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THE MOSAICISM GENETIC PATTERN FOR TIMOTHY SYNDROME WITH CACNA1C MUTATION G406R

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Objectives Timothy syndrome (TS), also known as LQT8, is a rare and severe form of Long QT syndrome (LQTS) and most patients are caused by the CACNA1C mutation, G406R. So far only 32 cases of TS have been reported. TS affects multiple systems and is characterised by malignant arrhythmias, syndactyly, immunodeficiency, intermittent hypoglycaemia, developmental delay, autism and evident facial features, while the arrhythmias being the major cause of death. Mosaicism signifies the presence of genetically distinct populations in the somatic and germline tissues, with tissue-to-tissue variations that may not follow Mendelian rules of inheritance. This study aimed to investigate the genotype and phenotypic characteristics of Chinese TS patients, and to determine whether mosaicism exists in Chinese TS patients.

Methods A 2-year-old girl with typical TS1 phenotypes was enrolled in Chinese National Channelopathy Register Study. Blood and oral mucosa samples of the family members and the father's sperm samples, as well as clinical data were obtained under written consents. A QTc (QT interval corrected by heart rate) >450 ms for male or>470 ms for female was considered to be QT prolongation. Mutational screening of CACNA1C gene was

performed via PCR and direct DNA sequence analysis. Genotype-phenotype evaluation was also performed for family members. Mutational analysis were based on NCBI standardised mRNA sequence (NM_000719.6). Specific primers for exon 8A was designed to amplify the mutated allele. Cloning sequencing and fluorescence quantitative PCR technique were performed to determine the quantitative distribution of mutant allele in suspected carriers of family members.

Results The baseline ECG of this infant showed markedly prolonged QTc of 580 ms, intermittent 2:1 AV block (AVB) and macro T wave alternans (TWA). Holter monitor revealed R-on-T extrasystoles during bradycardia when 2:1 AVB was present. The proband showed a typical TS1 with complete bilateral syndactyly of 2-3-4-5 fingers and cutaneously syndactyly of 2-3 left toes, a patent ovale foramen and delayed language learning skills. Candidate gene search identified G406R (1216G>A) on CACNA1C. The proband's father has congenital syndactyly, a mildly prolonged QTc at 470–490 ms and no other development retardations except for a slightly delayed language development at early age, indicating an atypical TS. Analysis of the family members' peripheral blood and oral mucosa DNA sample showed no abnormity, except for the presence of a minor 'A' peak in her father's DNA samples. The test with specific primers showed the 'A' rather than the 'G' signal at nucleotide 1216, confirming the somatic mosaicism in the father's three types of DNA samples. Via cloning sequencing technique, we found that approximately 22.2% (5 clones out of 45 colonies) of the oral mucosa cells carried the mutant allele in proband's father, his blood 17.02% (4 clones out of 47 colonies) and sperm 3.75% (3 clones out of 80 colonies).

Conclusions The present study is the first report of calcium channel mutation causing LQTS in Chinese patients. In addition, we have found a rare inherited pattern—mosaicism genetic pattern–in this TS family, indicating that an individual with mild phenotype may be a genetic mosaic and his child could have severe phenotype once inherited the mutated allele. This finding should give strong implication for considering the possibility of genetic mosaicism when gene screening shows a 'De novo' mutation in order to assist genetic counselling.