A novel SCN5A mutation associated with the linker between III and IV domains of Na_v 1.5 in a neonate with fatal long QT syndrome

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Title: A novel SCN5A mutation associated with the linker between III-IV domains of $Na_v1.5$ in a neonate with fatal long QT syndrome

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Abstract

A male newborn weighing 2334g was delivered at 37 weeks of gestation by caesarean section because of prenatal ultrasound findings of fetal hydrops with atrioventricualr block, ventriucular tachycardia (VT), and impaired ventricular function. In spite of the intravenous administration of lidocaine, VT continued. He developed poor perfusion and systemic hypotension. After the intravenous administration of amiodarone, VT was terminated. The electrocardiogram revealed an extremely prolonged corrected QT interval (860 ms) with 2:1 atrioventricular block. Unfortunately, he died eighteen hours after birth in spite of the administration of lidocaine, beta-blocker and magnesium. Mutational analysis identified a novel heterozygous *de novo* mutation (F1486del) in *SCN5A*. This mutation is associated with the IFM motif in the linker between III-IV domains of $Na_v1.5$, which serves as an inactivation particle binding within the pore of sodium channels. This report demonstrates an interesting relationship between the clinical phenotype and the location of the mutation in long QT syndrome.

1. Introduction

Congenital long QT syndrome (LQTS) is a genetically heterogeneous disorder caused by mutations in cardiac ion channels [1]. Patients with LQTS are predisposed to syncope, life-threatening arrhythmias and sudden death due to delayed ventricular repolarization. Clinical manifestations of LQTS are variable according to gender, age and genetic backgrounds. LQTS concurrent with lower heart rate or atrioventricular block is rare but fatal, which usually manifests itself before birth or during the neonatal period.

The mutation in *SCN5A*, which encodes the alpha subunit of cardiac voltage-gated sodium channel ($Na_v1.5$), is responsible for LQTS type3 (LQT3). As more than 150 mutations in *SCN5A* have been reported [2], several types of mutations such as P1332L and F1473C are associated with intrauterine and neonatal manifestations of LQT3 with the higher mortality [3].

We here present a notable case of a neonate with fatal LQT3 who pre- and postnatally developed atrioventricular block and ventricular tachycardia (VT). Genetic analysis demonstrated a novel *de novo* heterozygous mutation in SCN5A associated with the linker between III-IV domains of $Na_v1.5$.

2. Case report

Patient

A male newborn weighing 2334g was delivered at 37 weeks of gestation by caesarean section because prenatal ultrasound demonstrated fetal hydrops with atrioventricular block, incessant ventricular tachycardia and decreased ventricular function. There was no maternal obstetrical or medical history. As he had poor perfusion and respiratory insufficiency, assisted ventilation and administration of dobutamine were started. Irregular and weak pulsation was noted. Chest X-ray showed cardiothoracic ratio was 67%. Echocardiogram showed dilated left ventricle, decreased left ventricular ejection fraction (23%) and significant pericardial effusion. Electrocardiogram (ECG) demonstrated 2:1 atrioventricular block and polymorphic ventricular tachycardia (VT) (Fig. 1A). VT was refractory to intravenous administration of magnesium (50mg/kg) and lidocaine (3mg/kg). Although prenatal ultrasound raised the suspicion of LQTS, a definitive diagnosis was not made. To improve the circulatory instability, the patient was given a test dose of intravenous amiodarone (5mg/kg) which resulted in termination of VT. ECG in sinus rhythm showed 2:1 atrioventricular block (atrial rate of 112 bpm and ventricular rate of 56 bpm) with an excessive QT

prolongation (corrected QT interval, 860 ms) and late-appearing T wave (Fig. 1B). However, after a few minutes, ECG demonstrated VT again with following circulatory instability. Further administration of lidocaine, beta-blocker and amiodarone were ineffective. Cardiac pacing was intended to increase heart rate, but in failure. In spite of repetitive cardioversion and chest compressions, he died eighteen hours after birth. Autopsy was not performed.

There was no family history of prolonged QT interval, syncope, or sudden death. Both parents had screening electrocardiograms with normal QT intervals. There was no sibling.

Mutational analysis

Genetic DNA was extracted from venous EDTA blood of the present patient and his parents by standard procedure. Because of the ECG phenotype, all coding regions of *SCN5A* were first sequenced directly. Abnormal conformers were amplified by polymerase chain reaction, and sequencing was performed on an ABI PRISM 3100 DNA sequencer (Applied Biosystems, Foster City, California). A heterozygous deletion of TTC at nucleotide position 4456-4458 in exon 26 was detected in the present patient (Fig. 2A). No other mutations

were detected in *SCN5A*. We have also found no mutation in *KVLQT1* and *HERG* genes. This nucleotide deletion was predicted to cause an amino deletion of phenylalanine at 1486 (F1486del, III-IV linker of $Na_v1.5$). In a large control population, this mutation was absent, making it less likely that it was a rare polymorphism. Since the mutation was not identified in both parents, we considered it to be a de novo mutation.

3. Discussion

We present a notable case of a neonate with fatal LQT3 who had a novel *SCN5A* mutation associated with the III-IV linker domain of $Na_v1.5$. In the present case, the corrected QT interval (860 ms) was the longest among the LQTS patients in the previous reports [1, 3, 4]. To our knowledge, there were only seven case reports of fetal or neonatal onset LQT3 with *SCN5A* mutations [3-9]. A neonate with F1473C mutation in III-IV linker also presented the second longest corrected QT interval (825 ms) which suggested the III-IV linker plays an important role to regulate the sodium channel function [3].

Previous reports indicate that the intracellular loop between domains III and IV of $Na_v1.5$ forms the inactivation gate [10]. A three-residue

hydrophobic motif (IFM: 1485I-1486F-1487M) is an essential structural feature of the gate and serves as an inactivation particle that binds within the pore. F1486del mutation identified in the present case resulted in a deletion of the center of this hydrophobic amino acid cluster (Fig. 2B). We considered that F1486del mutation in *SCN5A* is critical to inactivate $Na_v1.5$.

The use of amiodarone was very controversial. ECG after birth was so complicated that we were unable to measure the QT interval exactly. Intravenous amiodarone might have some adverse effects, although it was described that intravenous administration of amiodarone had only little effect to QT intervals [11]. In the present case, the administration of lidocaine was unable to cease VT, although previous reports suggested the efficacy of lidocaine or mexiletine in LQT3 neonates with *SCN5A* mutations. Unfortunately, intravenous mexiletine was not available in our institute. Ruan et al. reported that the response to mexiletine varied among patients harboring different mutations in *SCN5A* [12]. It is assumed that the mutation in III-IV linker may be associated with the resistance to sodium channel blockers such as lidocaine or meciletine.

In summary, we identified a novel *de novo SCN5A* mutation in a neonate with extremely prolonged QT interval resulting in cardiac death in the first

day of life. This mutation is associated with the IFM motif in the linker between III-IV domains of $Na_v1.5$, which serves as an inactivation particle binding within the pore of sodium channels. This report demonstrates an interesting relationship between clinical phenotype and the location of the mutation and supported the importance of genetic analysis and tailored therapy in neonatal LQTS.

Acknowledgments

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [13].

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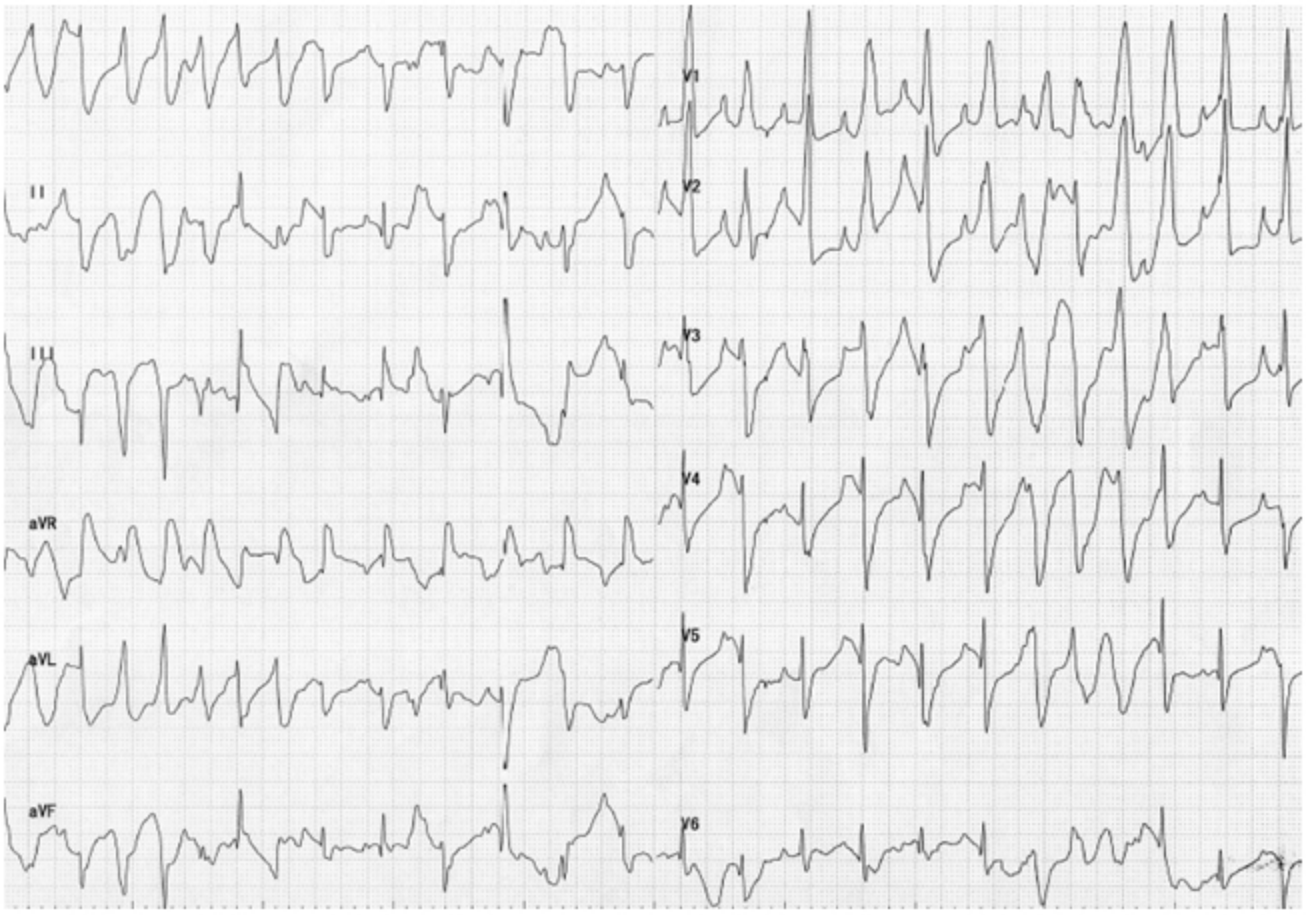
figure1

A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aVL
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V1
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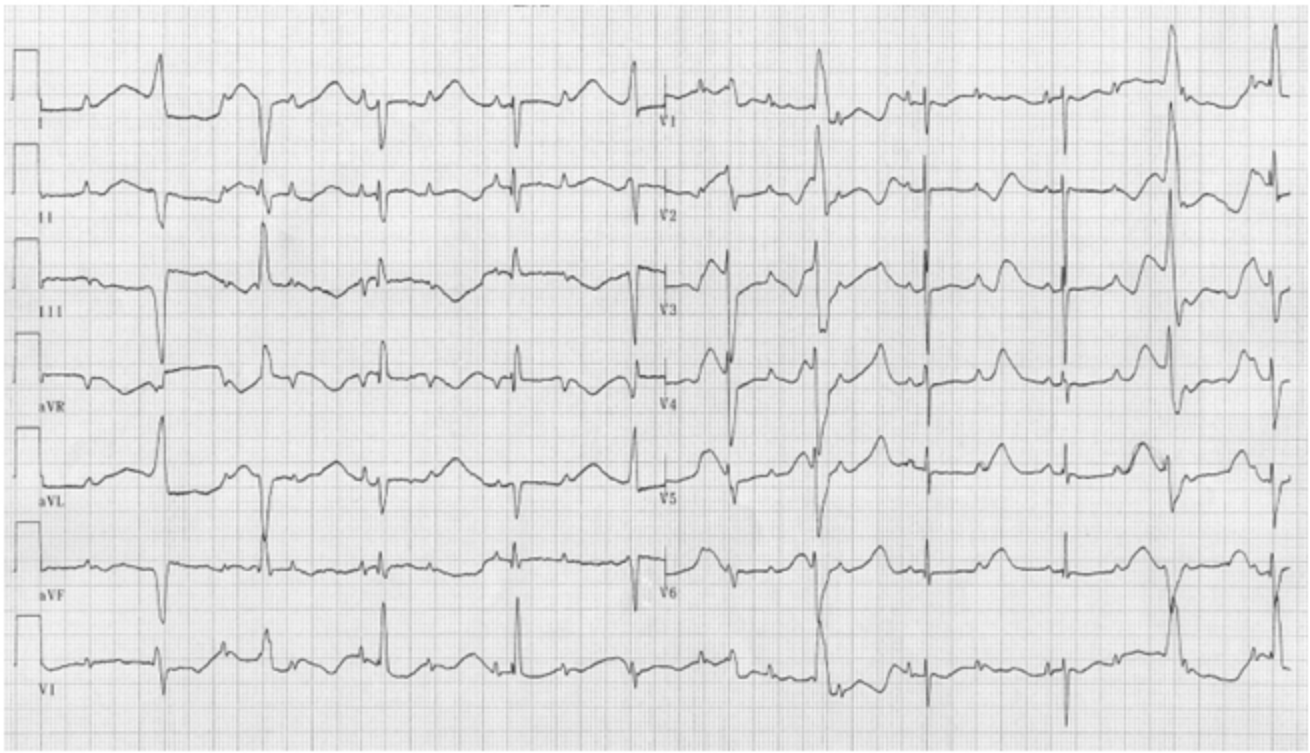
V6

B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VI
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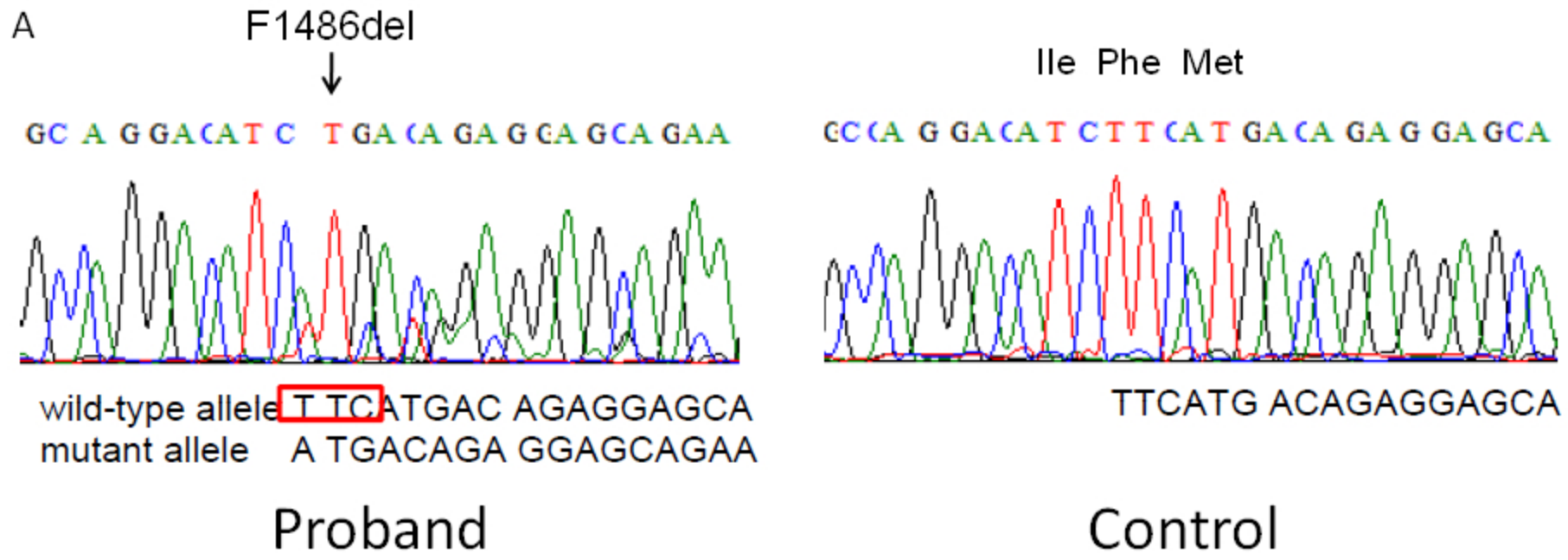
V2
V3
V4
V5
V6

Figure2


A
F1486del
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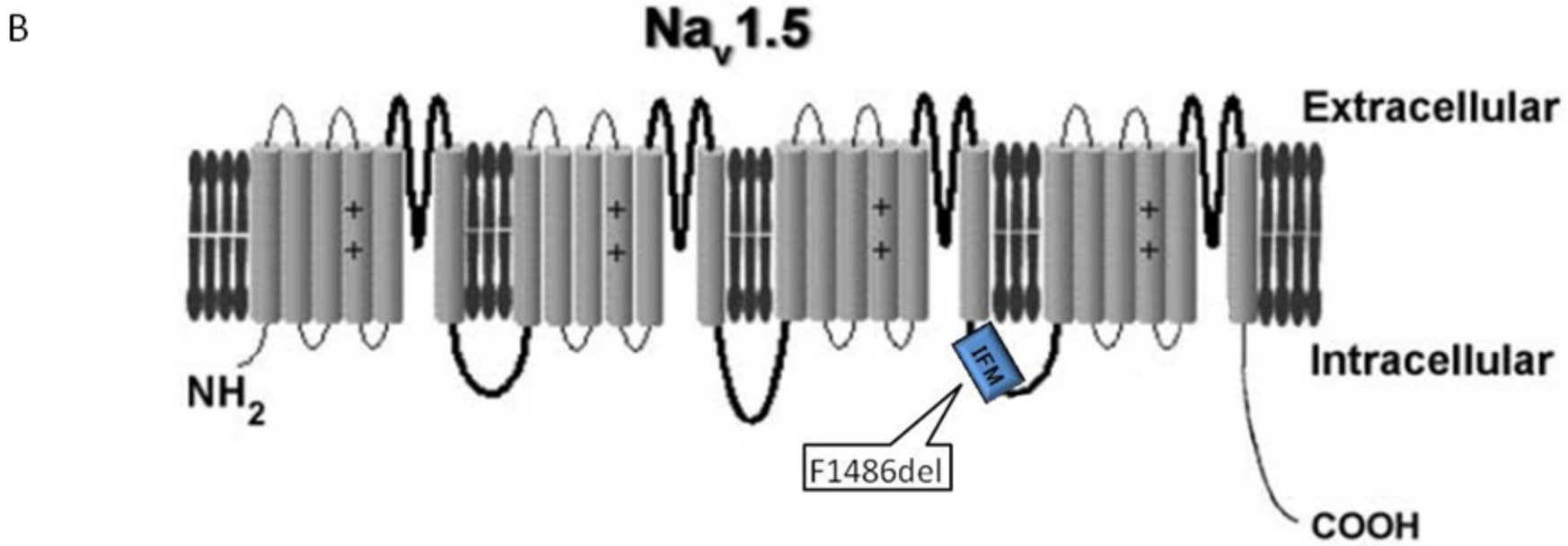
TTCATG ACAGAGGAGCA
Proband
Control


B
Na$_v$1.5
Extracellular
Intracellular
NH$_2$
IFM
F1486del
COOH