

## A GRIN2A Mutation (C.2T>C, P. Met1Thr) Identified in A Chinese Family with Epilepsy: A Case Study

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Received: 05 Apr 2022

Accepted: 21 Apr 2022

Published: 27 Apr 2022

J Short Name: AJSCCR

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### Citation:

Jianxiong Duan. A GRIN2A Mutation (C.2T>C, P. Met-1Thr) Identified in A Chinese Family with Epilepsy: A Case Study. *Ame J Surg Clin Case Rep.* 2022; 4(11): 1-3

### Keywords:

Chinese; Epilepsy; GRIN2A gene

### Abbreviations:

Glutamate Ionotropic Receptor NMDA type subunit 2A (GRIN2A); Landau-Kleffner Syndrome (LKS); Magnetic Resonance Imaging (MRI); Whole Exome Sequencing (WES); American College of Medical Genetics and Genomics (ACMG); Online Mendelian Inheritance in Man (OMIM); Human Gene Mutation Database (HGMD)

## 1. Abstract

**Objective:** To investigate the genetic causes of epileptic seizures in an 11-year-old Chinese male proband who had experienced them since he was five-year-old.

**1.2. Methods:** Clinical diagnosis and next-generation sequencing.

**1.3. Results:** The proband carries a heterozygous missense mutation (c.2T>C, p. Met1Thr) in the GRIN2A gene. This mutation was also found in the two affected family members including proband's father and his elder sister. This mutation was evaluated as a pathogenic mutation based on the standards and guidelines of ACMG, clinical database, and research publications.

**1.3. Conclusion:** The heterozygous missense mutation (c.2T>C, p. Met1Thr) in the GRIN2A gene is the genetic cause of the epileptic seizures for the 11-year-old Chinese proband and his affected family members. So far, this is a first report of this mutation of GRIN2A gene associated with epilepsy in the Chinese population.

## 2. Introduction

The GRIN2A gene is located on the short arm of human chromosome 16 (16p13.2). Disruption of this gene is associated with speech disorders and epilepsy, and the diseases are inherited in an autosomal dominant manner<sup>[1]</sup>. In this paper, we report a heterozygous mutation (c.2T>C, p. Met1Thr) in the GRIN2A gene which

is carried by three members of a Chinese family with epilepsy, including an 11-year-old male proband, his 13-year-old sister and their father. This mutation was evaluated as a pathogenic mutation based on the standards and guidelines of ACMG. Even though this mutation was previously reported in 3 members of an Austrian family with Landau-Kleffner Syndrome (LKS), this mutation has not yet been reported in either the Chinese population nor in Chinese patients with epilepsy.

## 3. Materials and Methods

### 3.1 Clinical diagnosis

An 11-year-old male Chinese proband who experienced an onset of sudden seizure when he was 5-year-old. The seizures happened again after 15 days and occurred an additional 4 to 5 times, which each instance involving 1 to 2 episodes of the seizures. The syndromes mainly included stiffness and convulsions of the arms and legs, blue lips, and bilateral eversion. The proband was hospitalized in earlier June of 2015 (Chengdu Shengkang Epilepsy Hospital), and the general physical examinations, MRI and EEG were performed. The same tests have also been carried on annually since the patient was discharged from the hospital.

### 3.2. Family history

The proband's 13-year-old elder sister had a sudden onset of ep-

ileptic seizures when she climbed up a flight of stairs at the age of five. She looked pale and experienced a convulsion on her right lower limb, but she showed a clear consciousness during the seizures. The symptoms lasted for approximately five minutes. The seizures happened again after one year and became more frequent as time went by. She was hospitalized (Chengdu Shengkang Epilepsy Hospital) on July 2015, and underwent the physical examinations, MRI and EEG. Since then, the same tests were performed annually. The proband's 36-year-old father experienced a single seizure when he was five-year-old, and the seizure never occurred again even without any medical treatment. The proband's 38-year-old mother is in good health condition.

### 3.3 Molecular Test

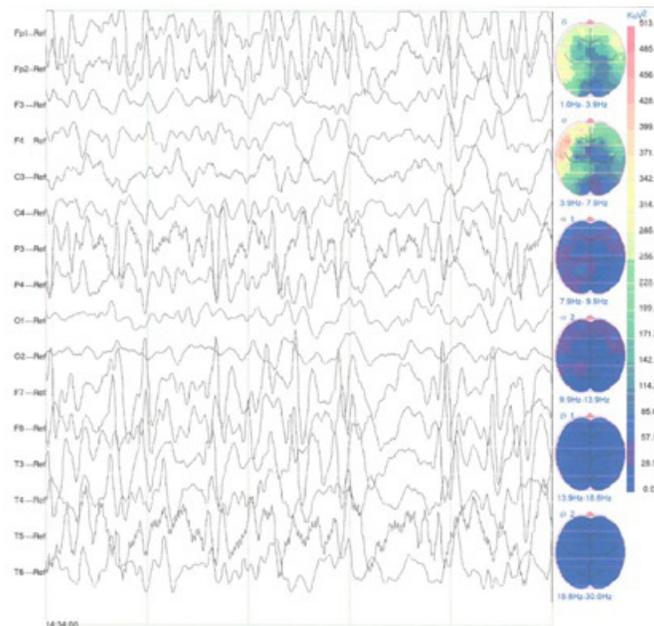
In order to study the cause of the epilepsy disease, a whole exome sequencing was performed for the proband. Furthermore, Sanger sequencing was used to verify the pathogenic mutation for the proband, the proband's affected elder sister and father, and his unaffected mother. Sequencing data was analyzed by using numerous bioinformatics' software and by professional analysis. The pathogenicity of the mutation was evaluated based on the standards and guidelines of Clinvar database, American College of Medical Genetics and Genomics (ACMG), Online Mendelian Inheritance

in Man (OMIM), Human Gene Mutation Database (HGMD), and clinical research papers that were published in scientific journals.

## 4. Results and Analysis

### 4.1 Clinical Data Analysis

The proband's physical examinations indicated no abnormality in his heart, lung, and abdomen. Blood routing and hematuria screening were normal as well. Brain MRI showed no abnormality in the proband's brain parenchyma. However, as displayed in Figure 1, the EEG showed sharp-and-slow-complex wave of amplitude, ratchet, and slow complex wave discharges. Even though the proband's elder sister had a normal physical examination as well, her MRI showed white matter degeneration in the brain. The EEG showed sharp and slow wave complexes, which were more severe on the left side. The EEG showed the similar results for both siblings. Sodium valproate 0.5 mg/BID, Levetiracetam 0.5 mg/BID, and Lamotrigine 50 mg/BID were prescribed for both of the siblings after they were hospitalized. Since then, the seizures for both have been controlled well, with no additional occurrences of seizure in more than five years, excepting for the proband's elder sister who experienced a brief episode during her first menstruation. However, the EEGs for both siblings never being improved and always showed sharp and slow-wave complexes to date.



**Figure 1:** The proband's abnormal Electroencephalography (EEG) shows sharp and slow complex wave of amplitude, ratchet and slow complex wave discharges.

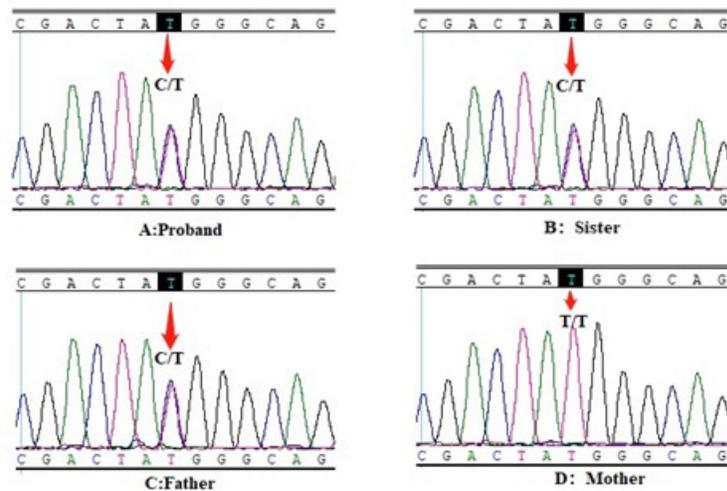
### 4.2. Molecular Biological Data Analysis

In order to identify the genetic causes of the proband's epileptic seizures, we conducted Whole Exome Sequencing (WES) based on Next-generation sequencing for the proband. We identified a heterozygous mutation c.2T>C transition in exon 2 of the GRIN2A gene, resulting a met1-to-thr (MIT) substitution (reference transcript, NM\_001134407). This mutation was further confirmed

by using Sanger Sequencing method and proved that the mutation is carried by the proband (Figure 2-A), proband's elder sister who had the similar syndromes and EEG with the proband (Figure 2-B, and the proband's father, who had a single episode of epileptic seizure at the age of five (Figure 2-C. The mutation was not detected in the proband healthy mother (Figure 2-D). The mutation of c.2T>C in the GRIN2A gene has not been recorded in Human ge-

nome databases (1000 Genome and Genome Mutation Frequency Database). This mutation was evaluated as a pathogenic mutation

based on the standards and guidelines of ACMG and clinical research publications. So far, this mutation of GRIN2A gene related with epilepsy is the first case reported in the Chinese population.



**Figure 2:** Sanger sequencing of the GRIN2A gene mutation (c.2T>C, p.Met1Thr). A, B and C: The proband (A), proband's elder sister (B), and their father (C), all carry a heterozygous mutation in the GRIN2A gene (c.2T>C), that results a Met1-to-Thr (MIT) substitution (red arrows). D: Wild-type sequence in proband's mother (red arrows).

## 5. Discussion

The GRIN2A provides instructions for making a protein called GluN2A. This protein is found in nerve cells in the brain and spinal cord. Pathogenic mutations in the GRIN2A gene can cause a spectrum of neurodevelopmental disorders that can include epilepsy, speech and language disorders, and developmental delays. The epilepsy syndromes that the mutations of GRIN2A can include but not limited to: Landau-Kleffner syndrome (LKS), epileptic encephalopathy with continuous spike-and-wave during sleep, childhood epilepsy with Centro temporal spikes, and atypical childhood epilepsy with Centro temporal spikes [1]. The mutation (c.2T>C, p.Met1Thr) in the GRIN2A gene is a heterozygous T-to-C start-loss/missense mutation in codon2 of exon 2. The alteration of this translation is likely to have detrimental effects on the GRIN2A protein synthesis, resulting in either complete absence of product due to failure of translation initiation at the start codon, or a truncated protein stemming from translation initiation at an alternate start codon [2]. We evaluated more than 400 Chinese patients with epilepsy by next-generation sequencing, and identified a mutation of the GRIN2A gene (c.2T>C, p.Met1Thr) in an 11-year-old male proband. This mutation was evaluated as a pathogenic mutation based on the standards and guidelines of ACMG, clinical database, and research publications. A further test (Sanger sequencing) confirmed that the same mutation was carried by his affected elder sister and their father. The three affected family members all had an onset of epileptic seizures at the age of five. The same mutation (c.2T>C, p.Met1Thr) of GRIN2A gene has been previously detected in an Austrian family, with the mutation detected for two sisters with Landau-Kleffner Syndrome (LKS) and their affected

father, but not detected in another sister who has febrile seizures and their mother who also has speech disorder problems [2]. Even though the mutation (c.2T>C, p.Met1Thr) in the GRIN2A gene was detected in the both of the Austrian family and Chinese family, the main symptoms of the disease were different. In the Austrian family, the two sisters and their father have aphasia and epilepsy. However, in the Chinese family, all affected members experienced epileptic syndromes, but all had normal hearing. In addition, Even though all three affected members of Chinese family carry the same pathogenic mutation (GRIN2A c.2T>C, p.Met1Thr), the severity of the epileptic syndromes are different as the two siblings experienced more severe and longer periods of epileptic seizures than their father. This may be considered as the expressions of incomplete penetrance, and indicated that the same gene mutation in different genetic backgrounds will lead to different clinical manifestations.

## 6. Conclusion

The heterozygous missense mutation (c.2T>C, p.Met1Thr) in the GRIN2A gene is the genetic cause of the epileptic seizures for the 11-year-old Chinese proband and his affected family members. So far, this mutation of GRIN2A gene related with epilepsy is the first case reported in the Chinese population.

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