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Identification of Autosomal Dominant Lateral Temporal Epilepsy Caused by A Novel Mutation in Reln in China

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1. Abstract

1.1. Purpose: Temporal lobe epilepsy is the most common focal epilepsy, whereas the genetic factors usually be ignored. Reelin (RELN) gene has been considered as the second pathogenic gene of Autosomal Dominant Lateral Temporal Epilepsy (ADLTE), mutation in which is rarely discovered in Chinese. A family with ADLTE caused by a novel missense mutation in RELN is explored in this paper.

1.2. Patients and Methods: The clinical data of an 8-year-old boy who had experienced general convulsions during sleep for 7 years was analyzed retrospectively. His mother also had a history of epilepsy since 1 year, in addition, a glioma was found when she was in pregnancy. A gene sequencing test was performed on the proband and his family members.

1.3. Results: The gene test results showed there were two most probable gene mutations related to epilepsy. A clear diagnosis of ADLTE was made after identifying the missense mutation in RELN (c.1799 C>T) as the pathogenic factor, his mother also carried the same mutation. The proband had no seizures after the treatment of levetiracetam (500mg twice daily), but his mother died from the recurrence of glioma several months ago.

1.4. Conclusion: Mutation in RELN is rarely explored in ADLTE of Chinese. Genetic factors should be paid more attention in temporal lobe epilepsy. Once genetic factor was identified as the pathogenesis, anti-seizure medications should be taken all the time. Otherwise, mutation in RELN is also related to the occurrence and development of glioma.

2. Introduction

Temporal Lobe Epilepsy (TLE) is the most common focal epilepsy [1]. However, the genetic factors of patients with TLE are usually ignored. The first case of Familial Temporal Lobe Epilepsy (FTLE) was reported in 1895, which described the clinical manifestations in 4 generations of a family with epilepsy [2]. It was reported in twins in 1994 [3], marking the beginning of hereditary studies of TLE. The following year, FTLE was reported for the first time in non-twin patients [4].

FTLE comprises 2 syndromes, Family Mesial Temporal Lobe Epilepsy (FMTLE) and Autosomal Dominant Lateral Temporal Epilepsy (ADLTE) [5]. The former is characterized by psychic and autonomic seizures and considered as a benign syndrome [6]. Most patients have no history of febrile seizures and no signs of hippocampal sclerosis. Genetics studies on FMTLE have mainly been at the level of chromosome. The DEP Domain-Containing Protein 5 (DEPDC5) has been linked to various types of familial focal epilepsy, including familial focal epilepsy with variable foci, autosomal dominant nocturnal frontal lobe epilepsy [7], benign

childhood epilepsy with centrotemporal spikes [8], focal cortical dysplasia [9], and FTLE. The rate of sudden unexpected death in epilepsy is higher in patients with DECDP-5 mutations than in those without mutations in this gene [9]. Nevertheless, there is no evidence that DECDP-5 is related to FMTLE or ADLTE, except for a nonsense mutation of DECDP-5 that was described in an FMTLE family in 2015 [7].

ADLTE was first reported in 1995 [4], the age of onset ranging from 1 to 60 years old [10]. A typical feature of ADLTE is auditory aura, that mostly associated with simple sounds such as voices, but sometimes with complex sounds such as music. It is also known as Autosomal Dominant Partial Epilepsy with Auditory Features (ADPEAF). Around 10% of patient's experience déjà -vu and fear just as mesial TLE, 90% of patients present focal to bilateral tonic–clonic seizures which usually occur during sleep. The history of febrile seizure is not common, and most patients' brain Magnetic Resonance Imaging (MRI) are normal. Abnormal discharges in the left hemisphere have always been observed in electroencephalogram (EEG) [11]. Several genes have been explored linked to ADLTE, such as Leucine-Rich Glioma Inactivated 1 (LGI1), reelin (RELN), and Molecule Interacting with Casl 1(MICAL-1). LGI1 is the main pathogenic gene and is mutated in 50% of ADLTE families. Mutations are located on 10q22–24 and were first identified in 2002 [12]. As the encoded protein is not an ion channel, the mechanistic link between these mutations and ADLTE is unclear. RELN is the second most frequently mutated gene in ADLTE, is located on 7q22.1 and encodes a large secretory protein. Mutations cause protein misfolding, which decreases the serum level of the protein and alter its secretion, resulting in functional abnormalities [13]. There are no obvious differences between ADLTE patients with LGI1 and RELN mutations except for left-sided EEG abnormalities in the latter [11]. Reelin and LGI1 have similar expression patterns in the cerebral cortex and hippocampus, suggesting that they act coordinately [13]. Mutation of MICAL-1 has been reported in 3 ADLTE families but was only clinically meaningful in 2 of the families. A possible pathogenic mechanism of MICAL-1 mutation is an increase in monooxygenase activity that impairs actin cytoskeleton dynamics and structure.

Most Anti-Seizure Medications (ASMs) are effective for the treatment of ADLTE, including carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, and topiramate, whereas only few patients respond to valproicacid [15]. However, there was no study comparing the efficacy of these medications directly. Nevertheless, 4 members of a family with FTLE that confirmed by intracranial EEG were successfully treated by surgery [16], although their clinical features differed from those of ADLTE. Here we report a family of ADLTE caused by a novel missense mutation in RELN.

3. Patient Information

3.1. Subjects and Family History

An 8-year-old boy was admitted to Epilepsy Centre on Nov. 11, 2019 with a 7-year history of paroxysmal seizures. The first convulsion occurred when he was 1-year-old after a fever with a temperature of 38.4%. The mouth was shut, and the limbs were straightened and stiff, which relieved spontaneously after 1 min. Similar convulsions occurred following low-grade fever (37.2%–37.5%) every year in the next 4 years, with no aura experienced. The patient was given levetiracetam 250 mg twice daily at the age of 4 years old and after that there was no seizure happened again. Levetiracetam was gradually discontinued when the proband was 6 years old. After that, the patient experienced frequent stumbling even when there was no obstacle at all. In 2021, the patient had another 6 convulsions occurred during sleep, of which 3 happened after low-grade fever and 3 were afebrile.

An examination of family history revealed that the patient's mother had experienced similar symptoms (Figure 1). The first seizure occurred when she was 1-year-old, the second during pregnancy, and the third when she was working at night. An MRI examination of brain revealed a glioma in her left temporal lobe, which was removed by surgery. However, his mother experienced seizure again 5 years later and was given sodium valproate 500 mg twice daily, after which there were no further seizures.

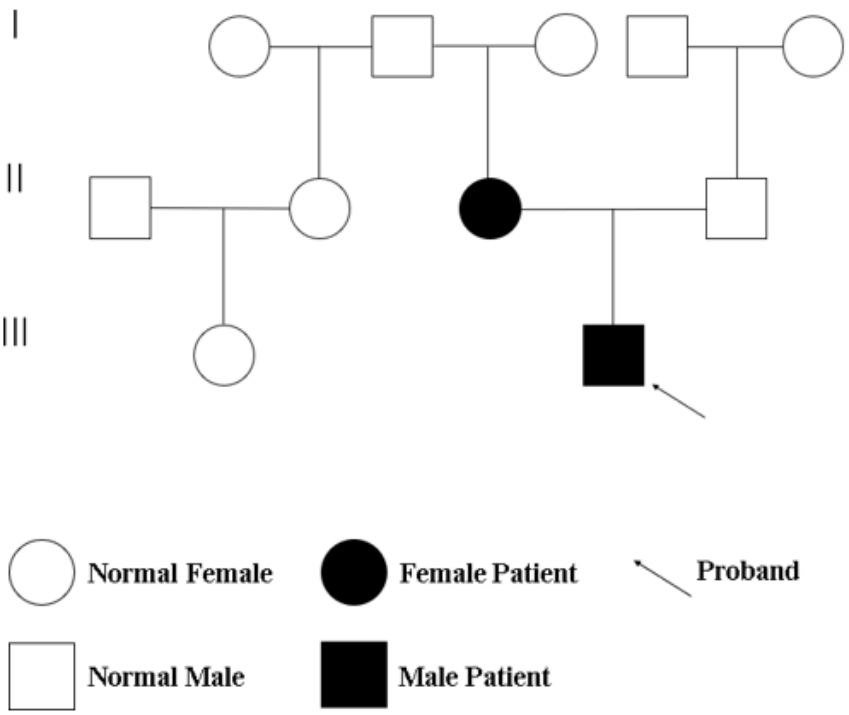
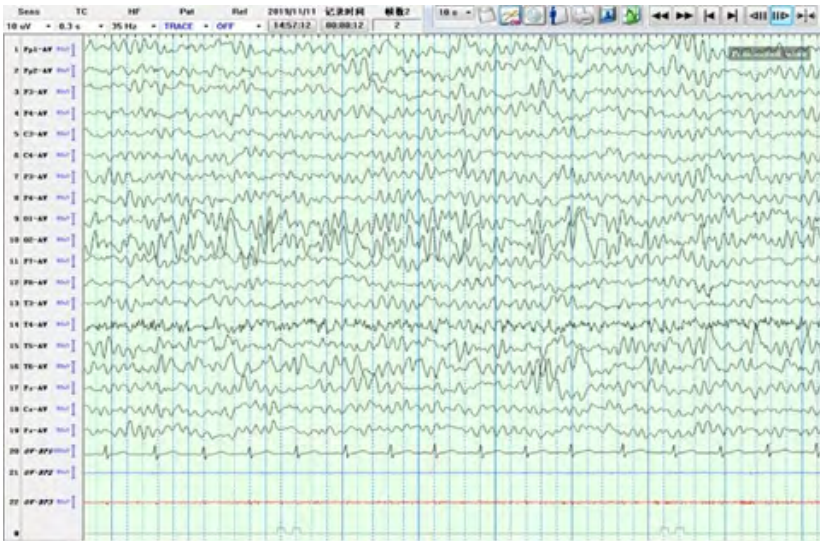


Figure 1: Family pedigree.

3.2. MRI and EEG

The proband's brain MRI (3.0T) was normal. The 24 hours' video-EEG results showed that the background was normal, although sharp waves of moderate amplitude, sometimes continuously distributed, were observed on the left temporal lobe (Figure 2). Other test results were normal, including routine blood and urine, biochemical and rheumatic immunity series, and homocysteine.

a



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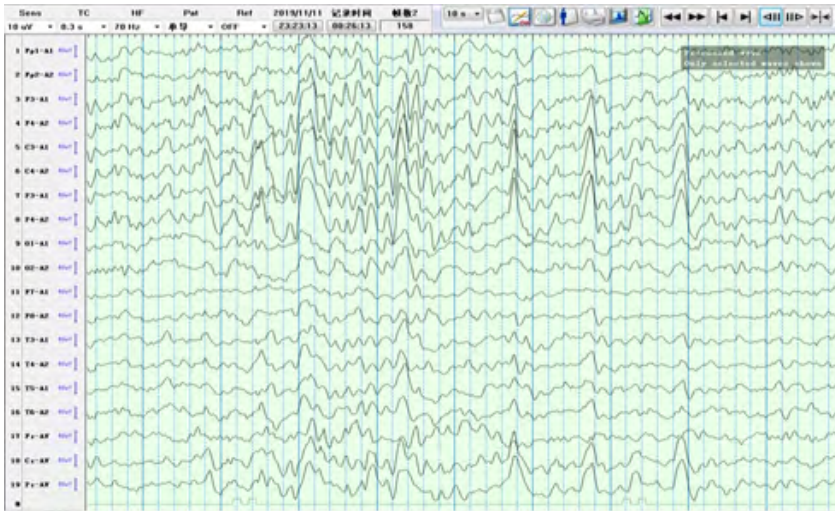

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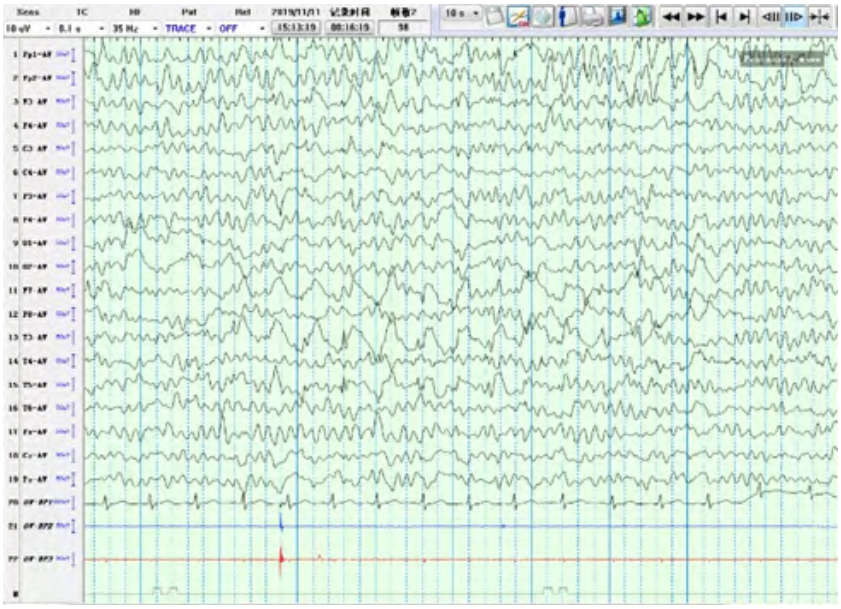

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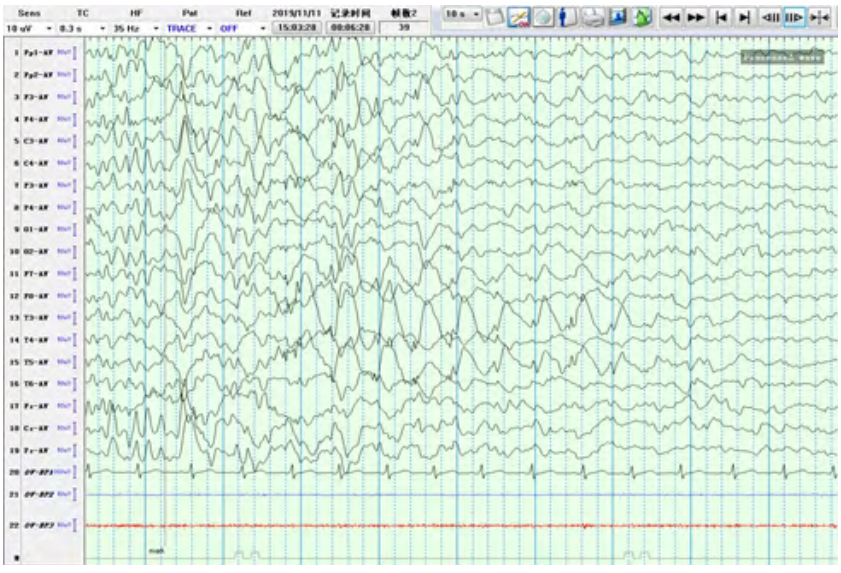


Figure 2: EEG of the proband.

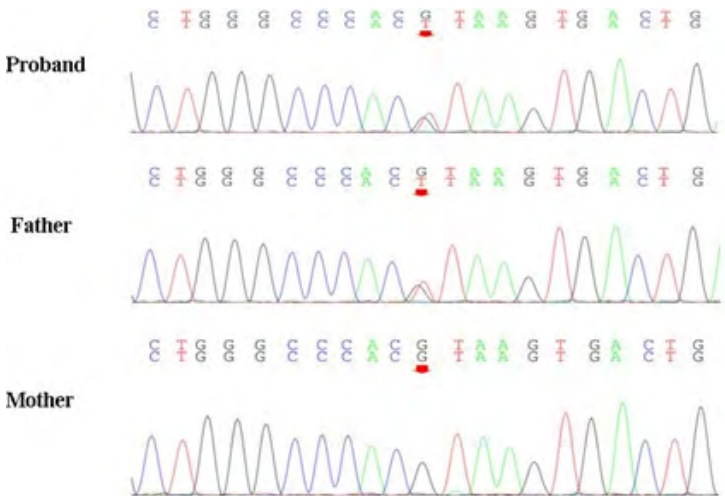
3.3. DNA Sequencing

Next-generation DNA sequencing was performed on the proband and validation analyses were carried on his mother and father. After obtaining informed consent, peripheral blood samples (5 ml from the proband and 2 ml from each parent) were collected and sent to Beijing Kangso Medical Inspection for epilepsy-related genetic testing (a total of 1741 genes). The results showed there were 2 most probable gene mutations related to FTLE (Figure 3). The c. 136+1G>T mutation in the galanin (GAL) gene was detected in the proband and his father; and the c. 1799C>T mutation in the RELN gene was presented in the proband and his mother, the latter was considered as the pathogenic gene of the proband.

The background was normal (a and b), sharp waves of moderate amplitude, sometimes continuously distributed, were observed in the left anterior and middle temporal lobes (c and d).

a

GAL (NM_015973)	
Chromosomal location of the gene	chr11:68453117
Nucleotide variation	c.136+1G>T
Amino acid change	–
Exon/intron	Intron3
Variation type	Heterozygote
Father	Heterozygote
Mother	Not found
Frequency of variation	
ExAC	Not included
ESP6500	Not included
1000 Genomes	Not included
1000 Genomes (Han Chinese in Beijing)	Not included
1000 Genomes (Southern Han Chinese)	Not included
Kangso Health	Not included



B

RELN (NM_005045)	
Chromosomal location of the gene	chr7:103292201
Nucleotide variation	c.1799C>T
Amino acid change	p.Ser600Phe
Exon/intron	Exon15
Variation type	Heterozygote
Father	Not found
Mother	Heterozygote
Frequency of variation	
ExAC	0.011
ESP6500	0.011
1000 Genomes	0.006
1000 Genomes (Han Chinese in Beijing)	0
1000 Genomes (Southern Han Chinese)	0
Kangso Health	0.001

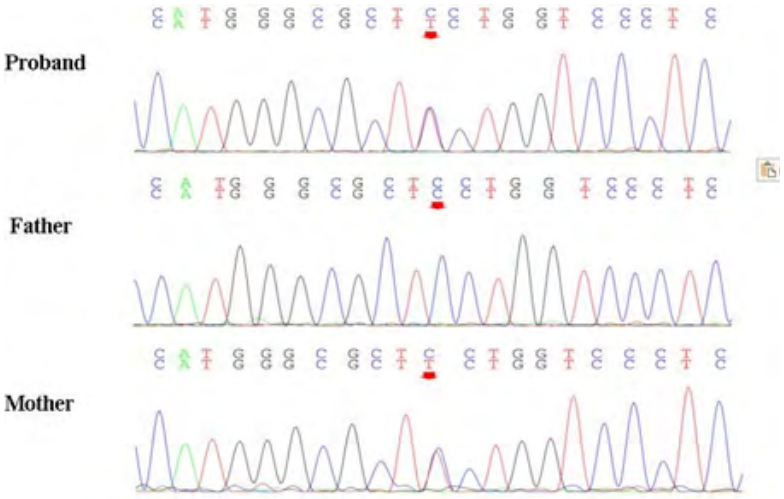


Figure 3: The results of DNA sequencing.

There were 2 possible gene mutations related to FTLE. The c. 136+1G>T mutation in the galanin (GAL) gene was detected in the proband and his father (a), and the c. 1799C>T mutation in RELN gene was presented in the proband and his mother (b).

3.4. Treatment and Outcome

The proband was initiated on levetiracetam 500mg twice daily and there was no recurrence of seizure after 2 years of follow-up. His mother died from status epilepticus caused by the recurrence of glioma 2 months ago.

4. Discussion

The diagnosis of epilepsy was identified undoubtedly based on the manifestations of the proband's convulsions and abnormal temporal lobe discharges observed in EEG. As there was no abnormal finding on the brain MRI, and blood test indicators were normal, in addition there was no sign of declining in memory or cognitive function, we did not consider the cause of the seizures to be structural, metabolic, or immune-related factors. The first 5 seizures occurred after a fever with low temperature, and the latter seizures were not associated with increasing in temperature, so they could not be described as febrile seizures. Although the proband's mother found a glioma in her left hemisphere of the brain when she was in pregnancy, she experienced seizure first at the age of 1-year-old, and both of the proband and his mother had similar seizures, we speculated that the patient's seizures were related to heredity.

It is interesting that the proband had 2 most possible pathogenic gene mutations, one inherited from his mother, the other from his father, making it difficult to identify which is the pathogenic one. Although there is high pathogenicity of the mutation (c.136+1G>T) in GAL, there was no history of seizures among the proband's father, grandfather, and his father's other relatives, we speculated that there was a compensatory or corrective mechanism, such as protein modification or increased translation, negating the effect of the GAL mutation, GAL was not the pathogenic gene of the proband. The frequency of RELN mutation in normal people ranges from 0.0 to 0.011, which is higher than the frequency of 0 reported among Han Chinese in Beijing and Southern Han Chinese in the 1000 Genomes Project. The results suggest that the missense mutation (c.1799C>T) in RELN has high pathogenicity

in Chinese. Based on the history of seizures with similar manifestations of the proband and his mother, both of them had the first seizure at the age of 1, in addition to this, they responded effectively to anti-seizure medications, we concluded that the missense mutation (c.1799C>T) in RELN inherited from his mother is the proband's pathogenic cause. It is a rare case of an ADLTE family with mutation of RELN in China, at a loci that has not been reported previously.

Literature shows that the age of onset of ADLTE ranges from 1 to 60 years, seizures are usually occurred from focal to bilateral tonic–clonic during sleep, a history of febrile seizures is uncommon. Hippocampal sclerosis is rare. Abnormal discharges in the left temporal are more common with RELN mutations than with LGI1 mutations. To sum up, the patient's clinical features were all consistent with ADLTE except for auditory aura. However, all of the patient's seizures occurred during sleep, it was possible that he was unaware of an aura even if it presented. Additionally, the proband achieved seizure free after treatment of anti-seizure medication and recurred after discontinuation, we identified that the seizures were the result of the missense mutation in RELN.

In particular, the history of both epilepsy and glioma of the proband's mother caught our attention. A glioma was found when she was in pregnancy, whereas her first seizure happened at the age of 1, so we considered the cause of the proband's mother's seizures was the mutation in RELN, not the glioma. Double immunofluorescence and confocal microscopy experiments have shown that LGI1 and reelin are both highly expressed in hippocampal and cortical neurons of mature but not young rats [14], suggesting that the two proteins act in the same pathway.

Research also has revealed that RELN signaling modulated the growth and migration of the glioblastoma [17]. Whether the proband's mother's history of both epilepsy and glioma was the result of mutation in RELN remains unknown, whether epilepsy and glioma act in a same pathway needs to be further researched. Unfortunately, the proband's mother had died when the boy returned the following year, we could not get his mother's results of the brain MRI.

5. Conclusion

Genetic factors should not be ignored in temporal epilepsy. ASMs needed to be taken all the time, not as common temporal epilepsy. This paper described a Chinese family with ADLTE associated with a novel missense mutation in RELN. The loci (c.1799 C>T) has not been

reported previously. Our findings also suggest that mutations in RELN be related to glioma, which may cause both epilepsy and glioma. Whether there is a common pathway between them needs to be further explored.

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