



Original article

Effective treatments for *FGF12*-related early-onset epileptic encephalopathies patients

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Abstract

Background: *FGF12* (*FHFI*) gene encodes voltage-gated sodium channel (Nav)-binding protein fibroblast growth factor homologous factor 1, which could cause seizures by regulating voltage dependence of Nav fast inactivation and neuron excitability. The most common pathogenic variant *FGF12* c.341G > A related early-onset epileptic encephalopathies (EOEE) was characterized by intractable seizures and developmental disabilities.

Results: Using whole exome sequencing, a de novo hotspot variant c.341G > A (NM_021032.4) of *FGF12* was identified in three unrelated EOEE probands. All probands were seizure free after a combination treatment of valproic acid (VPA) and topiramate (TPM). The motor and cognitive skills in two probands were improved due to the early and effective treatment. In order to compare the effectiveness of different treatment strategies for the disease, a review of treatments for *FGF12*-related epilepsy was made.

Conclusion: We reported three *FGF12* c.341G > A related EOEE patients responded well to a combination antiepileptic therapy of VPA and TPM. The current study is the first to describe the combination therapy of VPA and TPM in *FGF12* c.341G > A related EOEE patients. This study may contribute to future medication consultation for intractable epilepsy with *FGF12* hotspot variants. © 2021 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.

Keywords: *FGF12*; EOEE; Treatment; Epilepsy; Genetic

1. Introduction

FGF12 (*FHFI*) gene encodes voltage-gated sodium channel (Nav)-binding protein fibroblast growth factor homologous factor 1 and played a role in early-onset

epileptic encephalopathies (EOEE). *FGF12* variants acted as a gain-of-function manner in EOEE pathogenesis by elevating voltage dependence of Nav fast inactivation and increasing neuron excitability [1]. There were only 3 variants reported causing *FGF12*-related epilepsy since 2016 [1–3]. The most common pathogenic variant *FGF12* c.341G > A (NM_021032.4) related EOEE was characterized by intractable seizures and severe brain dysfunctions [1,3–8].

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Most *FGF12*-related epilepsy patients failed to response to anti-epileptic treatments which could lead to neurological impairments, developmental dysfunction and even brain atrophy. As a consequence, patients usually have poor life quality and bad prognosis [1]. Although traditional anti-epileptic drug (AED) phenytoin (PHT) and phenobarbital (PB) have been proved effective in some cases, they exerts multiple side effects on patients [9]. In our study, we applied a combination treatment of topiramate (TPM) and valproic acid (VPA) for *FGF12* c.341G>A related EOEE patients with improved clinical outcomes.

2. Case study

A de novo heterozygous missense hotspot variant c.341G>A was identified in *FGF12* gene in all three unrelated probands using whole exome sequencing (WES) and validated by Sanger sequencing (Fig. 1a-c). The patients were diagnosed according to the International League Against Epilepsy diagnostic criteria [10]. The clinical features were presented as following. All parents of participants signed informed consent forms, and the study was approved by the ethics committee of the Maternal and Child Health Hospital of Hunan Province (2020-S003).

Patient 1 The proband was born at full term (40 weeks) with normal pregnancy. Without any inducement, generalized tonic-clonic seizures occurred on the 15th day after birth. He presented upward twitching eyes and stiff body with hugging like actions after a sudden scream during sleep, followed by outward extending and shaking limbs which lasted for 2 min before the sei-

zures stopped. He fell asleep soon after the seizures and fecal incontinence was observed. The seizures occurred with a frequency of every three hours a day. The electroencephalogram (EEG) presented a suppression-burst pattern (Fig. 2a left). The magnetic resonance imaging (MRI) scans showed normal results. VPA was administered (15 mg/kg/d) and the frequency of seizures decreased after 2 months of treatment. Unfortunately, the epilepsy recurred due to urinary tract infection and pneumonia at the age of 3 months. An increase of the VPA dose was useless to control the seizures (50 mg/kg/d). Levetiracetam (LEV) was added to the anti-epileptic treatments and was gradually decreased for its ineffectiveness. Then, TPM began at 1 mg/kg/d was given to the patient accompanied with VPA. A combination of these two drugs were administered with gradually increasing doses. The epilepsy was controlled after 7 months of age (VPA: 30 mg/kg/d; TPM: 10 mg/kg/d). EEG presented central parietal low-to-medium-amplitude spikes (Fig. 2a right).

The patient showed global developmental delay. He had little intellectual or motor development after the infections when he was 3 months. After the usage of the combination of two drugs, the frequency of seizures reduced substantially by the age of 7 months and he began to be able to lift his head and roll over. After treatment he was gradually able to trace, sit up, scrawl and stand with support at the age of 1 year and 5 months. He was able to walk without assistance when he was 2 years old. However, he showed no language development and had no ability to make eye contact. No dysmorphisms or other neurological disabilities were observed.

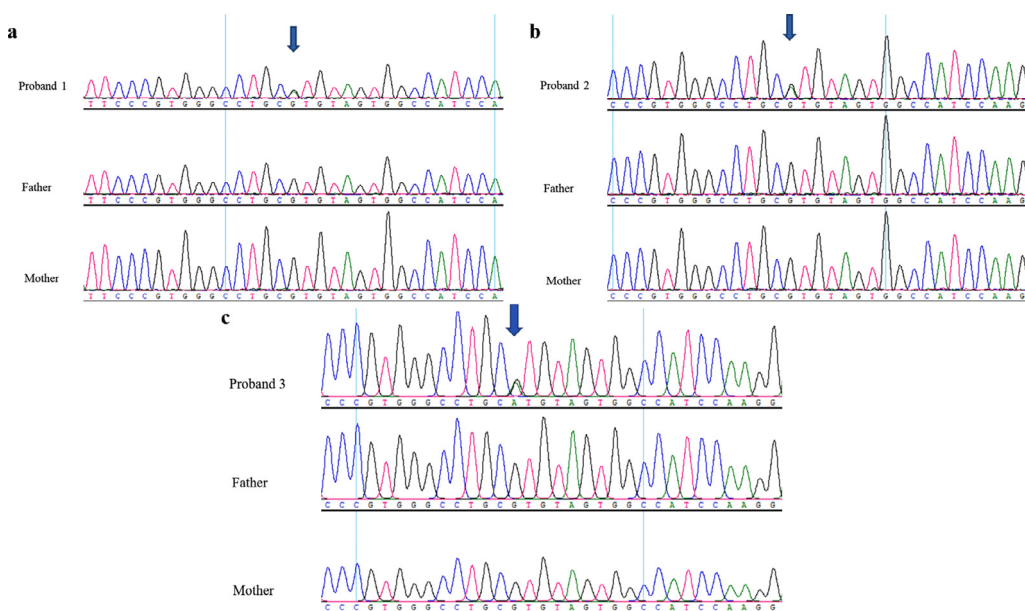


Fig. 1. a-c. Sanger sequencing results of the probands 1–3 and their parents separately. The arrows pointed to the heterozygous *FGF12* c.341G>A mutations.

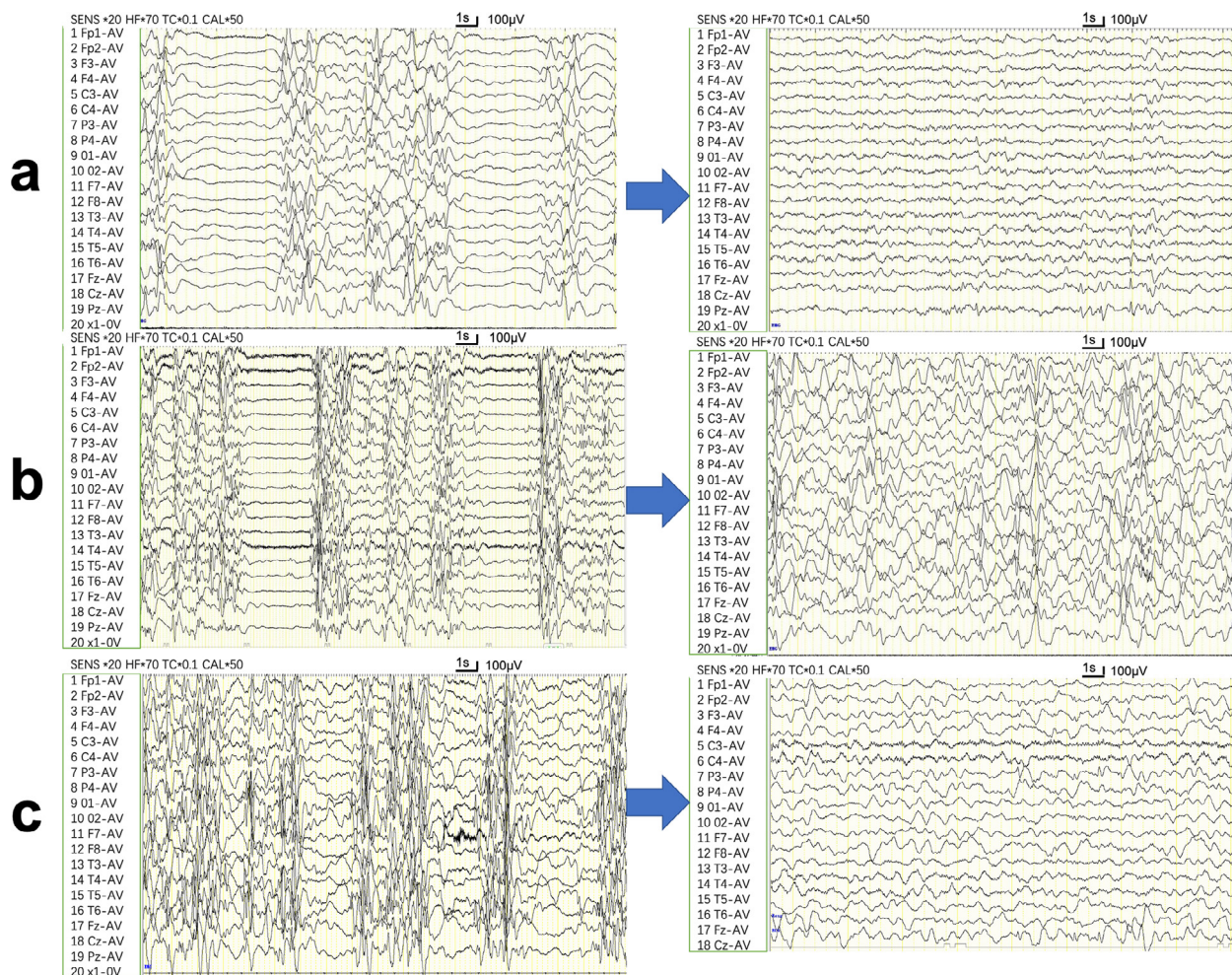


Fig. 2. **a-c. a left:** EEG in proband 1 presented a suppression-burst pattern. **a right:** EEG in proband 1 presented central parietal low-to-medium-amplitude spikes after using a combination of VPA and TPM for treatment. **b left:** EEG in proband 2 presented a suppression-burst pattern. **b right:** EEG in proband 2 showed extensive abnormal waves such as spikes, slow spikes, sharp waves, etc. after using a combination of VPA and TPM for treatment. **c left:** EEG in proband 3 presented hypsarrhythmia. **c right:** EEG in proband 3 showed small spikes in the central apical and midline regions.

Patient 2 The proband was born at full term (39 weeks) with no abnormality in pregnancy. She developed epilepsy at the age of 18th days. Sudden stiffening of the body accompanied by shaking of both arms and legs was observed by her parents. Her eyes and mouth closed tightly for at least 5 min before she gradually relaxed her body. The EEG presented a suppression-burst pattern (Fig. 2b left). MRI showed normal results. Single or combined use of LEV and TPM were ineffective and therefore stopped after 6 months. Without any anti-epileptic treatment, the proband continued to have seizures for about 5 times a day and there was no intellectual nor motor development in the patient. When she was admitted to the hospital at 3 years old, we gave the same prescription (VPA: 30 mg/kg/d; TPM: 10 mg/kg/d) and the seizures were controlled in less than 2 months. However, due to the long-time brain

impairments caused by frequent seizures, the cognition and motor skills failed to improve afterwards. No dysmorphisms or other neurological disabilities were observed. EEG showed extensive abnormal waves such as spikes, slow spikes, sharp waves, etc (Fig. 2b right).

Patient 3 The proband was born at full term (39 weeks) with no abnormality in pregnancy. She developed epilepsy at the age of 1st month. Sudden head nodding and arms wrapping was observed. The seizures occurred with a frequency of about 2 times a day and each time lasted for only few seconds. EEG presented hypsarrhythmia which was a typical EEG feature of infantile spasms (Fig. 2c left). PB and LEV were used (PB: 5 mg/kg/d; LEV: 50 mg/kg/d) and the seizures could not be controlled. A combination of VPA and TPM were then used and the doses were gradually increased and epilepsy was controlled at 3 months of

age (VPA: 30 mg/kg/d; TPM: 10 mg/kg/d). EEG showed small spikes in the central apical and midline regions (Fig. 2c right).

He had little intellectual or motor development before the age of 3 months. After the adoption of the VPA and TPM, the seizures were controlled. He began to develop the motor and intellectual ability and could almost reach the developmental milestones. No dysmorphisms or other neurological disabilities were observed.

3. Treatments on FGF12-related epilepsy

In our study, the seizures of all three patients were controlled in a month after the adoption of a combination of anti-epileptic drugs (VPA: 30 mg/kg/d; TPM: 10 mg/kg/d). At the time when seizures were relieved, the patients 1 and 3 began to develop intellectual and motor abilities. The patient 3 showed better cognitive and motor ability improvements than patient 1 for the earlier application of the drugs. In patient 2, although the seizures were free after the combination use of VPA and TPM, no developmental milestone could be reached for the long-time delayed use of these drugs. Therefore, an early adoption of VPA-TPM combination could help FGF12-related EOEE patients control seizures and reach developmental milestones.

We summarized the reported treatments on epilepsy patients with FGF12 variants. As can be seen from Table 1, there were only 8 reported articles including 6 studies on FGF12 c.341G > A variant and 2 studies on other variants (1copy-number gain variant and 1c.334G > A variant). Among the effective treatments for early onset epilepsy patients with FGF12 variants, PHT is the most effective drug which achieved 6/13 effective rate. The second effective therapeutic drug is PB with good seizures control in all 3 patients. Although different treatments including anti-epileptic drugs (carbamazepine [CBZ], lamotrigine [LTG] etc.) and vagal nerve stimulation (VNS) were proved to be effective in some cases, a majority of patients showed resistance to multiple antiepileptic treatments. In these previous treatments, VPA and TPM were not used as a combination. VPA or TPM usage in combination with other anti-epileptic drugs were reported in five patients with FGF12 c.341G > A mutation but with no unanimous response.

4. Discussion

The pathogenic variant FGF12 c.341G > A is the first and the most common pathogenic variant reported in FGF12-related EOEE[1]. The variant functioned as a gain-of-function variant and could elevate neuronal excitability by altering sodium channel fast inactivation. FGF12 c.341G > A-related EOEE patients manifested with severe clinical features including early-onset

Table 1
Reported treatment on epilepsy patients with FGF12 (FHFI) variants.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	
First author	Siekierska[1]	Siekierska[1]	al-mehmedi[4]	al-mehmedi[4]	al-mehmedi[4]	Guella[5]	Guella[5]	Villeneuve[6]	Shi[2]	Takeguchi[7]	Takeguchi[7]	Epilepsy Genetics Initiative [8]	Paprocka[3]	
Publication year	2016	2016	2016	2016	2016	2016	2016	2017	2017	2018	2018	2019	2019	
Variants	NM_021032.4: c.341G > A;p.R114H	NM_004113.5: c.155G > A; p. R52H	NM_004113.5: c.155G > A; p. R52H	NM_004113.5: c.155G > A; p. R52H	NM_004113.5: c.155G > A; p. R52H	NM_004113.5: c.155G > A; p. R52H	NM_004113.5: c.155G > A; p. R52H	NM_004113.5: c.155G > A; p. R52H	copy-number gain	copy-number gain	NM_021032.4: c.341G > A;p.R114H	NM_021032.4: c.341G > A;p.R114H	NM_021032.4: c.341G > A;p.R114H	NM_021032.4: c.334G > A;p.G112S
Diagnoses	EOEE	EOEE	EOEE	EOEE	EOEE	EOEE	EOEE	EOEE	EE	EOEE	EOEE	EOEE	EOEE	
Antiepileptic treatments	Multiple antiepileptic drugs (no details available)	LEV, PB, ketogenic diet	LEV, PB, ketogenic diet	PHT, VNS, PER	PHT, PGB, PER, VNS	PHT, CBZ, PB, TPM, MDZ	RUF, LTG, PB, CBZ, TPM, CBZ	CBZ, FXT	PB, CLB, VPA, potassiumbromide, PHT	PB, PHT, CZP, PB, PHT	PB, PHT, CZP, PB, PHT	Multiple antiepileptic drugs (no details available)	PHT, PB, CLB, VPA, LEV, VGB	
Effectiveness	Not efficacious	Not efficacious	Not efficacious	Relatively efficacious	Not efficacious	Efficacious	Efficacious	Efficacious	Efficacious	Efficacious	Efficacious	Not efficacious	Efficacious	
Treatments with valproate or topiramate	Unknown	Unknown	Unknown	No	No	TPM	TPM	No	VPA	VPA	No	NO	VPA	

Abbreviations: early-onset epileptic encephalopathies, EOEE; epileptic encephalopathies, EE; phenytoin, PHT; phenobarbital, PB; clonazepam, CZP; acetazolamide, AZA; Vagal nerve stimulation, VNS; clobazam, CLB; valproic acid, VPA; levetiracetam, LEV; vigabatrin, VGB; carbamazepine, CBZ; topiramate, TPM; rufinamide, RUF; lamotrigine, LTG; fluoxetine, FXT; perampanel, PER; Pregabalin, PGB; midazolam, MDZ.

intractable seizures, developmental delay, intellectual disabilities, cerebellar atrophy etc[7].

The treatment of *FGF12*-related epilepsy is difficult because most patients were resistant to multiple antiepileptic treatments according to our review (Table 1). The classic drugs for *FGF12* c.341G > A-related epilepsy were sodium channel blockers. Among the effective drugs used to treat *FGF12*-related epilepsy, PHT was the most commonly used and effective drug in treating *FGF12*-related epilepsy (Table 1). However, PHT has multiple inevitable adverse neurological effects such as cognitive impairment, ataxia, dysarthria, hypotonia and locomotor dysfunction etc[9,11]. The other effective drug PB could also cause neurological and behavioral side effects and was associated with high rate of adverse drug withdrawal reaction [9,12]. Although treatments other than these two drugs have been applied, there was no consistent clinical performance.

In our study, we used a combination of VPA and TPM for treatment of *FGF12*-related EOEE and all patients achieved seizure control. An early adoption of VPA-TPM combination could help to control seizures and meet developmental milestones. The anticonvulsant effect of VPA is not fully understood and it has been attributed to the blockade of the sodium channels and increased levels of elevated brain gamma aminobutyric acid (GABA) in brain, and the TPM could also rapidly elevate brain GABA level[13]. The combination of the two drugs may enhanced GABA level synergistically and the it has been proved that co-administer a sodium channel blocker with a GABA enhancer could be advantageous to controlling seizures in experimental models of epilepsy[14]. TPA and TPM were proved to be an optimal AED combination by isobolographic animal studies for evaluating synergistic and antagonistic effects of AED [15]. Preclinical data indicated that combination of VPA and TPM had synergy effect on seizures and were recommended for rational treatment of drug-resistant epilepsy[16]. Therefore, the combination of the two drugs might possibly elevate the treatment effectiveness in synergistic fashion. Our research indicated that when choosing antiepileptic drugs based on causative genes according to concept of precise medicine, the explorations of drug usage strategies especially in treating intractable epilepsy are important. Early seizure control in EOEE patients will greatly benefit patients' neurological development and affect the disease prognosis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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