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Case Report

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Improvement on BAF53B Mutation Caused Developmental and Epileptic Encephalopathy with a Ketogenic Diet

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Abstract

Purpose: Genetic mutation is the leading cause of Developmental and Epileptic Encephalopathy (DEE, OMIM 308350), a spectrum of disorders characterized by severe epilepsy and usually begins in infancy, accompanied with psychomotor development arrest and hypsarrhythmiaon electroencephalogram (EEG).Up till now, mutations of 101 genes were confirmed as the cause of DEE, and were categorized accordingly into 101 different sub-types (DEE1-101). Here, we report a case of DEE76 with a tortuous path to genetic diagnosis and an illuminating treatment of ketogenic diet (KD).

Methods: Through high throughput sequencing, we identified a DEE76 case caused by biallelic *BAF53B* mutation inherited in an autosomal recessive manner, and report the pathogenic variants NM_016188.4:c.892C>T (p.Arg298*) and NM_016188.4:c.991_996delinsAA (p.Gly331Asnfs*44) for the first time.

Results: The proband commenced seizures on day five after birth and rapidly deteriorated during development. After a series of therapeutic exploration, ketogenic diet turned out to be the most hopeful treatment available.

Conclusion: To ultra-rare conditions including DEE76, gene therapy seems to be a logical way to cure, which inevitably faces the challenge of very limited survival time that patients bear with. With application of KD, seizures could be alleviated, which not only expanded the usage of KD but also provided with a new inspiration to those with similar symptoms.

Keywords: Developmental and Epileptic Encephalopathy; BAF53B; Gene mutation; Ketogenic diet; Case report

Introduction

Genetic mutation is the leading cause of Developmental and Epileptic Encephalopathy (DEE, OMIM 308350), a spectrum of disorders characterized by severe epilepsy and usually begins in infancy, accompanied with psychomotor development arrest and hypsarrhythmia on electroencephalogram (EEG). Up till now, mutations of 101 genes were confirmed as the causes of DEE, and were categorized accordingly categorized DEE into 101 different sub-types (DEE1-101). These genes encode membrane receptors, ion channels, ATP transports and involved in neurotransmitter synthesis etc [1]. Here we report a DEE76 case caused by biallelic *BAF53B* mutation inherited in an autosomal recessive manner. Seizures commenced on day five and rapidly deteriorated. Patient's brain magnetic resonance imaging (MRI) revealed rare structural abnormalities, and the EEG confirmed severe

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epileptiform abnormalities. After a series of therapeutic exploration, the patient has currently following a ketogenic diet (KD) combined with medication treatment and got his DEE associated epileptic symptom under control. By far most types of DEE still lack of sufficient investigation of their underlying mechanisms and treatment approaches are urgently to be explored, while this case of DEE76 induced by compound heterozygous mutations in *BAF53B* gene highlighted the therapeutic potential of KD.

Case Study

The proband is the only child of healthy, nonconsanguineous parents. No history of neurological problems has been reported within the family. He was born by caesarean section at 39 weeks in the year of 2016. At birth his weight and length and head circumference (HC) were within the normal range. At day 5 he presented with frequently nodding-like myoclonic jerks accompanied with difficulties in feeding and dystonia. At 3 months of age, he was hospitalized for emergency laparoscopy surgery because of "umbilical hernia and inguinal hernia incarceration". After surgery, his symptoms of tonic and colonic seizures was noted by the doctor, EEG and brain MRI were arranged, revealed epileptiform activity in both occipital areas and brain structure abnormalities by imaging (Figure 1A). He showed no sustained response to oral valproate (Depakine) combined with topiramate (Topamax) and levetiracetam (Kaplan). Consequently a trio whole exome sequencing (Trio-WES) was performed but no specific pathogenic mutations or copy number variation (CNVs) were identified (not shown). As his symptoms deteriorated, his psychomotor developmental arrestment and intellectual disability were also been noticed. In the meantime, epileptiform activity have progressed to his right temporal region as detected by EEG (also not shown) and he showed signs of focal epilepsy. At 9-month-old, after supplemented with clonazepam and failed to response, he was treated with KD. After 3 months, a greater than 50% reduction in seizure frequency was reported by his guardians.

At 1.5 years old, EEG reassessment displayed severe multifocal epileptic activity over all his brain (Figure 1B), although his seizure attacks appeared to be less deteriorated reported by his guardians. He was then treated with high-dose intravenous corticosteroid therapy but without response, soon the proband resumed the V.T.L.C.K treatment (Valproate, Topiramate, Levetiracetam, Clonazepam and Ketogenic diet). At 2 years old, he had been briefly treated with vigabatrin (Sabril) at a dosage of 125 mg after each generalized seizure

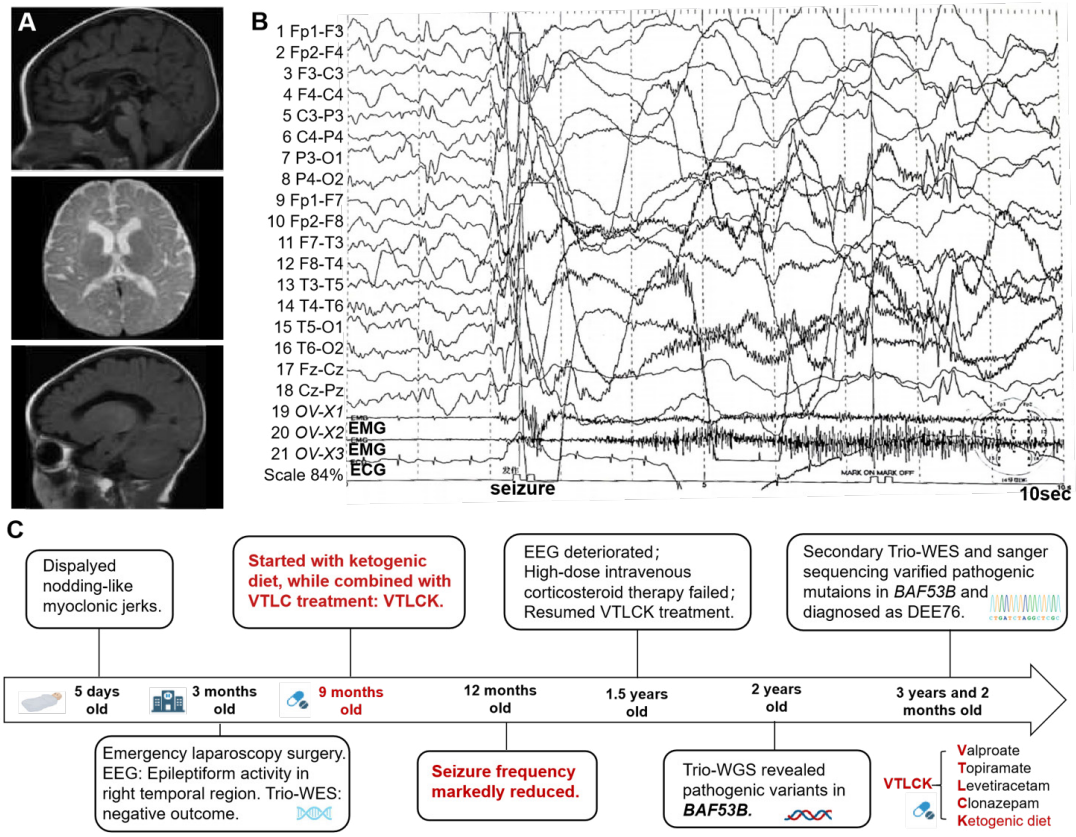

Figure 1: Pathological diagnosis and medical history summary of the proband. **A.** Brain MRI revealed widespread hypomyelination, cerebellar volume loss, enlarged ventricles, and extreme thinning of the corpus callosum at 3-month-old. **B.** Multifocal epileptiform activity revealed by EEG at 1.5-year-old. **C.** The medical history summary of the proband.

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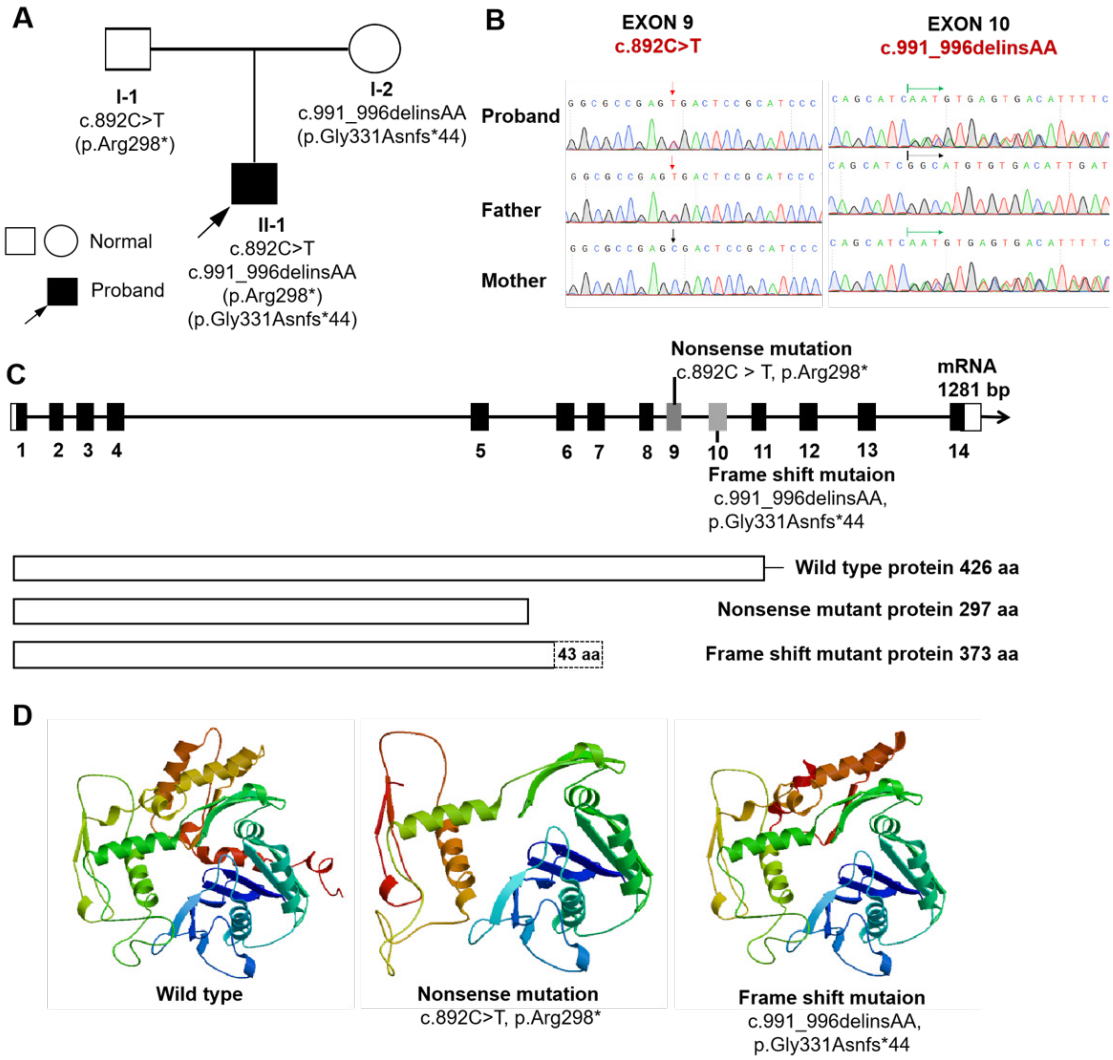

Figure 2: Schematic summary of the disease-causing mutations. **A.** Pedigree chart of *BAF53B* gene. Male is indicated by squares, and female is indicated by circles. Proband is marked with an arrow. **B.** The proband harbors *BAF53B* variants inherited from his parents which were verified by Sanger sequencing. **C.** Schematics showing mutations in *BAF53B* and the affected amino acids sequences, note that total amino acid length is not shown but the relative positions of residues been affected were depicted. **D.** 3D model generated with SWISS-MODEL based on human ACTL6A (Actin-like protein 6A).

attack, which characterized by lost consciousness briefly and shouting and crying afterwards. About the same time, persist in finding the genetic causes, his family attended a clinical trial (NCT03424772) which aimed to identify rare and undiagnosed diseases among Chinese children by whole genome sequencing (WGS). The Trio-WGS revealed that he inherited a different pathogenic variants in *BAF53B* from each parent (NM_016188.4:c.892C>T, NM_016188.4:c.991_996delinsAA) and the suggestive diagnosis could be DEE76 (OMIM 618468). When he was 3-year and 2-month old, the proband was carried to our hospital to verify the previous genome sequencing results. He had normal HC, and his weight and height was -4SD and -3SD, respectively. He suffered from seizure attacks about 20 times per day, and displayed severely impaired global development, non-verbal and non-ambulatory, unable to hold his head up or sit unassisted, displayed no purposeful movements, and unresponsive to any visual stimuli. After obtained written informed consent for genetic testing, Trio-WES was scheduled. The heterozygous variant c.892C > T (p.Arg298*) was identified in both the proband and his father in exon 9 in *BAF53B*, and the heterozygous variant c.991_996delinsAA (p.Gly331Asnfs*44) was identified in both the proband and his mother in exon 10 in *BAF53B* (Figure 2). Both variants were considered pathogenic in accordance with the PM1, PM2, PP3, and PP5 criteria. Sanger sequencing was also applied for variants validation. Together confirmed the genetic diagnosis of the proband is DEE76 induced by compound heterozygous mutants in *BAF53B*.

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Discussion

Human *BAF53B*, also known as *ACTL6B* (Actin Like 6B), which includes 1-14 exons, is located on chromosome 7q22.1 (Figure 2C). *BAF53B* plays a very important role in chromatin remodeling and histone acetylation and also regulates gene expression during neurodevelopment. A collection of *BAF53B* mutation related symptoms was reported in 2019 [2], summarized 11 children with various *BAF53B* variants presented with 2 major clinical phenotypes. One is DEE76 (OMIM 618468), an autosomal recessive neurodevelopmental disorder with severe, early-onset, refractory seizures and global developmental delay, caused by either homozygous or compound heterozygous mutation in *BAF53B*. Another is the autosomal dominant intellectual developmental disorder (OMIM 618470) with less severe symptoms caused by heterozygous mutation in the gene. Thus firstly illustrated the diagnostic clues for *BAF53B* mutants. Later study discovered the linkage between mutated *BAF53B* and heritable autism spectrum disorder [3]. As other rare genetic diseases, the diagnosis for *BAF53B* mutants carriers also highly dependent on high-throughput sequencing. KD is a high-fat, low-carbohydrate, adequate protein diet, promotes production of ketone bodies and physiological ketosis, and had been recommended as particularly useful for treatment of certain epilepsy and genetic syndromes [4]. Though seizures of DEE patients tend to be refractory to most treatment, but some may respond to KD [5]. In this case of DEE76 induced by rare variants in *BAF53B*, KD turned out to be the most applicable treatment that available, suggesting KD as a potentially therapeutic measure which could be advisable for epilepsy of DEE76.

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Disclosure statement

The authors declare no conflict of interest.

Ethical publication statement

The study was approved by the Ethic Committee of The Kaifeng Central Hospital of Henan University and written informed consent was obtained from the patient's guardian. We confirmed that this report is consistent with the journal's ethical guidelines.

References

1. Specchio N. and Curatolo P. Developmental and epileptic encephalopathies: what we do and do not know. Brain 144 (2021): 32-43.
2. Bell S, Rousseau J, Peng H, et al. Mutations in ACTL6B Cause Neurodevelopmental Deficits and Epilepsy and Lead to Loss of Dendrites in Human Neurons. Am J Hum Genet 104 (2019): 815-834.
3. Wenderski W, Wang L, Krokhotin A, et al. Loss of the neural-specific BAF subunit ACTL6B relieves repression of early response genes and causes recessive autism. Proc Natl Acad Sci 117 (2020): 10055-10066.
4. Li RJ, Liu Y, Liu HQ, et al. Ketogenic diets and protective mechanisms in epilepsy, metabolic disorders, cancer, neuronal loss, and muscle and nerve degeneration. J Food Biochem 44 (2020): e13140.
5. Ko A, Jung DE, Kim SH, et al. The Efficacy of Ketogenic Diet for Specific Genetic Mutation in Developmental and Epileptic Encephalopathy. Front Neurol 9 (2018): 530.