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Case Presentation

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Long-Term Clinical Course of a Korean Patient Diagnosed with Developmental and Epileptic Encephalopathy 91 Caused by Mutation of PPP3CA Gene

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Abstract

Background: Developmental and epileptic encephalopathy 91 (DEE91) is a rare autosomal dominant genetic disorder caused by a heterozygous *PPP3CA* mutation. Clinical features of DEE91 include delayed psychomotor development, intractable seizures with early onset, developmental regression, hypotonia, and behavioral abnormalities.

Case report: A 15-year-old Korean boy was diagnosed with DEE91 through trio-based whole exome sequencing, revealing a de novo heterozygous mutation at c.1253_1256dup (p.Ser419Argfs*33) in the PPP3CA gene. The patient exhibited a range of clinical features, including hypertelorism, seizures began at 2 months of age, intractable seizures unresponsive to multiple antiseizure drugs and a ketogenic diet, hypotonia, global developmental delay with language disorders, frequent infections such as pneumonia, and neurodevelopmental regression.

Conclusion: To aid in the management and treatment of DEE91 patients, we present a detailed report on the long-term clinical features of a Korean patient with DEE91.

Keywords: DEE91; *PPP3CA*; Calcineurin; Infantile spasms; Epilepsy; Global developmental delay

Introduction

Developmental and Epileptic Encephalopathy 91 (DEE91; OMIM #617711) is a rare autosomal dominant disorder caused by a heterozygous mutation in the PPP3CA gene on chromosome 4q24 [1]. The PPP3CA gene encodes the calmodulin-binding catalytic subunit of Calcineurin (CaN), a widely expressed calcium/calmodulin-regulated protein phosphatase [2]. DEE91 patients are often clinically diagnosed with West Syndrome (WS). However, unlike WS, which has various genetic causes, DEE91 is a well-defined single-gene disorder related to *PPP3CA*. In addition to intractable early-onset seizures, the clinical features of DEE91 patients include psychomotor developmental delay, developmental regression, hypotonia, and behavioral abnormalities [1]. Here, we report the case of a Korean patient diagnosed with DEE91 using trio-based Whole Exome Sequencing (WES). We present the patient's long-term clinical course over 15 years. Initially diagnosed with Early Infantile Epileptic Encephalopathy (EIEE) or WS, the patient later exhibited symptoms of intractable seizures, global developmental delay, and developmental regression.

Case Presentation

A 4-month-old male patient visited the outpatient clinic due to myoclonic-like seizures. He was born as the only child to healthy, non-consanguineous Korean parents at 36 weeks of gestation via cesarean section delivery with a birth weight of 2,600 g, height of 48 cm, and occipitofrontal circumference of 33 cm. His seizure symptoms began at 2 months of age, and the number of seizures seemed to increase over time. He visited an outpatient pediatric neurology clinic and was hospitalized for seizure evaluation. His initial brain MRI, blood tests, and metabolic work-up were normal, but 24-hour video Electroencephalogram (EEG) monitoring showed burst-suppression patterns with non-cluster generalized myoclonus symptoms. He was initially diagnosed with EIEE and treated with Anti-Seizure Medications (ASM) such as clonazepam and valproic acid. Despite ASM, the seizures were not controlled. At 5 months old, developmental delay was observed, and his seizures became spasm-like and clustered. His EEG showed a hypsarrhythmia pattern, leading to a diagnosis of WS. He started medication with vigabatrin and later valproic acid and ketogenic diet therapy, but his seizures remained uncontrolled **(Figure 1)**.

Figure 1: Serial photographs of the patient. (A) At 1 year of age, the patient exhibited hypertelorism, poor feeding, hypotonia, and multiple seizures. (B, C) At ages 3 and 7, the patient showed global developmental delay, delayed speech, intellectual disability, and refractory epilepsy. (D, E) At ages 9 and 10, the patient experienced developmental regression, spastic quadriplegia, and refractory epilepsy. (F) Currently at 15 years of age, the patient requires treatment with a home ventilator and continues to exhibit developmental regression, spastic quadriplegia, and seizures that are partially controlled with multiple antiseizure medications.

At 10 months old, the patient developed horizontal nystagmus of unknown cause, which gradually regressed to spastic quadriplegia, necessitating ongoing physical therapy. His seizure patterns varied over time, including myoclonus, generalized tonic-clonic seizures, and head drops, leading to a clinical diagnosis of Lennox-Gastaut syndrome. Despite treatment with topiramate, levetiracetam, pyridoxine, lamotrigine, clonazepam, and phenytoin, his seizures were not completely controlled. Additionally, he experienced frequent hospitalizations due to infections such as pneumonia, sepsis, and acute pyelonephritis. He underwent follow-up brain MRI at 18 months, and diffuse nonspecific brain atrophy was observed from that time. Subsequent brain MRIs performed at 9 years 10 months and 11 years of age showed hydrocephalus and marked diffuse brain atrophy **(Figure 2)**. He underwent chromosomal microarray testing in 2019, and no specific findings were found. In February 2023, trio-based WES

revealed a de novo heterozygous mutation (c.1253_1256dup) in the PPP3CA gene, confirming the diagnosis of DEE91 **(Figure 3)**.

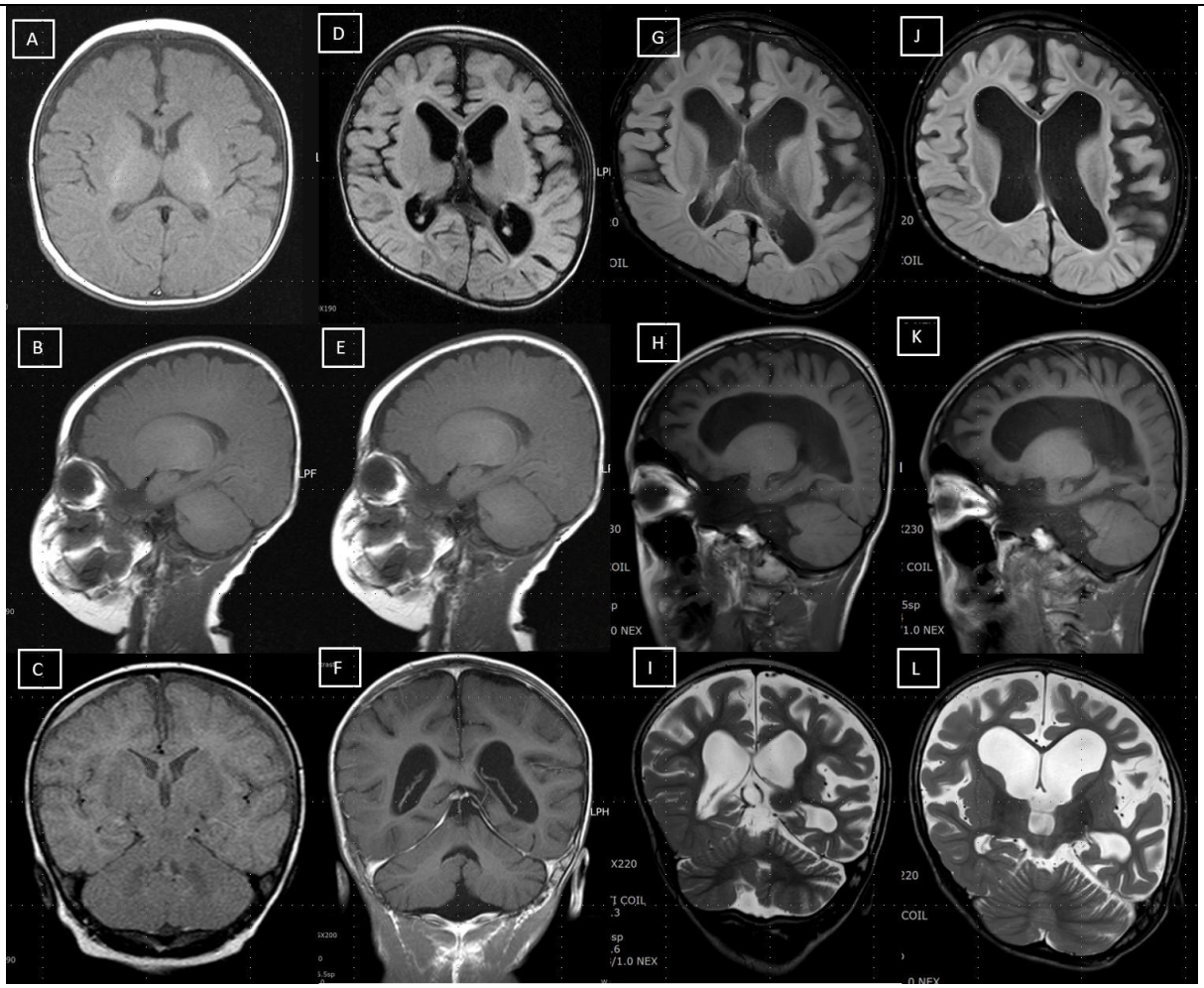

Figure 2: Serial MRI findings. (A-C) At 4 months of age, axial, sagittal, and coronal views show a normal brain MRI. (D-F) At 18 months of age, diffuse non-specific cerebral atrophy is observed. (G-I) At 9 years and 10 months of age, there is marked diffuse cerebral atrophy with hydrocephalus. (J-L) At 11 years of age, MRI reveals marked diffuse cerebral dysfunction with hydrocephalus and hypoplasia of the splenium and posterior part of the corpus callosum.

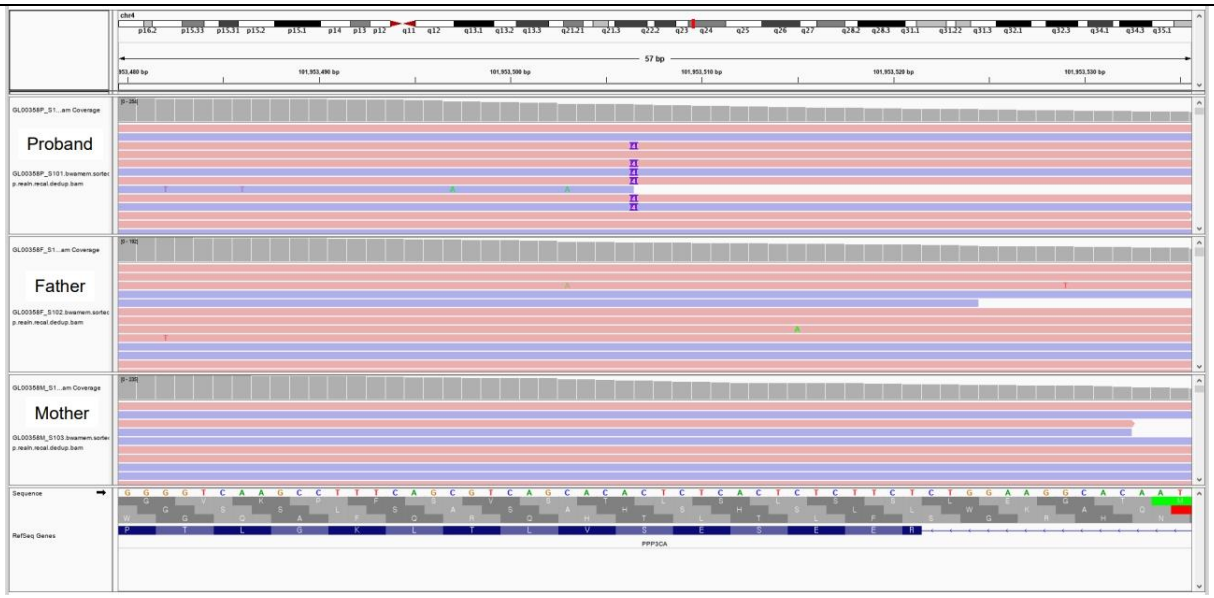

Figure 3: Identification of a de novo c.1253_1256dup heterozygote variant in *PPP3CA* (NM_000944.5) in the proband. The BAM file displayed in the Integrative Genomics Viewer (IGV) shows that the c.1253_1256dup heterozygote variant is observed in both the forward (red in IGV) and reverse (blue in IGV) strands.

Now 15 years old, the patient's development has gradually regressed, and he is bedridden with spastic quadriplegia. He receives nutrition via percutaneous endoscopic gastrostomy due to poor oral intake and continues to experience seizures about twice a day despite taking multiple ASMs, including levetiracetam, valproic acid, and clonazepam. He continues to receive physical therapy.

Discussion

The identification of *PPP3CA* mutations has significantly advanced our understanding of DEE91. Li and Cao described a novel truncating mutation within the *PPP3CA* regulatory domain in a Chinese patient, which resulted in severe developmental and epileptic encephalopathy [1]. This mutation disrupts the normal regulatory mechanisms of calcineurin, resulting in pathological overactivation or inactivation. Similarly, Rydzanicz et al. reported an epilepsy-associated *PPP3CA* mutation that causes constitutive activation of calcineurin and subsequent downregulation of protein expression [2]. These findings highlight the importance of balanced calcineurin activity for normal neurodevelopment. Furthermore, Mizuguchi et al. highlighted that both loss-of-function and gain-of-function mutations in *PPP3CA* can cause distinct neurodevelopmental disorders, confirming that precise regulation of calcineurin activity is essential for proper neuronal function [3]. This dual role of calcineurin suggests that dysregulation, either hypoactivity or hyperactivity, may contribute to the pathogenesis of DEE91. Calcineurin plays a central role in a variety of cellular processes, including neuronal signaling and synaptic plasticity. Dysregulation of calcineurin activity due to genetic mutations disrupts these processes, leading to the clinical manifestations of DEE91. Rusnak and Mertz have provided a comprehensive overview of the form and function of calcineurin, emphasizing its role in

unphosphorylating numerous substrates involved in neuronal function [4]. Cook and Creamer have also discussed the chaotic molecular environment in which calcineurin operates, emphasizing the need for precise regulation of calcineurin to maintain cellular homeostasis [5]. The clinical manifestations of DEE91 patients typically present with early-onset seizures, often accompanied by severe developmental delay and intellectual disability within the first year of life. These clinical features have been consistently observed in multiple studies, indicating a distinct phenotypic profile associated with *PPP3CA* mutations. In addition to seizures, patients also present with a range of systemic symptoms, including hyperophthalmos, cortical visual impairment, poor feeding, coccydynia, hypotonia, developmental regression, lack of independent walking, unsteady gait, rigidity, resistant seizures, nonspecific abnormalities seen on brain imaging, brain atrophy, delayed myelination, white matter changes, autistic features, and behavioral abnormalities. Myers et al. demonstrated that de novo mutations in *PPP3CA* lead to a severe neurodevelopmental disorder with seizures, further establishing the important role of this gene in brain development [6]. Current treatments for DEE91 primarily focus on controlling seizures with anticonvulsants, but these treatments are often of limited efficacy. Creamer suggested that targeted therapies that modulate calcineurin activity may offer a new therapeutic avenue [7]. As our understanding of the molecular basis of DEE91 deepens, it is hoped that more effective therapies will be developed in the future, leading to better outcomes for patients. In our study, the patient started with resistant seizures in infancy and presented with typical clinical features of DEE91, which was initially diagnosed as EIEE or WS. Global developmental delay and developmental regression were observed later. Despite the patient's mother's very active care, the patient had frequent infections such as pneumonia, sepsis, and pyelonepharitis, which are characteristic findings.

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