CASE REPORT

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Status epilepticus due to fructose-1,6-bisphosphatase deficiency caused by *FBP1* gene mutation

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ABSTRACT
Introduction: Fructose-1,6-bisphosphatase (FBPase) deficiency is a rare inherited disorder in gluconeogenesis, characterized by hypoglycemia, ketonuria, metabolic acidosis and convulsions.
Case presentation: We describe two brothers with FBPase deficiency. The proband developed severe hypoglycemia and progressed to status epilepticus, and the brother showed slightly hypoglycemia with a good prognosis. Whole exome sequencing (WES) identified compound heterozygous variants [c.333+1_333+2delinsTC and c.490G>A (p.Gly164Ser)] in fructose-1,6-bisphosphatase 1 gene in the two brothers, which were inherited from the father and the mother, respectively.
Conclusion: Genetic analysis provided a solid basis for a definite diagnosis and the determination of precision therapies for the patient.

KEYWORDS
Fructose-1,6-bisphosphatase deficiency, Hypoglycemia, Status epilepticus, *FBP1*, Mutation

INTRODUCTION

Fructose-1,6-bisphosphatase (FBPase) deficiency (MIM#229700) is a rare autosomal recessive inherited metabolic disease caused by a fructose-1,6-bisphosphatase 1 (*FBP1*) gene deficiency. FBPase is key regulatory enzyme during gluconeogenesis, which catalyzes the hydrolysis of fructose 1,6-bisphosphate to fructose 6-phosphate. FBPase deficiency is associated with hypoglycemia, ketonuria, metabolic acidosis, and convulsions.[1,2] Although it is a treatable metabolic disease, it can be dangerous and even lethal if it is not treated properly and effectively during infancy or early childhood. An early definitive diagnosis, appropriate diet

and effective treatment are critical factors for achieving a good prognosis.[3] In this study, we reported a case of FBPase deficiency that presented with status epilepticus and hypoglycemia, and retrospectively analyzed the clinical manifestations and genetic changes associated with the disease.

CASE REPORT

A 7-year-old boy (II2 in Figure 1) was admitted to our hospital with a 3-year history of intermittent seizures. Three days prior, he had described feeling hungry and sweating after waking up in the morning, and then suddenly experienced a seizure attack and loss of consciousness. The seizure was characterized by the uncontrollable jerking of the upper and lower limbs, tonic upward gaze, and cyanosis of the lips and face. The epileptic episodes lasted for 1–2 minutes, and relieved by itself. In the morning, three further epileptic episodes were observed, at intervals of 1–2 hours. He was admitted to the intensive care unit of the local people's hospital. Upon admission, he was found to be hypoglycemic with a blood glucose level of 0.3 mmol/L, and experienced a peak temperature of 40.0°C. After hospitalization, the child continued to experience frequent convulsions accompanied by fever. Phenobarbital was intramuscularly injected to control the seizures, and 50% glucose was intravenously injected immediately to treat the severe hypoglycemia. Cefotaxime, recombinant interferon α2a, mannitol, levetiracetam, sodium valproate, midazolam and Xingnaojing (formula of traditional Chinese medicine) were administered intravenously. Over the following 2 days, blood glucose became elevated to normal levels and no seizure attacks were observed; however, the patient remained unconscious. For further diagnosis, the patient was transferred to our hospital. A physical

examination revealed that the child was in slight coma with a temperature of 39.1°C, the bilateral light reflex was slow, and the patellar tendon and abdominal reflexes were absent. A routine blood test showed a white blood cell count of 9.35×10^9 cells/L, with 81.7% neutrophils, a C-reactive protein level of 208 mg/L, and a procalcitonin level of 22.55 ng/mL. Considering a possible bacterial infection, cefepime was applied, although a bacterial culture was negative.

The patient was born to healthy, non-consanguineous parents. He was full-term and naturally delivered in a hospital, and his physical and mental developments were a little behind other children before 2 years of age. He showed delayed language development, and he could say only few single words at 2.5 years old. The first epileptic seizure occurred at 4 years of age, and he was admitted to our neurology department for coma and intermittent convulsions 1.5 days after his first seizure. His parents denied obvious inducement. Magnetic resonance imaging (MRI) of the brain detected abnormal signals along the cortical regions of the bilateral hemisphere and basal ganglia, which indicated cytotoxic edema (Figure 2). Metabolic screening by tandem mass spectrometry (MS/ MS) and gas chromatography-mass spectrometry (GC/MS) found no obvious abnormal indications. He was vaccinated on schedule and was not exposed to infectious diseases or contaminated water during the past year. No infection indicators were detected in his central nervous system by routine laboratory tests such as complete blood count, serum electrolytes, calcium, procalcitonin and C-reactive protein. No clear diagnosis was made at that time. Methylprednisolone and symptomatic treatments were given due to suspicions of viral encephalitis or metabolic acidosis. Two weeks later, symptoms had improved.
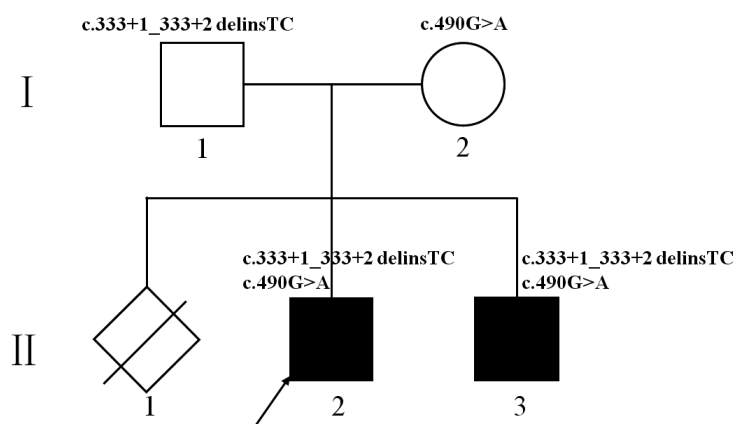
FIGURE 1 Mutation co-segregation in the pedigree. The proband and his younger brother suffered from fructose-1,6-bisphosphatase (FBPase) deficiency. The proband (II2) developed severe hypoglycemia, metabolic acidosis, and intermittent convulsions. The brother (II3) showed slight hypoglycemia, and suffered seizure once with a good prognosis. The mother's first pregnancy (II1) ended in an unexplained miscarriage at 14 weeks of gestation. No one else in the family had a history of seizures or hypoglycemia.
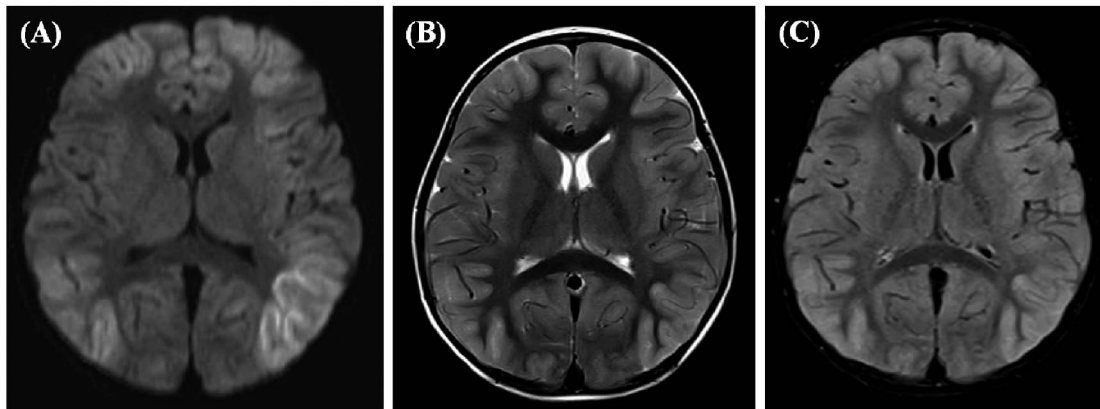
FIGURE 2 T1 (A) and T2 (B)-weighted MRI images showed linear high signal intensity selectively along the cortical regions of bilateral hemisphere and basal ganglia. Increased fluid-attenuated inversion recovery (FLAIR) signal in the cortical regions (C).

He was discharged and treated with phenobarbital and prednisone tablets, taken orally. Because of intermittent convulsions, he was presented to the First Hospital of Peking University at 4.5 years of age. Laboratory tests for growth hormone, cortisol, thyroid function, insulin, and C-peptide were normal. Metabolic screening did not show any clear positive indications, and an autoimmune antibody test was negative. He was diagnosed as having ketotic hypoglycemia, epilepsy, focal seizure, or cognitive retrogression. Levoethoxetam was given and phenobarbital was decreased. After partial improvement, oral levoethoxetam and phenobarbital tablets were given, and regular reviews were suggested. However, he did not take the medicine regularly following the doctor's advice, and he continued to experience intermittent convulsions at intervals of 2–4 months. His motor and intellectual developments were retrogressive after intermittent convulsions. According to his parents' memories, epilepsy recurrence most often occurred during the morning.

His younger brother (II3), gravida 3, para 2, a 4.5-year-old, always woke up hungry and sweating in the morning. He suffered one hypoglycemic seizure at the age of 3.5 years, and the prognosis was excellent after symptomatic treatment. The physical and mental development of the brother were acceptable, with no developmental or speech delays detected. A Denver Developmental Screening Test also showed the brother to be normal. No one else in the family was found to have a history of seizures or hypoglycemia.

For a genetic diagnosis, we performed whole exome sequencing (WES) on the patient and parents, and we identified compound heterozygous variants in *FBP1* [NM_001127628: c.333+1_333+2delinsTC and c.490G>A (p.Gly164Ser)], which were inherited from the father and the mother, respectively (Figure 3). Except that, no definite or suspected pathogenic mutations associated with the clinical symptoms were detected. The two variants of *FBP1* were confirmed by Sanger sequencing in the proband, his brother and their parents. The splicing mutation c.333+1_333+2delinsTC in exon 3-intron 3 was inherited from the patient's father, and the splice site mutation was speculated to result in the skipping of exon 3 in mRNA splicing. The missense mutation c.490G>A (p.Gly164Ser) in exon 5 was inherited from the patient's mother, which has previously been identified to be disease-causing.[4,5] The brother was found to carry the same compound heterozygous variants in *FBP1* with the patient. The splicing mutation c.333+1_333+2delinsTC has never been reported in the literature, single nucleotide polymorphism databases, or our in-house data from more than 500 healthy individuals. The in silico predictive algorithms of the MutationTaster (http://mutationtaster.org/) and SplicingFinder (http://umd.be/HSF3/) predicted this mutation to be pathogenic.

DISCUSSION

FBPase deficiency is an inborn error of metabolism characterized by an enzymatic block during the last steps of gluconeogenesis. FBPase defects block the conversion of substrates, such as amino acids, lactic acid, glycerol, and pyruvic acid, into glucose, resulting in hypoglycemia and the accumulation of gluconeogenic substrates.[3,6,7] Following exposure to triggering risk factors such as infection, long-time fasting, or a large fructose load, patients with FBPase deficiency present clinically with severe hypoglycemia, lactic acidosis, elevated liver enzymes and metabolic acidosis.[7,8] During infancy or early childhood, the patients are prone to experience acute episodes.[9] Severe hypoglycemia and lactic acidosis can lead to seizures and brain damage, and even death. It is easily confused with mitochondrial defects and other metabolic disorders, such as glucose-6-phosphatase deficiency. The rate of misdiagnosis for FBPase deficiency is high, especially without definitive biochemical indications.[1,10]

In our case, the proband and his younger brother suffered
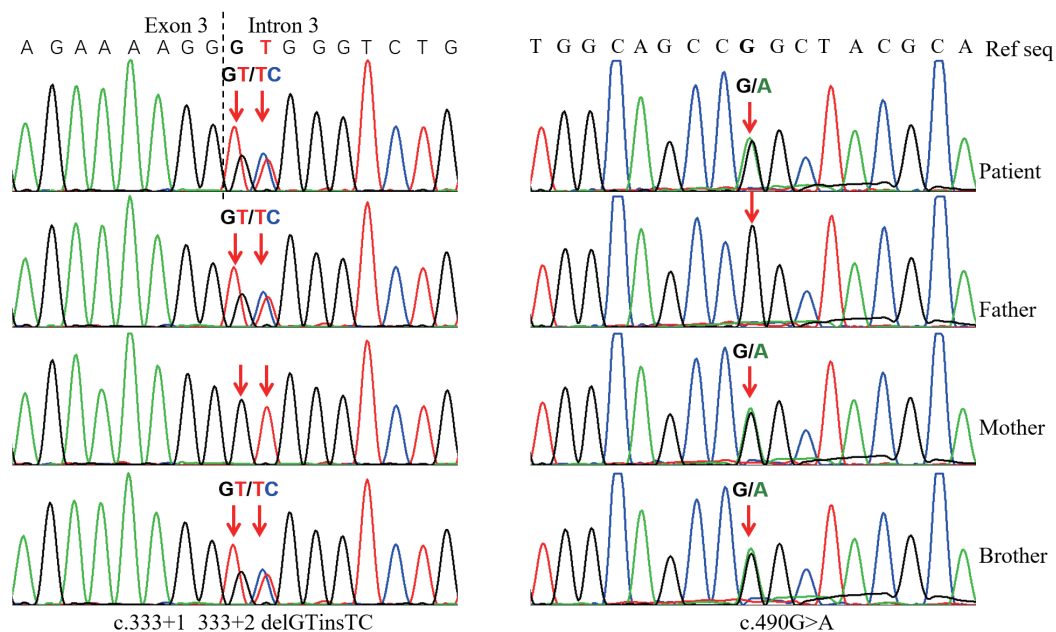
FIGURE 3 Sanger sequencing analyses of *FBP1* in the patient, the brother and their parents. The arrows indicate the mutated nucleotides. The patient carried a compound heterozygous splicing mutation, c.333+1_333+2delinsTC, and a missense mutation, c.490G>A (p.Gly164Ser), in *FBP1*. c.333+1_333+2delinsTC was inherited from a heterozygous father, and c.490G>A (p.Gly164Ser) was inherited from a heterozygous mother. The brother carried the same compound heterozygous variants with the patient.

from FBPase deficiency. The proband developed severe hypoglycemia and progressed to status epilepticus, and the brother showed slightly hypoglycemia with a good prognosis. Both boys always woke up hungry and sweating in the morning, and experienced the recurrence of hypoglycemia before breakfast. Hunger is a typical trigger for FBPase deficiency. In the early stages of epilepsy for the proband, no clear diagnosis was made, due to a lack of specific clinical features and a dearth of knowledge regarding FBPase deficiency. Because of frequent hypoglycemia and convulsions, there was obvious organic damage observed in the proband's brain, which affected his intellectual development. Prior to a clear diagnosis, the proband did not take medicine as prescribed by his doctor, which also made the treatment less effective. During the following period, although a great deal of rehabilitation treatment was provided, the proband experienced recurrent convulsions, and the prognosis has been barely satisfactory. For the brother, FBPase deficiency was diagnosed based on genetic feedback. The family members were educated in how to minimize or avoid late-onset hypoglycemia via nightly enteral nutrition, glucose supplementation, fructose restriction and anti-infection treatments. The brother developed healthily and did not exhibit similar syndromes as the proband. The prominent clinical feature of this patient was the benign course of the disease with age.[1,11] As the patients grew up, they showed improvement in tolerance to fasting and to fructose loading, and the clinical features were benign. Through our case, we learned that it is critical to make

an early definitive diagnosis and that an appropriate diet and effective treatment may result in good prognose for FBPase deficiency.

The diagnosis of FBPase deficiency was initially established based on clinical symptoms and FBPase activity.[7,12] FBPase activity was measured using liver biopsies or peripheral blood lymphocytes, but the results were not consistent and the reliability of these methods remains under debate.[4,6] The rapid progress that has been made in gene sequencing technologies has made genetic analysis an effective strategy for facilitating the diagnosis of rare inherited diseases. FBPase deficiency is an autosomal recessive disease caused by *FBP1* gene deficiency. Human FBPases are encoded by two distinct genes, *FBP1*, which is primarily expressed in the liver and kidney, and *FBP2*, which is primarily expressed in muscle. The *FBP1* gene, located on chromosome 9q22.32, consists of seven exons and spans over 31 kb.[13] Since the first three mutations reported by Kikawa et al[4], 48 different mutations have been described and enrolled in Human Gene Mutation Database (HGMD) professional 2018.4. Most of the mutations are widespread throughout the *FBP1* gene, and c.959dupG, c.490G>A and c.704delC are hot-spot mutations that occur primarily in East Asian populations.[4,5,14] Here, we report a case of FBPase deficiency with compound heterozygous mutations, c.333+1_333+2delinsTC and c.490G>A (p.Gly164Ser), which were inherited from the mother and father, respectively. The mutation 490G>A

(p.Gly164Ser) has previously been identified to be a disease-causing mutation.[4,5] The glycine at position 164 is well-conserved, and the mutation Gly164Ser results in the formation of an FBPase protein with negligible enzymatic activity. c.333+1_333+2delinsTC is a splice-site mutation that is speculated to result in the skipping of exon 3 during mRNA splicing. To our knowledge, c.333+1_333+2delinsTC is a novel mutation and has never been reported in the literature. According to the American College of Medical Genetics guidelines,[15] those compound heterozygous variants likely underlie the pathogenesis of FBPase deficiency in the proband and his brother. Our study enriched the mutation spectrum of *FBP1*. Genetic analysis provided a solid basis for a definite diagnosis and the determination of precision therapies for the patient.

CONFLICT OF INTEREST

The authors have no conflict of interest relevant to this article.

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