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Case Report

A Novo SCN1A Mutation Identified in a Chinese Family with Dravet Syndrome: A Case Study

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2. Key words

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1. Abstract

Dravet syndrome (DS), also known as severe myoclonic epilepsy of infancy (SMEI), is one of the rare early childhood intractable epileptic encephalopathies associated with pleomorphic seizure activity, cognitive decline, motor, and behavioral abnormalities. The convulsive seizure is the most common type seen in DS [1]. After the first episode of seizure-like activity, behavioral disorders and cognitive decline are progressive and long-lasting. The most common etiology identified in patients with DS is a de-novo genetic mutation alpha-1 subunit of the voltage-gated calcium channel gene (SCN1A) [1]. In this case, we report a 2.5-year-old Chinese male patient with Dravet syndrome due to a de-nove mutation c.2856G>A (p.Trp952X) in the SCN1A gene. This is a first report of this mutation in the Chinese population. This variant was evaluated as a pathogenic mutation based on the standards and guidelines of ACMG (American College of Medical Genetics and Genomics).

3. Brief Structured Abstract

3.1. Background: Dravet syndrome (DS) is considered to be one of the most severe types of genetic epilepsy. A previous study [5] reported one British male patient carried a nonsense mutation c.2856G>A (p.Trp952X) in the SCN1A gene among 1023 British patients with epilepsy, and the mutation is thought to be the cause of the disease. However, the inheritance of the mutation remains unknown. In this study we detected the same the mutation in a 2.5-year-old male Chinese patient with DS, among 239 Chinese patients with epilepsy. This is the first report of this mutation in the Chinese population.

3.2. Case Report: A 2.5-year-old male who was born with no family history of seizures or other types of neurological diseases, has experienced complex febrile seizures (CFS) since he was 10 months old. In order to identify the causes of his seizures, we conducted a Whole Exome Sequencing (WES) based on Next-generation sequencing, a heterozygous nonsense variant in SCN1A gene (c.2856G>A, p.Trp952X; reference transcript, NM_001165963) was detected in the patient. This variant was further confirmed by Sanger Sequencing, and not detected in either of the healthy parents, which indicated that this variant was de-novo. This variant was evaluated as pathogenic mutation based on the standards and guidelines of ACMG.

3.3. Conclusion: The identification of a de-nove mutation in the SCN1A gene (c.2856G>A, p.Trp952X) in the Chinese patient may further aid in the understanding of the causes of Dravet Syndrome.

4. Introduction

The genes which are related to DS or SMEI include SCN1A, SCN8A, STXBP1, GABRG2, SCN1B et al., and the SCN1A mutations take the major responsibilities for the disease. The mutations of *SCN1A* gene is associated with malfunction of sodium channel which may cause different epilepsy syndromes ranging from mild febrile seizure to some autosomal dominant diseases that can trigger severe myoclonic epilepsy in infants, also known as DS [2]. DS is a rare disease with an unclear prevalence ranging between 1/20,000 and 1/40,000 in different publications [3]. The syndrome is considered to be one of the most severe types of genetic epilepsy. Based on the research report in the Clinvar database, around 300 SCN1A mutations have been identified to be responsible for DS, and about 65% of these mutations render de-novo. A previous study [5] reported one British male patient carried a nonsense mutation c.2856G>A (p.Trp952X) in the SCN1A gene among 1023 British patients with epilepsy, and the mutation is thought to be the cause of the disease, however the inheritance of the mutation remains unknown.

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5. Case Report

A 2.5-year-old male who was born with no family history of seizures or other types of neurological diseases, has experienced complex febrile seizures (CFS) since he was 10 months old. Most of the seizures he experienced were presented as tonic-clonic seizure which lasted approximately one minute in length. The same symptom was triggered by a fever when he was 12 months old, but reoccurred with lower fever or without fever after he was one year old. The patient experienced tonic-clonic seizure without a fever since he was 2-year-old, so the clinical diagnosis was changed from complex febrile seizures to dravet syndrome. As displayed in (Figure 1), the patient's Electroencephalography (EEG) showed slow waves (single edge state) with no obvious epileptiform abnormalities despite his typical clinical features. Antiepileptic drugs of Sodium Valproate, Topiramate were prescribed, and the improvement of the syndromes of the patient was observed, as the patient experienced seizures from 10 more times yearly down to 1 or 2 times yearly.

In order to identify the causes of his seizures, we conducted a Whole Exome Sequencing (WES) based on Next-generation sequencing, a heterozygous nonsense variant in SCN1A gene (c.2856G>A, p.Trp952X; reference transcript, NM_001165963) was detected in the patient. The mutation does not exist in either the Chinese population or any other populations and was predicted to be pathogenic because it is located at conserved amino acid residues at the domain IV of SCN1A pathogenic or damage. This variant was further confirmed by Sanger Sequencing, and not detected in either of the healthy parents, which indicated that this variant was de novo (Figure 2). This variant was evaluated as pathogenic mutation based on the standards and guidelines of ACMG. No other pathogenic variants were detected in more than 800 genes that were defined by the OMIM database as related to epilepsy syndromes for this patient.

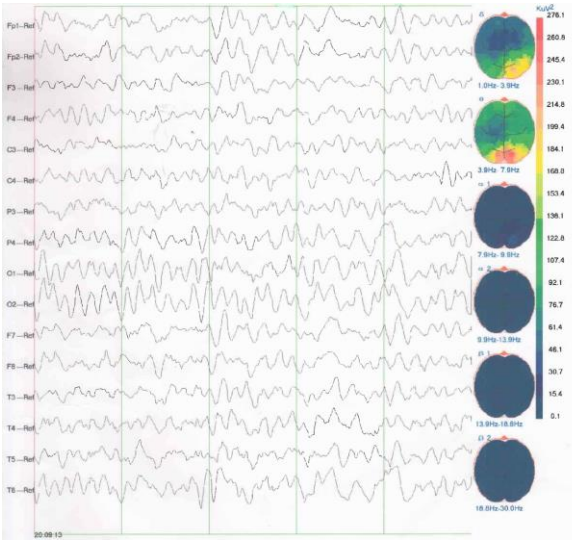

Figure 1: The patient's Electroencephalography (EEG) showed slow waves (single edge state) with no obvious epileptiform abnormalities

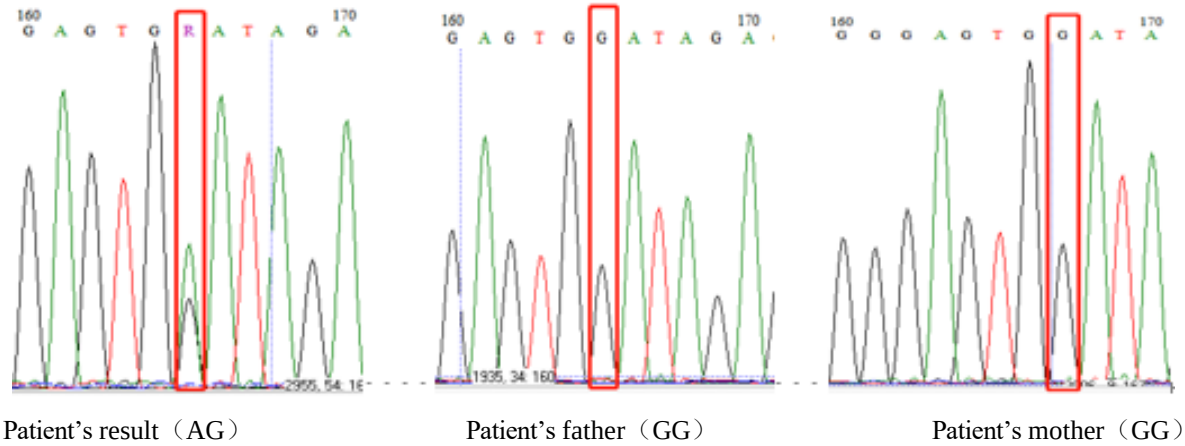

Figure 2: Sanger sequencing of the SCN1A gene mutation (c.2856G>A , p.Trp952X). A: sequencing result of the patient showed a heterozygous G-to-A de novo transition (red rectangle) at codon 2856 resulting in amino acid exchange (G->A; Trp->X). B and C: Wild-type sequence in patient's father and mother (red rectangle).

6. Discussion

In this case, we evaluated WES data from 239 Chinese patients with epilepsy and identified the de-nove nonessense mutation in SCN1A in one patient with DS. A previous study [5] reported one British patient carried the same mutation c.2856G>A (p.Trp952X) in the SCN1A gene among 1023 British patients with epilepsy, and the mutation was thought to be the cause of the disease. However, the inheritance of the mutation is unknown. Our data found that the mutation occurred in a Chinese patient with DS, among 239 patients with epilepsy and confirmed that the mutation is de-nove.

The mutation of the SCN1A gene we detected (c.2856G>A (p.Trp952X) has not been recorded in the Clinvar database as of today [6]. Our report provided further evidence for the cause of DS from a genetic level. Based on these studies, the interpretation of the clinical significance of this mutation in the Clinvar database may need to be modified accordingly.

Our identification of this de-nove mutation of SCN1A is also helpful for advancing our understanding of the role of SCN1A in DS. It provides a deeper insight for understanding SCN1A mutations in terms of its association with a broader clinical spectrum of seizures. Research showed that the absence of mutations in parental DNA, obtained from peripheral-blood lymphocytes are able to interfere with the usual mechanism that involves a spontaneous mutation in SCN1A in parental gonadal tissue (i.e., testicular or ovarian cells) [4].

7. Conclusion

The identification of a novel mutation in the SCN1A gene (c.2856G>A, p.Trp952X) in the Chinese patient may further aid in the understanding of the causes of Dravet Syndrome.

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