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Letter to the Editor

Dravet syndrome with autism inherited from a paternal mosaic heterozygous mutation on SCN1A

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Dear Editors,

Dravet syndrome (DS), which is an autosomal dominant epileptic disorder primarily caused by a heterozygous mutation in voltage-gated sodium channel type I α subunit (SCN1A) gene, is a relatively rare intractable childhood epilepsy with an estimated incidence of 1 per 40,000 live births [1–3]. Here, we report on the father, who exhibits mosaicism, and his two affected children, who exhibit the Dravet syndrome phenotype. All three individuals share the same point mutation, c.4284 + 2T>C.

Physical and neurological examinations were performed for all available family members enrolled in this study, and detailed information on family history was collected. The 15-year-old proband, whose myoclonic seizures were first triggered by fever at 6 months after birth, has the capacity to pronounce monosyllabic words and recite advertising words but displays impaired social interaction, gait disturbances and sialorrhea symptoms; his body weight was below the 5th percentile during development. The Romberg test was negative. His symptoms and seizures were in remission due to treatment with anticonvulsant drugs, including valproic acid and topiramate, which had reduced his frequency of seizure recurrence to two or three episodes per month, with each episode lasting for 1 to 2 min. To further investigate the etiology of the disease on the genetic level, blood samples were collected for denaturing high performance liquid chromatography (dHPLC) to examine the exons of the SCN1A gene. Subsequent mutation sequencing of a blood sample showed a point mutation, c.4284 + 2T>C. The final clinical diagnosis of the proband was Dravet syndrome with autistic tendencies.

The proband's father has had a limited number of seizures since 12 years of age. And myoclonic seizures with slobbering or absence seizures even with syncope episodes were only triggered by the chill stimulation or excessive fatigue, not fever. A blood sample showed that he carries the same mutation of the SCN1A gene but displays distinct symptoms that are milder than those of his son, including mild mental retardation and a lack of distinction with respect to living independently and occupational skills.

The proband's 3-year-old brother also shares the same SCN1A point mutation, which was first identified by extracting genomic DNA from the cells of the amniotic fluid at thirteen weeks gestation. He was born by uterine-incision delivery and also diagnosed with Dravet syndrome. The clinical onset of tonic seizures involving his limbs was triggered by influenza when he was 9 months old. No other abnormal symptoms, such as flowing sputum, have been observed. The seizures are usually relieved after 2 min. Compared with age-matched peers, no significant differences in motor function are apparent. His growth and development are relatively normal, and he has not been treated regularly with anticonvulsant drugs.

No point mutation has been identified in the proband's sister, who was born by uterine-incision delivery in 2015. The proband's mother is a healthy and normal-functioning individual.

The informed consent for tissue donations was obtained from the family members. The mutation screening of the peripheral blood cells and in vitro cultured fibroblasts was performed by whole exome sequencing (WES) and splice site sequencing (SSS) of the SCN1A gene to cover the potential mutation points of the splice sites. The experimental methods are presented in Supplementary methods. We then compared the sequencing results of the affected individuals with those of the unaffected mother, a healthy individual, and data downloaded from the NCBI database (NG_011906.1, NM 001165963.1).

According to the results of WES and SSS (Fig. 1A), the affected family members in this study all share the same heterozygous c.4284 + 2T>C mutation in the SCN1A gene, caused by a T to C transition in the second intron at the downstream of nucleotide position 4284, which suggests that the mutation may cause familial DS. Furthermore, previous studies showed that 95% reported mutations of the SCN1A gene associated with DS are de novo, while few of them occurred in familial cases [2,4]. Nevertheless, this percentage may be an overestimation, since some familial cases have been historically overlooked before the finding of de novo SCN1A mutations [5].

A heterozygous c.4284 + 2T>C mutation in the splice donor site of the SCN1A gene, causing the deletion of exon 21 [6], has been detected (Fig. 1B). This mutation may lead to a deficiency of the S5 segment (1350 aa to 1377 aa), which is a part of the loop between the S4 and S5 segments (1335 aa to 1350 aa), and the pore loop between the S5 and S6 segments (1377 aa to 1428 aa) in domain III (Fig. 1C). Current studies have demonstrated that the Nav1.1 channel is susceptible to impairments caused by SCN1A mutations in the pore region [7]. On the protein level, the c.4284 + 2T>C mutation of the SCN1A gene may cause complete loss-of-function, which may be the etiology of DS in this family.

A homozygous mutation in the SCN1A gene, c.3199G>A, detected in all family members' and in a healthy Chinese individual's genome (CJ) (Supplemental Fig. 1A and B), is recorded as a missense variant in the UCSC SNP database, suggesting that the conversion caused by the homozygous c.3199G>A mutation on exon 16 of the SCN1A gene may be race-specific. We also identified several other novel intronic variants among the individuals enrolled in this study (Supplemental Table 2). Some of these variants are presented on dbSNP (www.ncibi.nlm.gov/SNP/), and some are not.

Previous studies of SCN1A revealed that mutations of this gene are associated not only with DS but also with a variety of other types of

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epilepsy, familial hemiplegic migraines, and autism [8,9]. The clinical features of the proband were consistent with DS with autistic tendencies.

The sequencing results reported herein demonstrate that the c.4284 + 2T>C point mutation of the SCN1A gene exists in the peripheral blood cells of the proband's father, but not in the fibroblasts, suggesting that the proband's father has mosaicism (Fig. 1A, Supplemental Fig. 2). No other sense mutations of the SCN1A gene was observed among affected family members. The reported paternal or maternal mosaic mutation, which can be inherited by the next generation, is generally distributed across all tissues of the affected individual including somatic cells and germline [10,11]. The mosaic mutation mentioned above refers to a de novo sense mutation. In this case, a mosaic mutation refers to the same sense mutation distributed non-uniformly among different

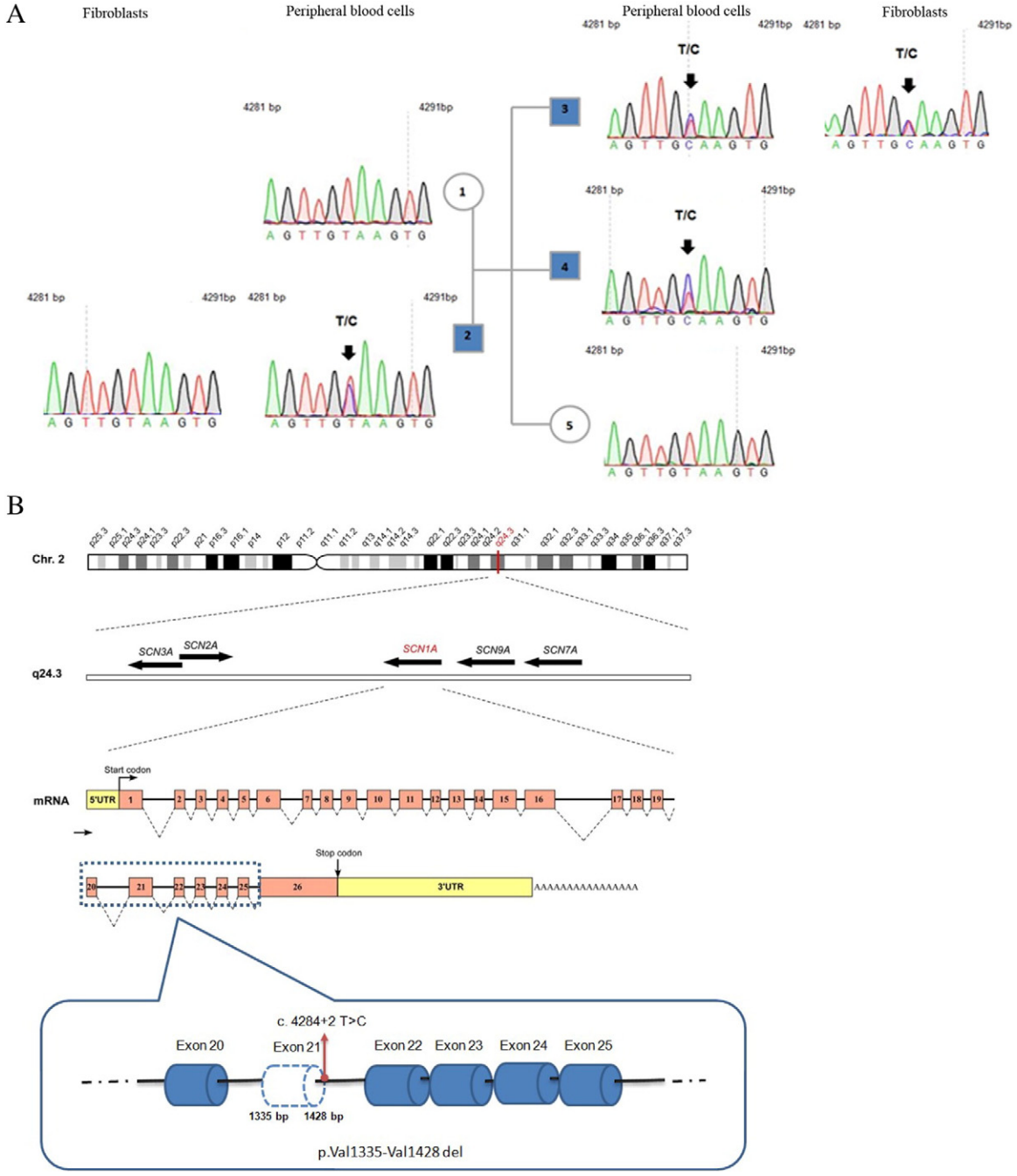

Fig. 1. The c.4284 + 2T > C mutation of the SCN1A gene. A) The family members are labeled as number 1 to 5 (proband's mother, proband's father, proband, proband's brother and proband's sister, respectively). A c.4284 + 2T>C point mutation of the SCN1A gene was detected in the peripheral blood cells of the proband, the proband's brother and the proband's father. And the mutation was not identified in the fibroblasts of the proband's father, but in the proband's. In the sequencing result, a split-blip representing the mutation appeared and shows a T (shown in red) to C (shown in blue) transition. B) SCN1A, encoding Nav1.1, is located from base pair 165,989,159 to base pair 166,149,131 on the long (q) arm of human chromosome 2 at position 24.3 (2q24.3). The SCN1A gene has 26 exons spanning approximately 100 kb of genomic sequence, which (shown in red) encodes the full-length of adult Nav1.1 (http://www.gzneurosci.com/scn1adatabase/). A c.4284 + 2T>C point mutation of the SCN1A gene causes the deletion of exon 21 (shown in the white column with the blue dashed line) from Val 1335 to Val 1428. C) The α subunit of sodium channel Nav1.1, which is encoded by the SCN1A gene, contains the voltage sensors and the ion-conducting pore in homologous domains (III to IV), each of which contains six α-helical transmembrane segments (S1–S6) and a pore loop between S5 and S6. The S4 segment confers the voltage-gating channel properties (shown in red). Each domain is connected by the cytoplasmic loop. A c.4284 + 2T>C point mutation of the splice donor site on SCN1A causes a deficiency of the S5 segment (1350 aa to 1377 aa), part of loop between the S4 and S5 segment (1335 aa to 1350 aa), and the pore loop between the S5 and S6 segment (1377 aa to 1428 aa) in domain III.