.5, INCLUDING THE *KVLQT1* MUTATION.*

MARKER	RECOMBINATION FRACTION						MAXIMAL LOD SCORE†
	0.00	0.001	0.01	0.05	0.1	0.2	
<i>TH</i>	4.70	4.70	4.63	4.31	3.89	2.98	4.70
<i>KVLQT1</i>	5.08	5.07	4.98	4.60	4.09	3.03	5.08
<i>DIIS1318</i>	5.46	5.45	5.37	4.99	4.50	3.44	5.46

*Markers at chromosome 11p15.5 were completely linked to the disease phenotype. Lod scores were computed with the assumption of 95 percent penetrance, a frequency of 0.001 for the disease allele, and equal recombination frequencies in both sexes. When penetrance was varied from 60 percent to 100 percent, the maximal lod scores ranged from 4.09 to 4.81 for *TH*, from 4.38 to 5.19 for the *KVLQT1* mutation, and from 4.77 to 5.57 for *DIIS1318*.

†The estimated recombination fraction at the maximal lod score for each marker was 0.00.



in affected members of the family, but not unaffected ones (Fig. 1 and 2). The proband with the Jervell and Lange-Nielsen syndrome (Patient V-5) had two copies of the abnormal SSCP band. Linkage analysis indicated that the abnormal band was completely linked to the long-QT syndrome phenotype in this family, with a lod score of 5.08 at a recombination fraction of 0.00 (Table 1). This indicates odds of more than 100,000 to 1 in favor of linkage and corresponds to $P < 0.001$. The abnormal SSCP band was not observed in DNA samples from 200 unrelated control subjects (a total of 400 chromosomes).

DNA-sequence analysis revealed that the abnormal SSCP band contained the insertion of a single nucleotide (G) after nucleotide 282 of the *KVLQT1* sequence (numbering started at the A nucleotide in the ATG initiation codon; GenBank accession number U89364). This insertion causes a frame shift, disrupting the coding sequence after the second putative membrane-spanning domain of the *KVLQT1* protein and leading to a premature stop codon at nucleotide 564.

We next assessed the range of QTc intervals in this genotypically defined population. For the proband, who had a homozygous mutation of *KVLQT1*, the mean (\pm SD) QTc as calculated on the basis of eight electrocardiograms was 0.54 ± 0.05 sec^{1/2}. By contrast, the mean QTc in 24 persons with one mutant *KVLQT1* allele (who were tested with one electro-

cardiogram each) was 0.47 ± 0.04 sec^{1/2}. In the 28 family members with no *KVLQT1* mutations, the mean QTc was 0.43 ± 0.02 sec^{1/2}. Although no formal statistical analysis could be performed because there was only one homozygote in the family, the QTc interval of the proband (0.54 sec^{1/2}) was markedly higher than the mean value in the heterozygotes (0.47 sec^{1/2}). This suggests that patients with two copies of a mutant *KVLQT1* gene may have longer QTc intervals than those with a single mutant copy.

DISCUSSION

We have described a family with an autosomal dominant long-QT syndrome resulting from a mutation of *KVLQT1*. Family members with one mutant *KVLQT1* allele had the long-QT syndrome but had normal hearing. One family member had the typical features of the Jervell and Lange-Nielsen syndrome: marked QTc prolongation and congenital sensory deafness.^{1,2,4} This person presented with bradycardia in utero. She was the offspring of a consanguineous marriage and had two copies of the mutant *KVLQT1* allele. We conclude that homozygous mutation of *KVLQT1* causes the Jervell and Lange-Nielsen syndrome.

Recent genetic and physiologic data support the conclusion that homozygous *KVLQT1* mutations cause deafness. We and others recently discovered that *KVLQT1* protein joins with minK protein to

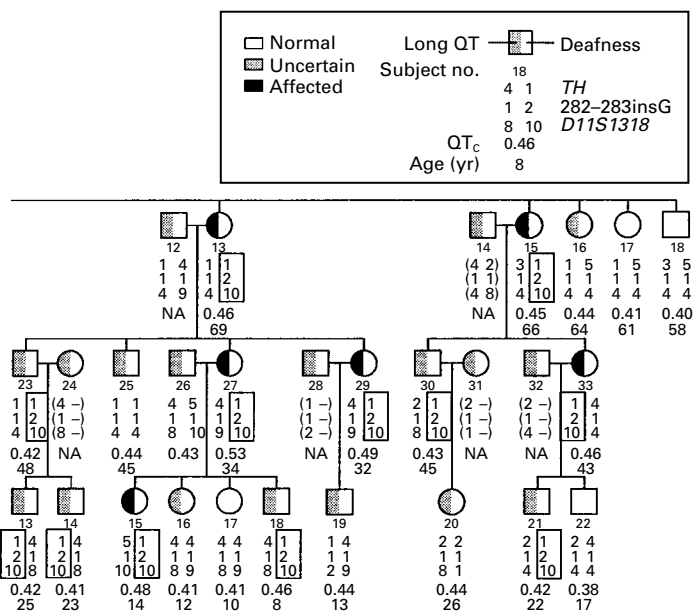


Figure 1. Genotypic Analysis of the Kindred of the Proband with the Jervell and Lange-Nielsen Syndrome, Showing the Linkage between *KVLQT1* and the Phenotype of the Long-QT Syndrome.

Circles indicate female family members, squares male family members, and slashes deceased family members. The left side of each symbol indicates whether the subject had the phenotype of the long-QT syndrome; the right side denotes the subject's hearing status. Black denotes affected status, gray uncertain status, and white unaffected status. The proband (Patient V-5) is indicated by the solid circle representing both the long-QT syndrome and deafness. The genotypes of the polymorphic markers *TH* and *D11S1318* and the *KVLQT1* mutation (282-283insG) are shown beneath each symbol, with inferred genotypes given in parentheses and hyphens indicating unknown alleles. For *KVLQT1*, the normal allele is designated by 1 and the mutant allele by 2. Genotypes associated with the long-QT syndrome are shown in boxes. The subjects' QTc intervals are given immediately below the genotypes, with their ages (in years) below the QTc intervals. NA denotes not available. The *KVLQT1* mutant allele cosegregates with the phenotype of the long-QT syndrome in this family, and the proband with the Jervell and Lange-Nielsen syndrome is homozygous for the mutation.

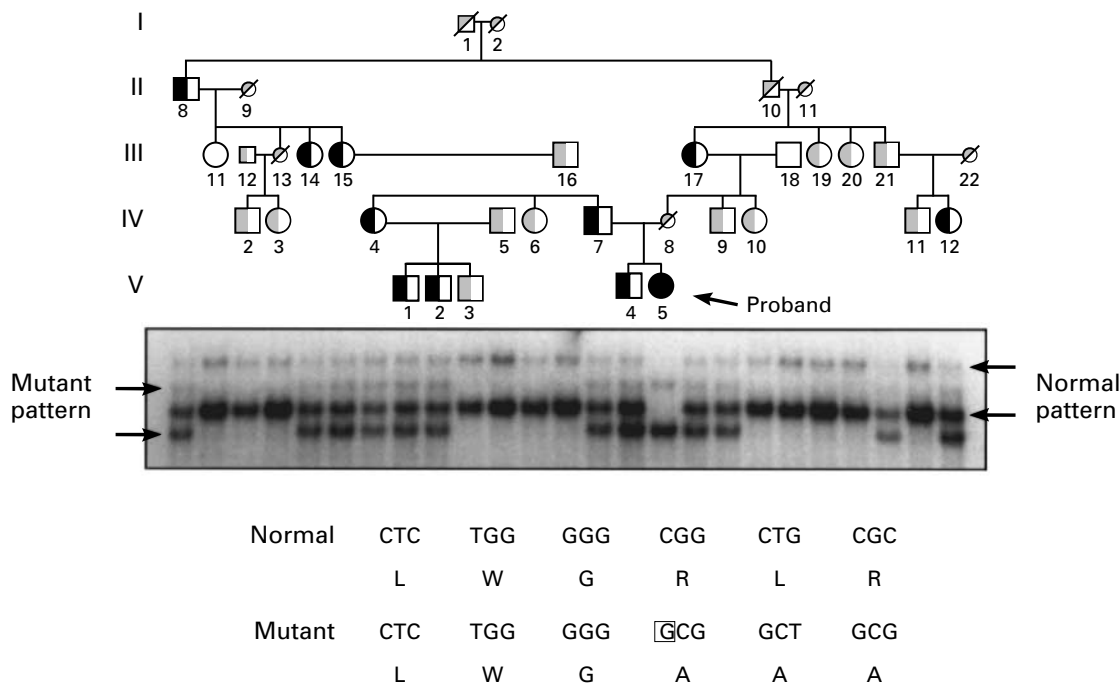


Figure 2. Cosegregation of the Abnormal SSCP Band with the Phenotype of the Long-QT Syndrome in the Kindred of the Proband with the Jervell and Lange-Nielsen Syndrome, with the DNA Sequence of the *KVLQT1* Mutation.

The top panel shows a subgroup of the kindred. The symbols are as described in the legend and key to Figure 1. Small symbols denote family members for whom no bands are shown but who are included to clarify the family relationships. The abnormal SSCP band cosegregates with the phenotype of the long-QT syndrome. The bottom panel shows the DNA and protein sequences of the normal and mutant *KVLQT1* alleles. The mutant allele contains an insertion of a single nucleotide (G) after nucleotide 282. This insertion causes a frame shift that leads to a premature stop codon.

TABLE 2. MOLECULAR GENETICS OF THE LONG-QT SYNDROME.

SYNDROME, TYPE OF INHERITANCE, AND LOCUS	CHROMOSOME	GENE
Romano-Ward syndrome (long QT)		
Autosomal dominant		
LQT1	11p15.5	<i>KVLQT1</i>
LQT2	7q35-36	<i>HERG</i>
LQT3	3p21-24	<i>SCN5A</i>
LQT4	4q25-27	?
LQT5	?	?
Jervell and Lange-Nielsen syndrome (long QT and deafness)		
Autosomal recessive		
LQT1	11p15.5	<i>KVLQT1</i>

form cardiac I_{Ks} potassium channels.^{19,20} Although most studies have focused on the function of minK in the heart, the gene that encodes it is also expressed in the inner ear. *MinK* knockout mice are deaf and have inner-ear disease similar to that of patients with the Jervell and Lange-Nielsen syndrome.^{25,26} The loss of functional minK protein apparently disrupts the production of endolymph, leading to deafness. Recently, Neyroud and colleagues showed that *KVLQT1* is expressed in the stria vascularis of the inner ear in mice.²⁷ Other known genes located near *KVLQT1* (*p57^{KIP2}*, *H19*, and the genes for insulin-like growth factor II, insulin, and tyrosine hydroxylase) are not likely to contribute to the disease observed in the Jervell and Lange-Nielsen syndrome. These data are consistent with the finding that homozygous mutations of *KVLQT1* cause deafness in humans.

The *KVLQT1* mutation described here causes a frame shift, disrupting the coding sequence and leading to a premature stop codon. The resulting truncated protein would lack a pore region and could not function as an ion channel. Thus, the proband represents a case of functional knockout of *KVLQT1*. The result is prolonged myocellular repolarization, lack of

homogeneity of cardiac repolarization, increased risk of torsade de pointes arrhythmias, and deafness.

It is not yet clear whether *KVLQT1* is the only gene responsible for the Jervell and Lange-Nielsen syndrome. Genetic heterogeneity has been identified in the autosomal dominant long-QT syndrome (Table 2),¹⁵⁻¹⁷ and Jeffrey and colleagues described a family with the Jervell and Lange-Nielsen syndrome in which the phenotype was not linked to a chromosome 11p15.5 marker.²⁸ In findings consistent with ours, Neyroud and colleagues recently reported homozygous *KVLQT1* mutations associated with the Jervell and Lange-Nielsen syndrome in two kindreds.²⁷ Because minK joins with *KVLQT1* protein to form I_{Ks} channels, *minK* is another excellent candidate gene for this disorder.^{19,20}

Previous reports describing the clinical characteristics of patients with the Jervell and Lange-Nielsen syndrome have focused on the dramatic features observed, which generally include marked prolongation of the QTc interval, frequent tachyarrhythmias, and deafness. Some studies have documented moderate prolongation of QTc in family members with normal hearing, but the Romano-Ward long-QT syndrome was not diagnosed.^{2,3} The family described in our study came to our attention because the proband's mother died suddenly, presumably of a cardiac arrhythmia. Phenotypic evaluation of the extended family revealed autosomal dominant inheritance of the long-QT syndrome in other family members. Deafness, however, was found only in the proband, who was homozygous for the *KVLQT1* mutation. Thus, one feature of the phenotype of the Jervell and Lange-Nielsen syndrome, deafness, is inherited as an autosomal recessive trait. QTc prolongation, by contrast, is inherited as a dominant trait, but that phenotype may be more severe if both alleles are mutant. It is important to note that the parents (and possibly other family members) of patients with the Jervell and Lange-Nielsen syndrome are obligate heterozygotes for long-QT-associated mutations and are at increased risk for arrhythmia. The untimely death of the proband's mother points to the importance of electrocardiographic and genetic screening of families with the Jervell and Lange-Nielsen syndrome.

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