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Article

WWOX Gene Disease as Infantile Catastrophic Epileptic Encephalopathy (WOREE Syndrome Plus): A Comprehensive Case Study with Brief Literature Update

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Abstract

The WWOX gene, well-known as tumor suppressor, has also a crucial role as transcription factor in the developing brain. The bi-allelic loss of WWOX gene causes a condition characterized by drug-resistant epilepsy, developmental delay, and neurological impairments, often resulting in mortality within the first year of life, known as WOREE syndrome (MIM: 616211). Whole Exome Sequencing (WES) analysis was performed on a female patient who died within three months of birth and was diagnosed with microcephaly, severe early-onset refractory seizures, and drug-resistant epileptic encephalopathy. WES revealed a 38 kb CNV deletion spanning WWOX exons 6-7, and a known frameshift variant in exon 8, impairing a highly clinically significant region of the encoded protein. Clinical and genetic features of reported WOREE patients with WWOX gene deletions similar to our patient were analyzed. Our case highlights the clinical heterogeneity of WWOX variants in WOREE syndrome and suggests that the novel compound heterozygous deletion may contribute to poor prognosis. A "WOREE syndrome plus" phenotype can be defined by severe neurological disorder, microcephaly, and a fatal outcome within the first year of life. Further researches need to elucidate WWOX pathophysiology and improve diagnostic and therapeutic strategies.

Keywords: autosomal recessive spinocerebellar ataxia 12 (SCAR12; MIM:614322); infantile epileptic encephalopathy 28 (IEE28; MIM:616211); WW domain-containing oxidoreductase (WWOX) gene (MIM: 605131); WWOX-related epileptic encephalopathy (WOREE) syndrome; Whole Exome Sequencing (WES)

1. Introduction

The WW domain-containing oxidoreductase (WWOX) gene (MIM: 605131) is situated within the fragile site FRA16D on chromosome 16q23.3-q24.1, one of the common hot spots of genomic

instability for germline and somatic copy number variations (CNVs) [1,2]. Germline mutations of *WWOX* are rare and primarily associated with severe developmental disorders, while somatic mutations causing the cancer predisposition [2]. Widely known as tumor suppressor, the *WWOX* gene encodes a 414-amino acid enzyme belonging to the short-chain dehydrogenases/reductases (ADH/SDR), which in the role of transcription factor exerts pleiotropic functions regulating various cellular pathways (e.g. cell proliferation, apoptosis and steroid metabolism) [1]. Even if less studied in the brain, *WWOX* seems to hold a pivotal position in the central nervous system's biology, significantly contributing to neuronal development, migration, and proliferation [3]. Normally expressed in neurons, oligodendrocytes, and astrocytes, it serves as a scaffold protein due its WW domain and interaction ability to counteract various proteins, e.g. cytoskeleton proteins, cellular trafficking and microtubule-based transport [3].

Bi-allelic or pathogenic variants in *WWOX* are implicated in autosomal recessive conditions, such as spinocerebellar ataxia type 12 (SCAR12; MIM:614322) and infantile epileptic encephalopathy 28 (IEE28; MIM:616211) [2]. These disorders often present with neurological manifestations including epilepsy, developmental delay (DD), and motor impairments [2]. Animal models have provided critical insights into *WWOX* deficiency, demonstrating phenotypes resembling epilepsy. The *WWOX* knockout (KO) mouse model mirrors human symptoms such as epilepsy, structural brain malformations, and learning impairments, alongside severe metabolic disorders and premature death within weeks of birth [4]. Currently, 88 disease-causing variants in *WWOX* are cataloged in the Human Gene Mutation Database (HGMD) database (www.hgmd.cf.ac.uk/), illustrating distinct genotype-phenotype correlations: (i) null genotypes: absent psychomotor development, poor spontaneous motility, absent eye contact from birth, drug-resistant epilepsy starting in the 1st weeks of life, as well as possible retinal degeneration, premature death, and acquired microcephaly; (ii) compound heterozygous genotypes with one null allele and one missense mutation: less severe encephalopathy combining IEE with delayed psychomotor development and increased life expectancy; (iii) genotypes with biallelic hypomorphic missense mutations: SCAR12 [5].

Homozygous and compound heterozygous variants in the *WWOX* gene have been linked to *WWOX*-related epileptic encephalopathy (WOREE) syndrome (more details in the official website of 'WWOX foundation for WWOX-related syndromes': www.wwox.org/what-is-wwox). WOREE has been characterized by severe early-onset epileptic encephalopathy, resistant seizures to conventional antiseizure medications (ASMs) and diverse brain anomalies including impaired myelination, thickened corpus callosum, white matter abnormalities, and/or cerebral atrophy [6,7], accompanied by DD, psychomotor impairments, spasticity with hyperreflexia and hypokinesia, and an inability to walk or communicate verbally. Microcephaly was also reported [8,9] and most affected of them succumb within the first year of life [2]. Despite advancements, the full spectrum and precise genotype-phenotype correlations of *WWOX*-related disorders remain areas of ongoing research.

In this study, we present a case report of a female patient died early at a few months of age, affected by microcephaly and severe early-onset refractory seizures, and exhibited a drug-resistant epileptic encephalopathy. A trio-based whole-exome sequencing (WES) identified two mutations in the baby girl, a 38 kb CNV deletion spanning *WWOX* exons 6-7, and a known frameshift variant c.1043del (p.Phe348Serfs*57) in exon 8 (ClinVar ID: 421407); both absent in her parents.

There appear to be no similar cases in the literature that report the same genotype associated with early death. Our study would shed light on the rare condition of *WWOX*-associated phenotype, investigating both her distinct clinical and genetic features.

2. Materials and Methods

2.1. Ethical Compliance

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of the University of Catania, Italy (Ethical Committee Catania 1 Clinical Registration n. 210/2023/PO). Written informed consent was

obtained from the parents of the patient for publication of the details of their medical case and any accompanying images.

2.2. Genetic Testing and Genomic Data Analysis

The genomic Deoxyribonucleic Acid (DNA) of proband and her parents was extracted from a buccal swab to perform the clinical whole exome sequencing (WES) using the Blueprint Genetics Whole Exome Plus Test (version 3, February 2023). Variant data were annotated using tools like VcfAnno and Variant Effect Predictor (VEP), referencing public databases such as gnomAD SVs v2.1, ExAC, ClinVar, and HGMD. Variant classification followed Blueprint Genetics Variant Classification Schemes modified from the American College of Medical Genetics and Genomics (ACMG) guideline 2015 [10]. WES findings were also analyzed using the database tracks (OMIM Allelic Variants, ClinVar Variants, dbSNP, and Decipher v.21.11) available from UCSC genome browser (genome.ucsc.edu). The study was approved by the NICU ethics committee, and the proband's parents provided written consent in accordance with the Declaration of Helsinki.

3. Results

3.1. Case Presentation

The patient, a female infant, was admitted to the neonatal intensive care unit (NICU) due to seizures after few hours from birth. She was born after an uneventful pregnancy and spontaneous vaginal delivery at full term, the birth weight was 3.100 grams (-0,88 SDS - Standard Deviation Score), the length was 50 cm (-0,2 SDS), and the head circumference was 32 cm (-2,07 SDS), consistent with microcephaly. Apgar score was 9 and 10 after 1 and 5 minutes, respectively. The familiar medical history was unremarkable. Seizures, characterized by body stiffening, horizontal nystagmus, eyelid myoclonus and epileptic spasms, began shortly after birth and were accompanied by vomiting. There was no significant family history or dysmorphic features noted upon examination. The infant was started on levetiracetam for seizure management. The first electroencephalogram (EEG) was normal, but due to the persistence of seizures, treatment with levetiracetam as an ASM was initiated.

Neurological examination revealed several abnormalities, including lack of gaze fixation with horizontal nystagmus, axial hypotonia with spastic hypertonia of the limbs, reduced general movements, and reduced patellar reflexes. At 8 days of life, she presented multi-daily asymmetric tonic seizures with eye deviation to the left and left arm hyperextension. A second EEG performed during sleep, showed multifocal interictal epileptiform discharges (IED) with a focus on the bilateral centro-temporal areas. The ictal EEG revealed spikes on the right occipital derivations. Based on the electrical pattern and the persistence of critical episodes, carbamazepine was added as an adjunctive ASM. At this stage, the differential diagnosis included early infantile epileptic encephalopathy, neonatal encephalopathy secondary to hypoxic-ischemic encephalopathy, and encephalopathy due to structural brain abnormalities. The EEG pattern strongly indicated early infantile epileptic encephalopathy. Blood tests for metabolic disorders were performed, resulting within normal limits. Brain MRI at 10 days of age was unmarkable. Unfortunately, the infant passed away for cardiac arrest after three months of ages due to pulmonary infections and respiratory failure.

3.2. Mutational Analysis

WES analysis (hg19) identified two heterozygous pathogenic variants of WWOX gene (NM_016373.4) (Figure 1).

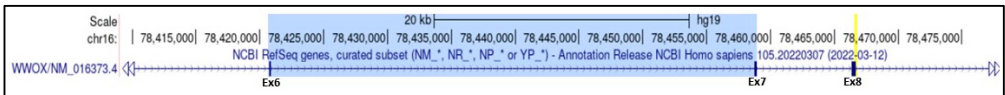


Figure 1. UCSC Genome Browser illustration of pathogenic variants of WWOX (NM_016373.4) found in the proband. UCSC genome browser (genome.ucsc.edu) shows the 38 kb CNV deletion (chr16:78420649-78459043;

hg19) shaded in blue, while in yellow the frameshift variant c.1043del (p.Phe348Serfs*57) (ClinVar ID:). Only for illustrative purpose, the two variants are represented within the same gene sequence, without indicating the location on specific allele and their cis/trans effects. Coding exons (ex) are represented by bars and introns with horizontal lines.

The first is a CNV deletion c.(516+1_517-1)_(791+1_792-1)del, which involves exons 6-7 (chr16:78420649-78459043; at least 38 Kb), resulting in the disruption of open reading frame. Coordinates of CNV represent an estimate of the alteration's genomic position, since we are unable to determine the exact breakpoints using the current next-generation sequencing method. The second is a known frameshift variant c.1043del (p.Phe348Serfs*57) (ClinVar ID: 421407) in exon 8 of WWOX gene (chr16:78,466,634-78,466,634) (Figure 1). In detail, the present CNV loss, also confirmed by digital Polymerase Chain Reaction (PCR), results in an out-of-frame deletion of exons 6-7 of the WWOX gene, potentially leading to the disruption of the open reading frame and, consequently, protein truncation or nonsense-mediated mRNA decay. Deletions encompassing WWOX exons 6-7 have been reported in one individual in the ExAC control cohorts. In addition, overlapping deletions involving exon 6 or 7 or both have been detected in 17 individuals in the ExAC control cohorts and in 4 individuals in the gnomAD control cohorts (gnomAD SVs v2.1, ExAC data available in the gnomAD browser). Furthermore, the same rearrangement has not been found in Decipher database v.21.11. Instead, the variant c.1043del (p.Phe348Serfs*57) (ClinVar ID: 421407) appears to induce a frameshift in the penultimate exon of the gene, resulting in a premature stop codon in the final exon. No additional genetics findings were reported. Analysis of asymptomatic parental samples would have required for the inheritance pattern determination of variants but did not perform.

4. Discussion

WWOX genetic variants exhibit a certain degree of heterogeneity from a phenotypic perspective. The clinical wide spectrum ranges from a mild phenotype, SCAR12, to a severe condition known as WOREE syndrome, depending on the specific mutation and its impact on WWOX gene expression [7]. Consequently, the diagnosis and the treatment are challenging due to the different phenotypes observed among affected individuals. Diseases caused by WWOX variants is inherited in an autosomal recessive manner. WOREE syndrome typically manifests with early-onset epilepsy, growth impairment, delayed psychomotor development, and progressive microcephaly correlated with a high mortality rate in first years [3].

The first animal model, a spontaneous 13-bp deletion in exon 9 of the WWOX gene in the lde/lde (lethal dwarfism with epilepsy) rat, was reported associated with dwarfism, ataxic gait, a high incidence of epileptic seizures, and postnatal lethality, highlighting the WWOX role in developmental neurobiology [11]. This preclinical model showed a post-natal lethal phenotype, with severe neurological disorder, early mortality before the first year of age and possible association with microcephaly. This phenotypic picture could be defined as 'WOREE syndrome plus'.

The WWOX gene would be linked to neuronal migration and therefore involved in the growth of cranial circumference, hence the microcephaly. However, the pathophysiological mechanism driving the development of WOREE syndrome due to the complete or partial loss of function of WWOX remains incompletely understood. A more comprehensive overview of phenotypic and genetic features of WOREE patients aligned with our case was provided in Figure 2.

STUDY	EPIDEMIOLOGICAL DATA			NEUROLOGICAL EXAMINATION						SURVIVAL	GENETIC INFORMATION		
Ref.	Sex	Ethnicity/ Consanguinity	Microcephaly	Seizure	Age of onset	Freq. of seizures	Drug resistance	EEG	MRI	Premature death (< 3 month)	Genotype	Exon	Protein change
[7]	F	Italian/no	no	focal, tonic and spasms	20 d	daily	no	disorganized, multifocal and disorganized, but without epileptic discharges	CC hypoplasia, expansion of the CSF spaces	na	c.606_791del (in frame deletion)	6-7	p.Pro203_Arg264del
	F	Caucasian/no	no	focal (hemiclonic) and generalized spasms during the course	2-3 d	daily	yes	abnormal background activity and bimtemporal paroxysmal anomalies	CC hypoplasia, cerebral atrophy	na	c.953C>T c.517_1056del (in frame deletion)	8 6-7	p.Ser318Leu p.His173_Met352del
	F	French/no	no	focal at onset (occipital: eye movements) and tonic-clonic with eye movements	2-3 d	daily	yes	disorganized and SBA. Epileptiform activity: occipital spikes	CC hypoplasia, subarachnoid space enlargement	6 m	c.606_791del (in frame deletion)	5-7	p.Pro203_Arg264del
	M	Sub Saharan African/yes	no	focal seizures hemitonic/polymorphic: focal (hemitonic) and myoclonic jerks/perioral myoclonia	1 m	daily	yes	disorganized and SBA. Epileptiform activity: occipital spikes	cerebral atrophy, subarachnoid spaces enlargement, CC hypoplasia, white matter hypersignal	2,25 y	c.517_1056del (in frame deletion)	6-8	p.His173_Met352del
	M	West Indian, Britain/no	no	infantile spasms	2-3 d	daily	yes	hypsarrhythmic pattern	thin CC, abnormal lateral	2,5 y	c.517_791del (in frame deletion)	6-7	His173Ilefs*5
	F	Britain/no	no	infantile spasms	2-3 d	daily	yes	modified hypsarrhythmic pattern	normal	2,5 y	c.517_1056del (in frame deletion) c.705dupG (frameshift)	6-8 7	p.His173_Met352del p.His236Alafs*34
	M	French/no	no	focal clonic I and generalized with dialeptic seizures and myoclonic seizures	2-3 d	daily	yes	abnormal sleeping background with focal temporal spikes on initial EEG	thin CC	na	c.517_791del (in frame deletion)	6-7	p.His173Ilefs*5
	M	French/no	no	focal and clonic at onset then spasms and myoclonic seizures	2-3 d	daily	yes	abnormal sleeping background with focal temporal spikes on initial EEG	CC hypoplasia, cerebral atrophy	na	c.517_791del (in frame deletion)	6-7	p.His173Ilefs*5
[13]	F	Chinese/no	no	seizures characterized by clenched teeth, cyanosis around the lips and tetanic twitch of the limbs	15 d	daily	yes	slow weakened of background activity observed in both hemispheres and and polyspikes low-wave discharge in bilateral temporal	white matter hyperintensity and delayed myelination in the brain	2,5 y	c.517_605del (frameshift) c.517_1056del (in frame deletion)	6 6-8	p.His173AlafsTer67 p.His173_Met352del
	Present case	F	Italian/no	yes	body stiffening, horizontal nystagmus, eyelid myoclonus and epileptic spasms	2 d	daily	yes	spikes on the right occipital derivations	normal	3 m	c.516-1_517-1_791+1_792-1 (out of frame) c.1043delT (frameshift)	6-7 8

Abbreviations: CC, corpus callosum; CTT, central tegmental tracts; D, days; F, female; ID, intellectual disability; M, male; m, months; na, not available; SBA, slow background activity; SWs, slow waves.

Figure 2. A focused summary of main clinical and genetic features of the our proband and WOREE patients with 6-7 exon containing CNV variants.

According to our results, no cases with similar our CNV deletion on *WWOX* gene, reported the clinical sign of microcephaly (Figure 2). To note, evidence of microcephaly was associated with other genotypes [9,12]. As highlighted in Figure 2, Piard et al. reports another patient who experienced early death at 6 months of age, similar to our patient (who passed away at 3 months), with epileptic encephalopathy onset at 2 days of life in both cases [7]. In addition, there are other studies describing a clinical picture characterized by very early infantile-onset epileptic encephalopathy. Mallaret et al. reported a homozygous missense variant c.139C>A, p.(Pro47Thr), within the WW domain, in four siblings with childhood-onset cerebellar ataxia, generalized tonic-clonic epilepsy, and intellectual disability [4]. They also identified a homozygous missense variant c.1114G>C, p.Gly372Arg, within the C-terminal part of *WWOX* dehydrogenase/reductase domain, in another family with two affected siblings exhibiting generalized tonic-clonic epilepsy, intellectual disability, and ataxia. Moreover, early death was rarely reported [7]. Abdel-Salam et al. identified, through exome sequencing, a homozygous nonsense pathogenic variant c.160G>T, p.Arg54* in a girl from a consanguineous family with severe growth retardation, microcephaly, epileptic seizures, retinopathy, and early death [8], as in our patient. Additionally, Mignot et al. identified biallelic pathogenic variants in patients with infantile epileptic encephalopathy, including deletions, truncating and missense variants, and delineated the phenotypic spectrum of *WWOX* variants [13].

Regarding the patient genotype, we detected a double pathogenic alteration of *WWOX* gene, most likely associated with inauspicious prognosis, the rapidity of progression until the exitus after a few months of life, incompatible with the postnatal life. WES data infact, showed that both

pathogenic variants, the CNV and the frameshift, disrupt a clinically significant region of the protein regarding the C-terminus of the ADH/SDR and the mitochondrial binding region translated by exon 6-8 of the gene.

The frameshift variant has been already reported in trans with exon 7–8 out-of-frame deletion or in the homozygous state in at least two individuals with WWOX-related developmental and epileptic encephalopathy [9,14]. Instead, establishing a causative and contributory role of the CNV to the fatal for the child's survival is more complex. Similar rearrangements to our CNV have been documented in the ExAC (17 individuals) and gnomAD SVs v2.1 (4 individuals) control cohort databases. However, WWOX exons 6-7 deletion has been previously described in trans with a WWOX missense variant in at least 3 individuals with WOREE syndrome [7]. In addition, out-of-frame deletion of exon 6 or in-frame deletion of exon 7 have been found in several individuals with WWOX-related phenotypes [7,12,15]. Currently, there are no available data or indications correlating the protein damage caused by the frameshift mutation in exon 8 with the CNV deletion in exons 6-7. In the absence of this information, the functional loss in ADH/SHR domains and mitochondria targeting sequence of the protein is to be considered to be plausibly deleterious. Our patient exhibited microcephaly, which it has already been reported in the literature to be associated with deletions in exons 2, 6, and 7 [8,9], as well as with the very early onset of epileptic encephalopathy in the first days of life. However, the progressive clinical deterioration of our patient, leading to death within the first 3 months of life, demonstrates the "catastrophic" impact that the specific WWOX genotype might have on lifelong prognosis.

5. Conclusions

To date, only one other patient has been described with a genotype characterized by compound heterozygous deletion of the WWOX gene in WOREE syndrome [16]. Both this case and our case involve newborns who experienced seizures shortly after birth with refractoriness to ASMs. In the first case, MRI images showed hyperintensity of white matter and delayed myelination, while in our case, MRI findings were unremarkable. Literature reports other MRI anomalies such as hippocampal hypoplasia, corpus callosum abnormalities, or even enlargement of subarachnoid spaces and asymmetry of lateral ventricles. These alterations suggest a role of the WWOX gene in brain homeostasis and developmental processes. Early mortality was a common outcome in both cases, emphasizing the low life expectancy in these individuals.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the University of Catania, Italy (Ethical Committee Catania 1 Clinical Registration n. 210/2023/PO).

Informed Consent Statement: Written informed consent was obtained from the parents of the patient for publication of the details of their medical case and any accompanying images.

Data Availability Statement: The data that support the findings of this study are not publicly available due to reasons of sensitivity, but are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ADH/SDR	Short-chain Dehydrogenases/Reductases
ACMG	American College of Medical Genetics and Genomics
ASMs	Anti-Seizure Medications
bp	Base pairs
CNVs	Copy Number Variations
DD	Developmental Delay
DNA	Deoxyribonucleic Acid
EEG	Electroencephalogram
ExAC	Exome Aggregation Consortium
HGMD	Human Gene Mutation Database
IEE	Infantile Epileptic Encephalopathy
IEE28	Infantile Epileptic Encephalopathy 28
IED	Interictal Epileptiform Discharges
KO	Knockout
MIM	Mendelian Inheritance in Man
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
PCR	Polymerase Chain Reaction
SCAR12	Autosomal Recessive Spinocerebellar Ataxia
SDS	Standard Deviation Score
VEP	Variant Effect Predictor
WES	Whole Exome Sequencing
WOREE	WWOX-Related Epileptic Encephalopathy
WES	Whole Exome Sequencing

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