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NOVEL MUTATIONS ON SCN5A CAUSED FATAL ARRHYTHMIA SYNDROME IN CHINESE[1]

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Objectives Background SCN5A is encoding human sodium channel protein Nav1.5. Mutations on SCN5A have been found to induce multiple fatal arrhythmia syndromes, such as Long QT syndrome (LQTS), atrioventricular block (AVB) and Brugada syndrome. This study aimed to explore the pathogenic spectrum, characteristics and therapeutic outcomes of the syndromes caused by mutations on SCN5A.

Methods One LQT3 kindred and an AVB kindred from the Chinese National Channelopathy Registry Study were investigated. Blood samples and clinical data were obtained under written consents. Mutational screening of SCN5A gene was performed via PCR and direct DNA sequence analysis. LQTS or AVB phenotype and therapeutic outcomes were evaluated for all probands and family members. Genotype-phenotype evaluation was also performed for family members. Mutational analyses were based on NCBI standardised mRNA sequence (SCN5A: NM_198056.2).

Results The LQTS proband was a 1-year-old girl (test-tube baby). She had her first syncope at 9-month-old in night sleep. Afterwards several episodes of syncope occurred, often accompanied by Torsades de Pointes (TdP) and ventricular fibrillation. ECG showed a maximum QTc of 690ms, while no abnormality was found on ECG of her parents. Gene screening of SCN5A identified a novel mutation F1473S (4418 T>C) on the proband, but this mutation was not detected on the parents, indicating a de novo mutation. Medication with propranolol (2.5 mg/kg/d) alone did not improve the symptoms. Additional use of mexiletine (12.5 mg/kg/d) showed some improvement, but syncopes still occurred now and then. Then the dosage was adjusted to propranolol (2.5 mg/kg/d) and mexilatine (15 mg/kg/d). The girl died at 23-month-old, though the external defibrillator was used at home.

The AVB proband is a 57-year-old male. He showed symptoms of bradycardia, short of breath and even inability to lie down. ECG indicated complete right bundle branch block (RBBB) and

left anterior fascicular block. He has received pacemaker implantation in March of 2011 and no symptoms occurred since then. A novel mutation F919L (2757C>A) on SCN5A was found. No AVB related symptoms were found on his family members, except for RBBB showed in the ECG of his son and brother. Gene screening detected the same mutation in both persons. To note, the proband's father had sudden death at age of 57, but no DNA sample is available to determine his genotype.

Conclusions The present study revealed two novel mutations, F1473S and F919L on SCN5A, which have not been reported. The two novel mutations induced distinct but equally lethal arrhythmia syndromes, LQTS and AVB, respectively. In consider of the reports in western countries of relatively severe LQTS-causing mutation F1473C (4418 T>G) on SCN5A, we may also conclude that the site SCN5A1473 is a mutational "hot spot", which characterises an early onset and severe phenotype of LQT3.