

Case Report

# A 16q22.2-q23.1 deletion identified in a male infant with West syndrome

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## Abstract

In partial monosomy of the distal part of chromosome 16q, abnormal facial features, intellectual disability (ID), and feeding dysfunction are often reported. However, seizures are not typical and the majority of them were seizure-free. Here we present the case of a 16q22.2-q23.1 interstitial deletion identified in a male patient with severe ID, facial anomalies including forehead protrusions and flat nose bridge, patent ductus arteriosus, bilateral vocal cord atresia treated by tracheotomy, and West syndrome, which were developed 10 months after birth. Although phenobarbital, sodium valproate (VPA), and zonisamide were not effective as monotherapies or combination therapies, the patient's epileptic seizures and electroencephalogram anomalies disappeared following combined therapy with lamotrigine and VPA. Although WW Domain Containing Oxidoreductase (WWOX), which is known as a cause of autosomal recessive epileptic encephalopathy, was included within the 6.8-Mb deleted region which identified by targeted panel sequencing and validated by chromosomal microarray analysis, no pathogenic variants were detected in the other allele of WWOX. Therefore, it is possible that other genes within or outside of the long deleted region or their interactions may cause West syndrome in this patient.

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## 1. Introduction

Chromosome 16 deletion is a rare genetic condition in which genetic material is missing from chromosome

16, one of the body's 46 chromosomes. In chromosome 16 deletion cases, the likelihood and severity of problems depend on which regions of the chromosome are missing. In a study of 13 patients with distal interstitial deletions between 16q21 and 16q24, abnormal facial features, intellectual disability (ID), and feeding dysfunction were commonly reported [1]. However, those cases did not include any indication of epilepsy.

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In this report, we describe the case of a Japanese boy who presented West syndrome and interstitial 16q22.2-q23.1 deletion. The patient did not respond to various antiepileptic drugs, but eventually responded to a combined treatment with lamotrigine (LTG) and sodium valproate (VPA).

## 2. Case report

A 4-year and 7-month-old Japanese male was the first child of non-consanguineous, healthy parents who had no notable family disease history. The patient was born at 38 weeks of gestation with a birth weight of 2508 g, body height of 49 cm (+0.2 SD), and head circumference of 31 cm (−1.6 SD). The patient exhibited severe developmental delay from birth. He began to gain head and neck stability at 8 months of age and rolled over at 1 year and 10 months of age. And several facial anomalies including forehead protrusions, a flat nose bridge, and low-set ears were observed (Fig. 1). Patent ductus arteriosus (PDA) was also detected in the patient. Consequently, catheter embolization of PDA was performed at 3 years old. After endotracheal intubation and artificial ventilation due to respiratory syncytial virus infection, bilateral vocal cord atresia occurred. Tracheostomy was performed to enable respiration. Conventional chromosome analysis revealed a normal male karyotype of 46,XY, and all subtelomeric fluorescence *in situ* hybridization tests revealed normal patterns. At 10 months old, the patient's mother observed periodic abnormal activity in his upper limbs immediately after waking, but the observation was not considered serious. At 1 year and 4 months of age, the patient's mother consulted an attending doctor regarding this periodic symptom. The patient was diagnosed with West syndrome based on serial spasms observed in a video of the patient's motor activity and hypsarrhythmia recorded by electroencephalogram (EEG) (Fig. 2A). A slight cisternal expansion was observed in the brain

magnetic resonance imaging; however, no further abnormal findings were noted. Considering the patient's severe inborn ID and tracheostomy, we concluded that treatment with antiepileptic drugs was preferable to adrenocorticotrophic hormone (ACTH) therapy to avoid the severity of potential side effects from ACTH. Pheno-barbital (PB) was initially administered, but its effect was insufficient. Several health problems must be managed, and due to the side effects of the rapid increase in the dosage of antiepileptics, caution must be observed when administering such drugs. At 2 years and 3 months of age, PB was replaced with VPA, which was also insufficient. Zonisamide (ZNS) treatment was commenced at 2 years and 10 months of age; however, an increase in sputum prompted discontinuation of the treatment. At 2 years and 11 months of age, the EEG displayed diffuse polyspikes and polyspikes and waves (Fig. 2B). Antiepileptic drug treatment was switched to a combination of VPA and LTG, which was followed by complete disappearance of epileptic seizures. By the time the patient was 3 years and 5 months old, EEG abnormalities had also disappeared (Fig. 2C). After the recession of spasms and improvement of EEG abnormalities, emotional expression and sitting position stability gradually improved. The patient remained seizure-free at 4 years and 7 months of age, and he was able to feed orally, which allowed him to consume one-third of his daily energy needs.

An overview of the clinical course of this case is illustrated in Fig. 3.

## 3. Molecular genetic analysis

This study was performed in accordance with the Declaration of Helsinki Principles and was approved by the ethics committee of Tokushima University. Blood samples were obtained from the patient upon receiving written informed consent from his parents.



Fig. 1. Facial appearance at 4 years and 5 months old. Several facial anomalies, such as forehead protrusions, flat nose bridge, and low set ears, were observed. We got the permission from his parents to post this photograph.

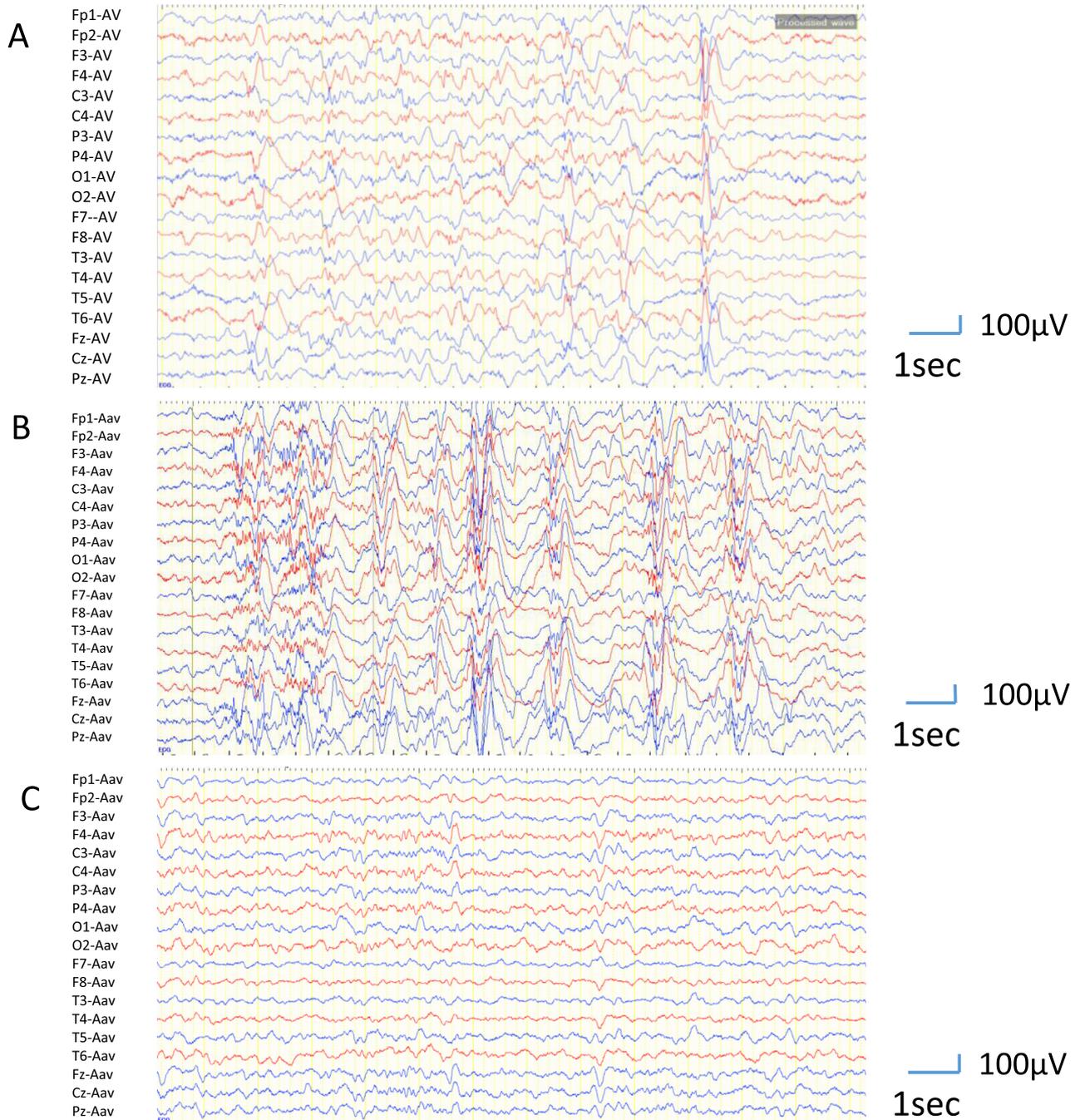


Fig. 2. A: Electroencephalogram (EEG) at 1 year and 4 months old (before treatment). Irregular multifocal spikes and slow waves were observed occasionally; we diagnosed this EEG as mild type of hypsarrhythmia. B: EEG before adding on lamotrigine (LTG) at 2 years and 11 months old. Diffuse polyspikes and polyspikes and wave were found. C: EEG after adding LTG at 3 years and 5 months old. The epileptic discharge disappeared, and sleep spindle was observed.

We conducted a targeted panel sequencing (TPS) for the targeted exons of 4813 disease-related genes using a TruSight One Sequencing Panel and MiSeq (Illumina, San Diego, CA, USA) with our pipeline for next-generation sequencing data analysis, as previously described [2,3]. The detection of copy number variations using TPS data with a resolution ranging from a single

exon to several exons, depending on the exon sizes, was performed as previously described [2]. These analyses revealed no disease-causing single-nucleotide variations or small indels but did detect an interstitial gross deletion between the *PH Domain And Leucine Rich Repeat Protein Phosphatase 2 (PHLPP2)* and *WW Domain Containing Oxidoreductase (WWOX)* genes

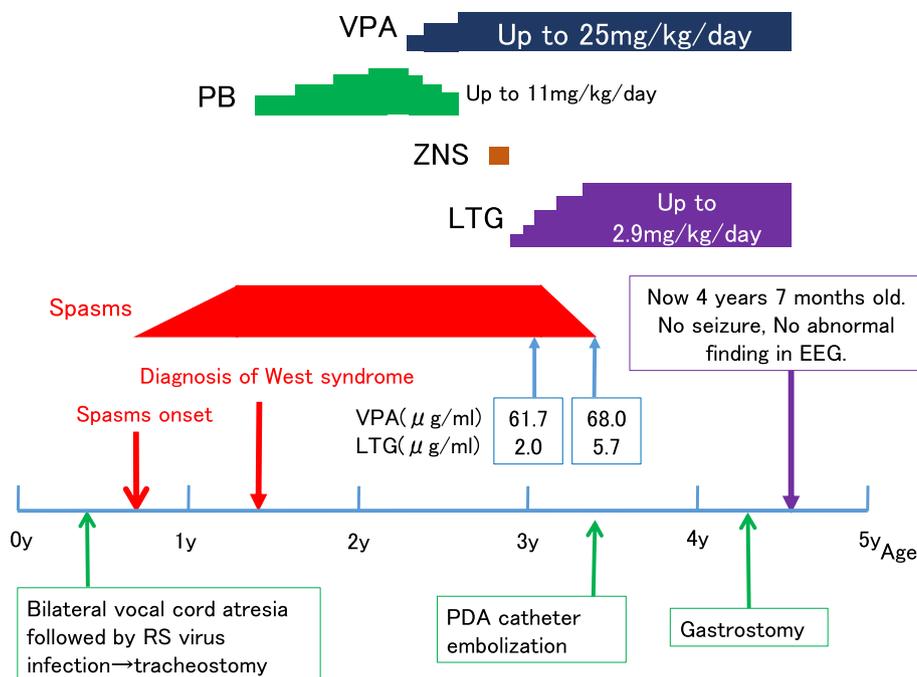


Fig. 3. Clinical course of the present case. Spasms decreased according to the increase of LTG dosage and elevation of LTG blood concentration. PB, phenobarbital; VPA, valproic acid; ZNS, zonisamide; LTG, lamotrigine; PDA, patent ductus arteriosus.

within 16q22.2–q23.1. Both breakpoints of the deleted region were located within those genes. All the sequenced positions of 12 targeted genes located within the deleted region were inspected by visual verification of the alignment file using the Integrative Genomics Viewer (IGV) to ascertain whether the “no call” status was due to insufficient coverage, any artifacts, or misalignment. Subsequent chromosomal microarray analysis was conducted for validation and fine mapping of the deleted region using an Affymetrix CytoScan HD chromosome microarray platform (Affymetrix, Santa Clara, CA, USA) [2]. A 6.8 Mb heterozygous chromosomal deletion was detected within 16q22.2–q23.1, which contains 57 Refseq genes including *PHLPP2* and *WWOX*, as 46,XY.arr[hg19] 16q22.2q23.1(71,689,186–78,530,357)x1 (Supplementary Table S1).

Parental DNA was unavailable; therefore, the deletion was not confirmed as occurring *de novo*.

#### 4. Discussion

Among the genes within the 6.8 Mb interstitial 16q22.2–q23.1 deletion detected in the present case, *WWOX* and *Fatty acid 2-hydroxylase (FA2H)* have been reported as causes of epilepsy according to ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>). *WWOX* is a well-known cause of early-infantile epileptic encephalopathy 28 (EIEE28). Hussain et al. reported that *WWOX* deletion leads to a reduction in GABAergic

inhibitory interneurons, along with the activation of microglia and astrocytes in the mouse hippocampus [4]. However, all reported cases of EIEE28 show that patients with epilepsy present homozygous or compound heterozygous pathogenic *WWOX* variants including deletions. Through screening cases with (1) pathogenic/likely pathogenic deletions overlapped with the deleted region in our case and (2) epileptic encephalopathy/seizures as phenotypes in the DECIPHER v9.28 database (<https://decipher.sanger.ac.uk/>), we only identified two cases (#354399 and #384984), that had the same deletion partially containing the coding exons of *WWOX* inherited from the mother and the same missense variant with uncertain significance, NM\_016373.3:c.49G>A/p.(Glu17Lys) within the other allele of *WWOX*. In the DECIPHER database, no cases with epileptic encephalopathy/seizures caused by gross heterozygous deletions largely overlapped with the deleted region in our cases were observed. Thus, the relationship between haploinsufficiency of *WWOX* and/or other genes located around *WWOX* and West syndrome remains unclear, although only 12 of 37 Online Mendelian Inheritance in Man (OMIM) genes were included in the sequencing panel used in this study (Supplementary Table S1).

Homozygous or compound heterozygous pathogenic *FA2H* variants cause fatty acid hydroxylase-associated neurodegeneration, which is characterized by effects of the central nervous system including impaired corti-

cospinal tract activity (spasticity), mixed movement disorders (ataxia/dystonia), and eye conditions (optic atrophy and oculomotor abnormalities) early in the disease course and by progressive intellectual impairment and epilepsy later in the disease course [5]. Epileptic seizures, which can be caused by pathogenic *FA2H* variants, are typically infrequent and respond relatively well to anti-convulsants. *FA2H* was included in the sequencing panel. However, no pathogenic variants were detected using our TPS (Supplementary Table S1). Because it is possible that genes, which are not included in the sequencing panel used in this study, may cause West syndrome, further whole exome or whole genome sequencing may enable the identification of the candidate disease-causing genes.

When children fail to achieve complete cessation of infantile spasms after treatment with ACTH or vigabatrin, or when they cannot be treated with these drugs, second-line medications are necessary. In uncontrolled studies, these medications may include topiramate, ZNS, VPA, nitrazepam, LTG, levetiracetam, felbamate, high-dose pyridoxine, liposteroid, ganaxolone, or thyrotropin-releasing hormone [6]. There are various reports that evaluate the efficacy of LTG in the treatment of West syndrome. In a single-blind, placebo-controlled, add-on study, 30 patients with infantile spasms refractory to conventional antiepileptic drugs and to vigabatrin and corticotropin were treated with LTG. Nine patients showed a >50% decrease in infantile spasms, five of which achieved complete cessation [7]. Additionally, three infants affected with symptomatic West syndrome who were unresponsive to vigabatrin and ACTH were successfully treated with very small doses of LTG [8].

In this patient, changes in the EEG findings eventually suggested Lennox–Gastaut syndrome. Rational multidrug therapy should be considered for intractable epilepsy patients if surgical intervention is too difficult. Lennox–Gastaut syndrome (LGS) is a well-defined epileptic encephalopathy that is highly drug resistant. The first-line treatment is valproate (VPA) combined with lamotrigine [9].

The clinical efficacy of combined VPA and LTG therapy has been previously confirmed. Brodie et al. recruited 347 patients with epilepsy that was not fully controlled by VPA, carbamazepine (CBZ), phenytoin (PHT), or PB monotherapy into an LTG substitution study [10]. The addition of LTG to VPA produced a significantly improved response rate (64%) compared with the addition of CBZ (41%) or PHT (38%). This effect was also observed in the treatment of partial and tonic–clonic seizures. These data provide evidence for the beneficial therapeutic synergy between LTG and VPA observed in our study. During combination therapy with antiepileptic drugs, differences between functional mechanisms are important factors underlying

the success of treatment. LTG acts through voltage-sensitive sodium channels, stabilizing neural membranes and inhibiting the release of excitatory neurotransmitters [11]. VPA promotes the elevation of gamma-aminobutyric acid (GABA) levels, dopamine levels, and serotonin metabolism, which contributes to the activation of an intracerebral suppression network. These unique pharmacological attributes may explain the observed success of LTG+VPA therapy in West syndrome. As mentioned above, various genes may be associated with the cause of epilepsy in this patient. Our findings suggest that a combination of antiepileptic drugs with different functional mechanisms might contribute the success of treatment in West syndrome.

## 5. Conclusions

A male patient with an interstitial 16q22.2–q23.1 deletion presented West syndrome, which has never been reported as a phenotype in cases with deletions in this region. The patient's seizures were successfully treated with the combination of LTG and VPA therapies. Although *WWOX* is a well-known cause of autosomal recessive epileptic encephalopathy within the 6.8-Mb deleted region, no pathogenic variants were identified in this gene. Therefore, it is possible that other genes within or outside of the long deleted region or their interactions may be associated with the distinctive features of this patient.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.braindev.2019.07.005>.

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