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http://dx.doi.org/10.1016/j.ijcard.2012.08.033

Novel deletion mutation in the cardiac sodium channel inactivation gate causes long QT syndrome

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ARTICLE INFO

Article history:
Received 27 June 2012
Accepted 23 August 2012
Available online 12 September 2012

Keywords:
Long QT syndrome
Sodium channel
Cardiac arrhythmias
SCN5A
Electrophysiology

Disturbances in cardiac sodium channel function are associated with inherited arrhythmia susceptibility. Mutations in *SCN5A*, which encodes the cardiac sodium channel ($Na_V1.5$), cause congenital long QT syndrome type 3 (LQT3), Brugada syndrome (BrS) and a variety of cardiac conduction disorders (CCD) [1,2]. These disorders can have complex genotype-phenotype relationships [3,4]. Here we report the clinical features of an LQTS family segregating a novel amino acid deletion mutation (N1472del) in *SCN5A* that produces a unique pattern of biophysical disturbances consistent with the clinical phenotype.

Nine members of a three-generation Italian LQTS family were evaluated clinically by the Cardiology Division of the Monaldi Hospital (Naples, Italy) or in other hospitals (Fig. 1A). Investigations included a complete medical history, physical examination, 12-lead ECG recording, 24-h Holter recording and echocardiogram at different times during a follow-up of at least 3 years. Informed consent for genetic studies was obtained from all subjects.

The proband (III-3, Fig. 1A) was a 27-year-old female who had postpartum cardiac arrest shortly after an uncomplicated Caesarian section while receiving erythromycin. An ECG performed during adolescence reportedly exhibited normal QT intervals, but her QTc was prolonged (480 ms) following successful resuscitation (Fig. 1B). She was treated with metoprolol, mexiletine and had an ICD implanted. During the following 8 years, she remained asymptomatic with a QTc ranging between 410 and 445 ms without conduction disturbances. There was a significant family history of unexplained syncope and sudden death. Particularly, the proband's uncle (II-6, Fig. 1A) experienced syncope at age 12, then died suddenly overnight at age 13. In retrospect, an ECG obtained at age 12 demonstrated a prolonged QTc and periods of 2:1 AV block (Fig. 1B).

The proband was screened for mutations in *SCN5A*, *KCNQ1*, *KCNH2*, *KCNE1* and *KCNE2* genes. Genetic analysis revealed a novel *SCN5A* in-frame deletion mutation (c.4414-4416delAAC) predicting the deletion of asparagine-1472 (p.N1472del). The mutation deletes a conserved residue within the DIII–DIV cytoplasmic loop, which is an essential structural determinant of sodium channel fast inactivation [5,6]. The mutation was present in all clinically affected relatives who were genotyped (Fig. 1A) but was absent in 500 chromosomes from control subjects.

Mutation N1472del was generated by site-directed mutagenesis of recombinant human $Na_V1.5$ (GenBank M77235) inserted into the expression vector pRc/CMV. To determine the functional consequence of the mutant channel, sodium current was recorded by whole cell patch-clamp in transiently transfected tsA201 cells as previously described [7]. Peak current density recorded from cells expressing

Abbreviations: AV block, Atrio-ventricular block; Bpm, Beats per minute; BrS, Brugada syndrome; CCD, Cardiac conduction defects; ECG, Electrocardiogram; HR, Heart rate; ICD, Implantable cardioverter defibrillator; K, Slope factor; LQTS, Long QT syndrome; QTc, QT interval corrected for heart rate; TTX, Tetrodotoxin; $V_{1/2}$, Membrane potential at half-maximal activation or inactivation.

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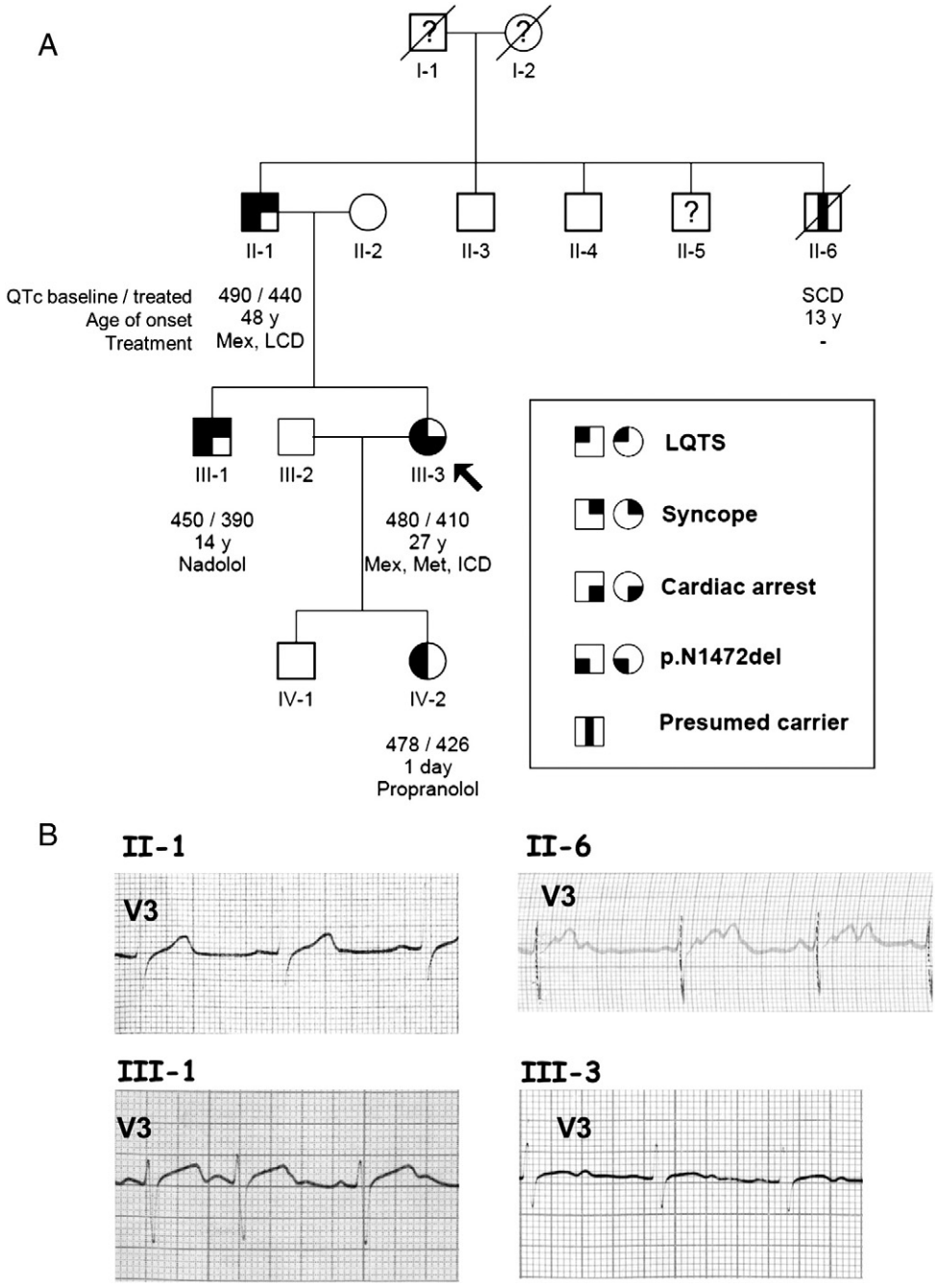

Fig. 1. Pedigree of a LQTS family with representative ECG traces. (A) Genotype and phenotype are defined according to the legend inset. Open symbols represent subjects with a negative genotype and phenotype. An arrow marks the proband (III-3). Symbols with a question mark represent subjects with unknown phenotype. The QTc interval, the age of onset and the treatment are reported below each subject symbol (abbreviations: Mex, mexiletine; Met, Metoprolol; LCD, left cardiac sympathetic denervation; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death). (B) Representative ECG traces from four genotype positive family members.

N1472del was ~50% smaller than that of cells expressing WT-$Na_V1.5$ (p.N1472del: 160.5 ± 21 pA/pF, n = 25; WT-$Na_V1.5$: 344.8 ± 52 pA/pF, n = 21; $p<0.05$) and the peak current of N1472del was shifted to a more positive potential (Fig. 2A). Correspondingly, there was a +15 mV depolarizing shift in the voltage dependence of activation observed for mutant channels (N1472del, $V_{1/2}$: −28.9 ± 0.7 mV, n = 23; WT-$Na_V1.5$, $V_{1/2}$: −44.4 ± 1.1 mV, n = 21; $p<0.001$) (Fig. 2B). Mutant channels also exhibited a +12 mV depolarizing shift in steady-state inactivation (N1472del, $V_{1/2}$: −72.6 ± 0.5 mV, n = 21; WT-NaV1.5, $V_{1/2}$: −85.0 ± 2.2 mV, n = 21; $p<0.001$) (Fig. 2C). In addition, the time course of recovery from fast inactivation observed for WT-$Na_V1.5$ was monoexponential described by a single time constant (6.8 ± 0.01 ms, n = 10), whereas recovery for N1472del was biexponential characterized by fast (4.3 ± 0.4 ms, 60%; n = 20) and slow time constants (200 ± 33 ms, 38%; n = 21). The additional slow component explains the significantly slower recovery from inactivation exhibited by the mutant channel (Fig. 2D). Finally, the N1472del channel showed a greater level of TTX-sensitive persistent sodium current compared with WT-$Na_V1.5$ (N1472del: 2.6 ± 0.2%, n = 5; WT-$Na_V1.5$: 0.1 ± 0.02, n = 5; $p<0.001$) (Fig. 2E), a common feature of *SCN5A* mutations associated with LQT3 [8].

This family exhibited a heterogeneous phenotype with variability in severity and clinical presentation. Among the four documented and one presumed mutation carrier (Fig. 1A), the presentation ranged from late onset syncope (subject II-1) to sudden unexplained death during adolescence (subject II-6) or post-partum cardiac arrest (proband, III-3).

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