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SHORT REPORT

Recessive Romano-Ward syndrome associated with compound heterozygosity for two mutations in the *KVLQT1* gene

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We describe a Swedish family with the proband and his brother suffering from severe Romano-Ward syndome (RWS) associated with compound heterozygosity for two mutations in the *KVLQT1* (also known as *KCNQ1* and *KCNA9*) gene (R518X and A525T). The mutations were found to segregate as heterozygotes in the maternal and the paternal lineage, respectively. None of the heterozygotes exhibited clinical long QT syndrome (LQTS). No hearing defects were found in the proband. The data strongly indicates that the compound heterozygosity for R518X and A525T is the cause of an autosomal recessive form of RWS in this family. Our findings support the implication of a higher frequency of gene carriers than previously expected. We suggest that relatives of 'sporadic RWS' patients should be considered potential carriers, at risk of dying suddenly from drug-induced LQTS.

Keywords: recessive Romano-Ward syndrome; long QT syndrome; *KVLQT1*; mutation detection; carrier screening

Introduction

Hereditary long QT syndrome (LQTS) is characterised by a prolonged QT interval on the ECG, and a propensity for developing ventricular tachyarrhythmias causing syncopes and sudden cardiac death.[1] Mutations in one of the genes encoding cardiac sodium- or potassium-ion channel subunits (*SCN5A*, *KVLQT1*, *HERG* and *KCNE1*) may cause LQTS.[2–5] Two clinical forms of LQTS have been recognised: Romano-Ward syndrome (RWS) with an autosomal dominant pattern of inheritance,[6] and Jervell and Lange-Nielsen syndrome (JLNS)[7] with an autosomal recessive pattern of inheritance and association with sensorineural deafness. However, a relatively high frequency of sudden cardiac death, or clearly prolonged QT_c interval among relatives of patients with both RWS[8] and JLNS,[9] and the recent description of recessive RWS associated with homozygosity for a *KVLQT1* mutation[10] suggest that the pattern of inheritance may be more complicated.

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Here we describe the first case of autosomal recessive RWS caused by compound heterozygosity for mutations in *KVLQT1*.

Materials and Methods

The clinical examination, performed at the Department of Pediatrics, Visby Hospital, included a thorough clinical history, and a 12-lead surface ECG. Patients were particularly questioned carefully on the occurrence of syncopes or near syncopes throughout life. QT_c values > 440 ms were considered prolonged. Genetic analyses were performed on chromosomal DNA essentially as described.[3,11,12]

Results

The four-year-old proband (III.6, Figure 1) was born with bradycardia, and developed severe clinical LQTS with recurrent syncopes and torsades de pointes ventricular tachycardia shortly after birth. The ECG revealed prolonged QT_c and T-wave alternans. No hearing defects were found in two audiograms.

The brother of the proband (III.9, Figure 1) was also born with bradycardia and ECG, 2 days after birth, revealed prlonged QT_c (Figure 1).

None of the other family members had ever experienced symptomatic LQTS, but several were found to have prolonged QT_c (Figure 1).

The proband and the parents (II.3 and II.4, Figure 1) were screened for mutations in *KVLQT1*, *HERG*, *SCN5A*, and *KCNE1* by single strand conformation polymorphism (SSCP) analysis.[3,11,12] DNA sequencing of PCR products displaying abnormal conformers revealed that the father (II.4) and mother (II.3) were heterozygous for a non-sense mutation, R518X, and a missense mutation, A525T, respecitvely, in *KVLQT1*. The proband had inherited both mutations and was

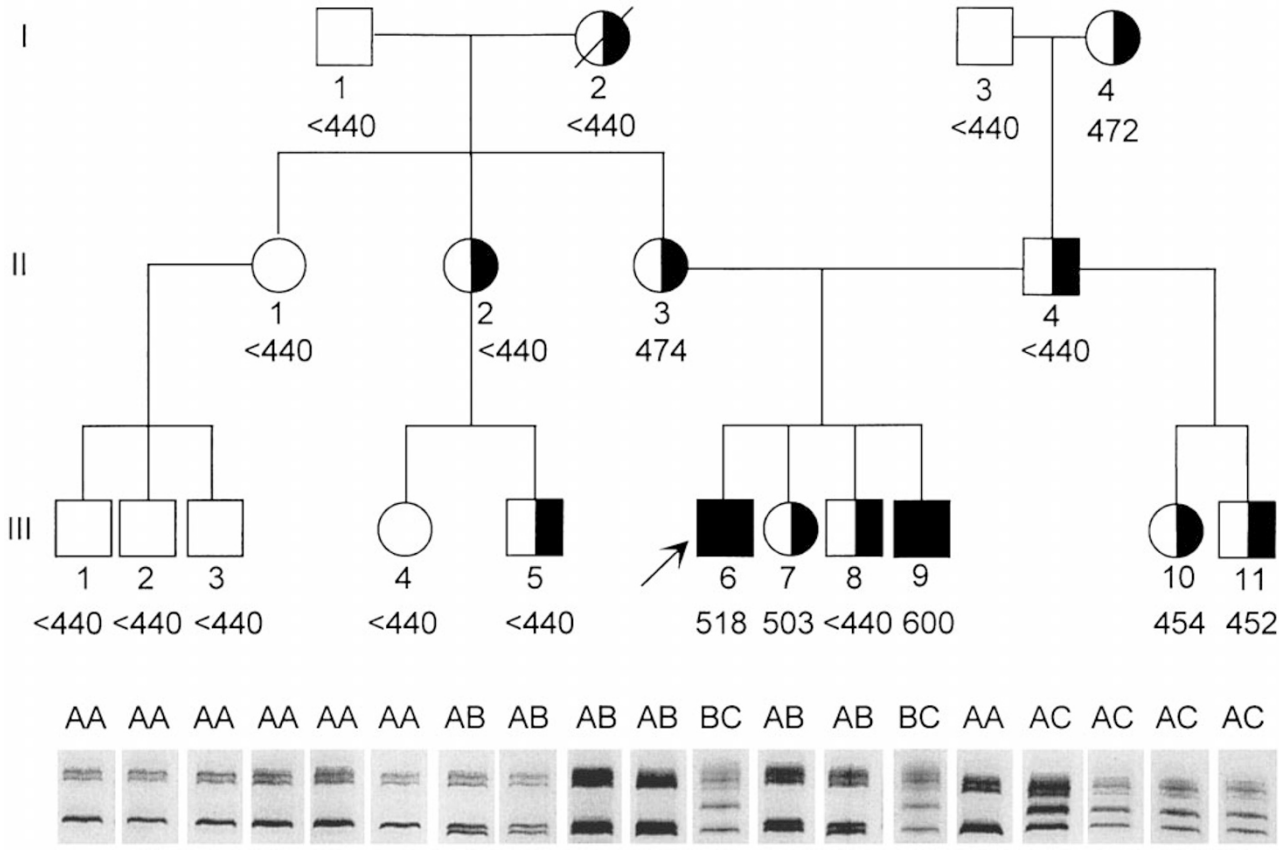

Figure 1 *Pedigree of a Swedish family with recessive RWS. Half filled squares (males) and circles (females) indicate asymptomatic carriers without clinical LQTS. Solid squares indicate males with clinical RWS. The proband is indicated by the arrow. Slash indicates a female deceased from cancer. QT_C intervals are shown below each family member. The SSCP conformers and the genotype are indicated below. A: Normal; B: A525T; C: R518X*

compound heterozygote for the two mutations (Figure 2). Analysis of all other family members showed that the mutations segregated in the maternal and paternal lineage (Figure 1). SSCP analysis of 100 normal chromosomes excluded the possibility of common polymorphisms. The newborn brother of the proband (III.9) was also found to be compound heterozygous for R518X and A525T (Figure 1).

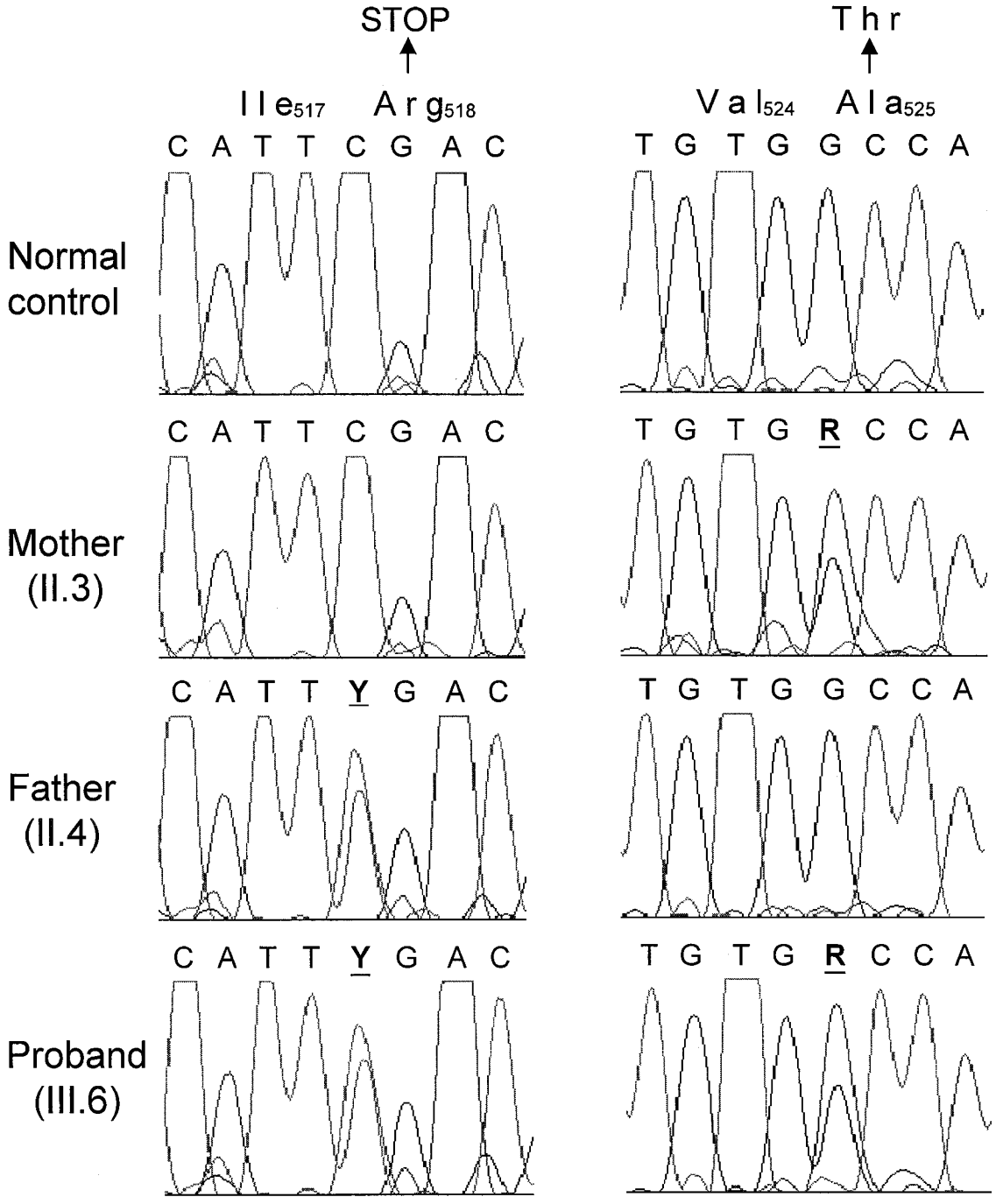

Figure 2 *Direct sequencing of PCR products. The DNA sequence of* KVLQT1 *codon 517–518 and 524–525 is shown. The deduced amino acid sequences and the coding effect of the mutations are shown on top. Y indicates C/T heterozygosity and R indicates A/G heterozygosity*

Discussion

The association between severe clinical LQTS and compound heterozygosity strongly indicates that compound heterozygosity for KvLQT1 R518X and A525T is the cause of RWS in this family.

The heterozygote carriers of the mutations are asymptomatic, and clinical RWS in this family thus exhibits an autosomal recessive pattern of inheritance. However, prolonged QT_c values were found in some heterozygote carriers; thus QT_c abnormality exhibits a dominant pattern of inheritance with reduced penetrance.

Both homozygosity for mutations in *KVLQT1*,[13,14] and compound heterozygosity for mutations in *KCNE1*[15] have been shown to cause JLNS. *KVLQT1* and *KCNE1* encode ion channel subunits which assemble in stria vascularis of the inner ear and are necessary to maintain the composition of the endolymph,[14] and the absence of a hearing defect in our family and that of the other recently described recessive RWS family,[10] is probably explained by the mutations not completely abolishing channel function.

This is the third description of a RWS family with mutations in the region of the *KVLQT1* gene encoding the C-terminal part of the channel subunit, outside the important transmembrane segments.[16,17] In a French family[16] and the family described here, the heterozygotes displayed minor or no QT-prolongation, indicating that C-terminal mutations may have a relatively mild effect on the potassium channel function. However, LQTS symptoms had appeared in some members of the French family upon administration of drugs prolonging ventricular repolarisation.[16]

The findings of recessive RWS caused by compound heterozygosity, as in our family, and by homozygosity in a consanguinous family[10] imply that the frequency of gene carriers is much higher than inferred from the rarity of RWS if the pattern of inheritance was strictly dominant. Therefore 'sporadic RWS' should be considered as potentially recessive RWS, and efforts should be made to determine the molecular defects and identify carriers in the family, since they may be at risk of dying suddenly from drug-induced LQTS. Furthermore, carrier screening on a broader basis may be considered if adequate technology becomes available in the future.

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