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CASE REPORT

WW domain-containing oxidoreductase-related epileptic encephalopathy in two Omani children

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ABSTRACT

Background: Developmental and epileptic encephalopathy type 28 (DEE28) is a rare genetic disorder that affects children in the early months of life. It is proved to be caused by a pathogenic variance in WW domain-containing oxidoreductase (*WWOX*) gene.

Case Presentation: Here, we report a 5-year-old male patient with DEE28. The whole exome sequencing (WES) test was conducted and resulted in a pathogenic result on *WWOX* gene pathogenic variant. To our knowledge, these are the first cases reported in Oman.

Conclusion: For patients with DEE28, it is essential to take the full family history and genetic workup to assist in the diagnosis. In the future, gene therapy—which is currently being investigated—may help those patients to have a good quality of life and improve the prognosis of the disease.

Keywords: *WWOX*, epileptic encephalopathy, DEE28, WOREE syndrome.

Background

WWOX is a gene located on the long arm of chromosome 16 (OMIM 605131; HGNC 12799). It is composed of nine exons and is spanning over 1 Mb in size (1). It is a known tumor suppressor gene that is important in inducing apoptosis. However, any defect in it can cause specific types of malignancies (2). According to previous studies, this gene has multiple functions apart from its conventional role. Furthermore, Tanna and Aqeilan (3) published a study in 2019 highlighting the effect of *WWOX* deletion in animal models which helped in understanding the gene's tumor suppressor functions and its roles in different human pathologies (Figure 1).

A study published in 2020 highlighted the important neurological function of *WWOX* in contributing to the signaling pathways regulating central nervous system (CNS) development and neural differentiation (4). Developmental and epileptic encephalopathy-28 (DEE28) which is also known as *WWOX*-related epileptic encephalopathy (WOREE) syndrome is considered as a rare neurodevelopment disease. The disease first appeared as drug-resistant epilepsy and global developmental delay, and it causes severe disabilities, ataxia, and eventually premature death within the first few years of life if not discovered and managed early (5). Furthermore, A similar gene disruption can cause autosomal recessive spinocerebellar ataxia 12 (SCA12) (6). This report will present the history, clinical manifestations, and progression of two cases of Omani children who were confirmed to have DEE28.

Case Presentation

Case 1

A 5-year-old male was referred to the metabolic and genetic clinic in the National Genetic Center of the Sultanate of Oman for the evaluation of global developmental delay, failure to thrive, recurrent seizures (infantile spasms), and recurrent chest infections.

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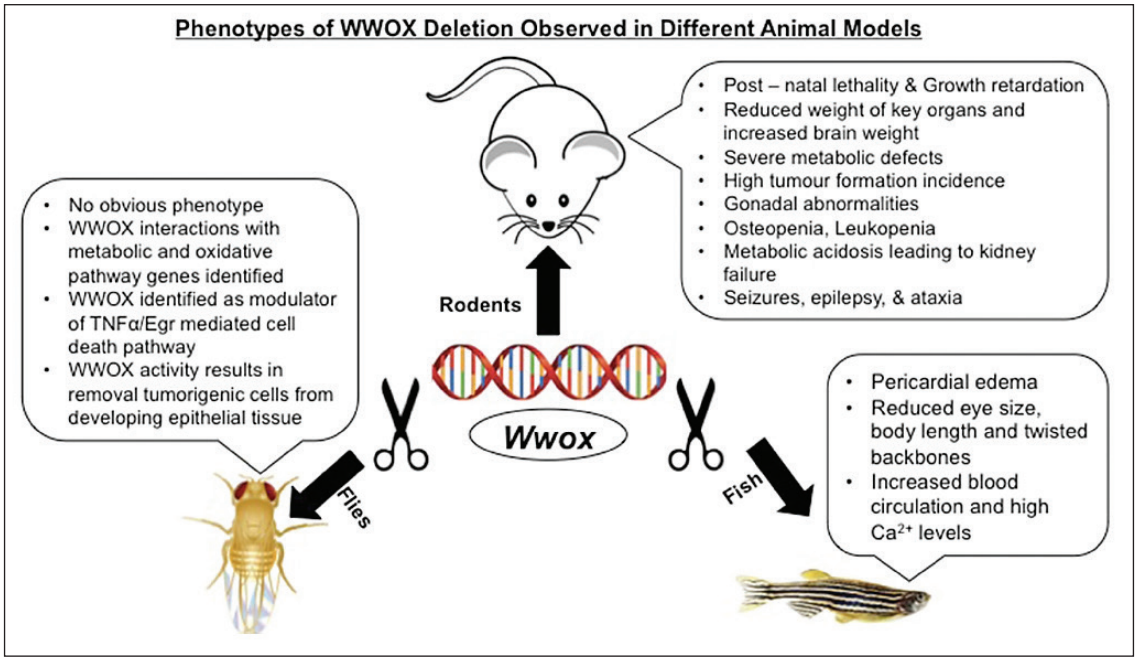

Figure 1. *Phenotypes of WWOX deletion observed in different animal models (rodents, fish, and flies) (3).*

He was born term by spontaneous vaginal delivery at 37 + 1 weeks of gestation. Antenatally, he had a normal growth scan that did not show any anomalies. At birth, the child had a good appearance, pulse, grimace, activity, and respiration score with a birth weight of 2.5 kg, he was diagnosed with neonatal jaundice and was admitted to the hospital for phototherapy. The family history was positive for first-degree consanguineous marriage and had an elder daughter who had progressive spasticity and developmental delay and died at the age of 21 months; she was born with some dysmorphic features and was suspected to have cerebro-occult-facio-skeletal syndrome. In addition, the patient has three cousins who had progressive CNS manifestations from their mother's side and passed away.

At the age of 4 months, the child was brought to the emergency department for 1-minute episodes of generalized stiffening of the body multiple times per day and child returned to baseline after each episode. Pediatric neurology service was consulted, and an electroencephalogram was done for him showing modified hypsarrhythmia. He was diagnosed with infantile spasm and was started on steroids without any response. He was then started on vigabatrin, and the child continued to have around three spasms a day. Therefore, vigabatrin was stopped and alternatively started on clobazam; some improvement was noticed after switching to clobazam and no spasms were noted.

In addition to experiencing spasms, the child suffered from global developmental delay and failure to thrive. At the age of 8 months, the child was admitted with an impression of pneumonia with increased respiratory effort, and he was noticed to have head lag and poor head control as well as the inability to transfer or grasp things and the inability to visually track his mother. The child continued to have developmental delay, as a result, he was having recurrent chest infections because of aspiration pneumonia and some choking episodes. His magnetic resonance imaging (MRI) that was done showed abnormal white matter changes with thinning of the corpus callosum. In addition, the latest anthropometric measurements at the age of 5 years include a weight of 9 kg.

As part of the workup, a comparative genomic hybridization (CGH) microarray was done which showed a benign result. The whole exome sequencing (WES) test was done which identified a pathogenic (class I) variant; a homozygous pathogenic deletion of the chromosomal region chr16:78181520-78206429, encompassing exon number four of the *WWOX* gene (7), identified. The genetic diagnosis of autosomal recessive DEE28 was confirmed (7). In addition, he was found to be a carrier of three other pathogenic variants: *ATP8B1* NM_005603.4:c.1581_1599del p.(Phe528Alafs*26), *EVC* NM_153717.2:c.496C>T p.(Gln166*), and *GALC* NM_000153.3:c.956A>G p.(Tyr319Cys) rs183105855. Targeted genetic tests were done for the parents to identify their carrier statuses for the four identified genes; the mother was found to be a heterozygous carrier for the four pathogenic variants identified with her son, while her husband was a carrier for two variants only: GALC and *WWOX* genes. After the index patient's birth, the mother had a child who had similar clinical features and died at the age of 1 year. In addition, the mother is currently pregnant in her third trimester; she underwent chorionic villus sampling at 12 weeks of gestation and the fetus was found to be a carrier for *WWOX* gene. The pedigree chart of the family is displayed in Figure 2.

Case 2

A 2-year-old male child was first seen in the neurology clinic at the age of 6 months for evaluation of global developmental delay and uncontrolled seizures. The child's background was not significant for any adverse perinatal events, but the child required admission in the NICU for

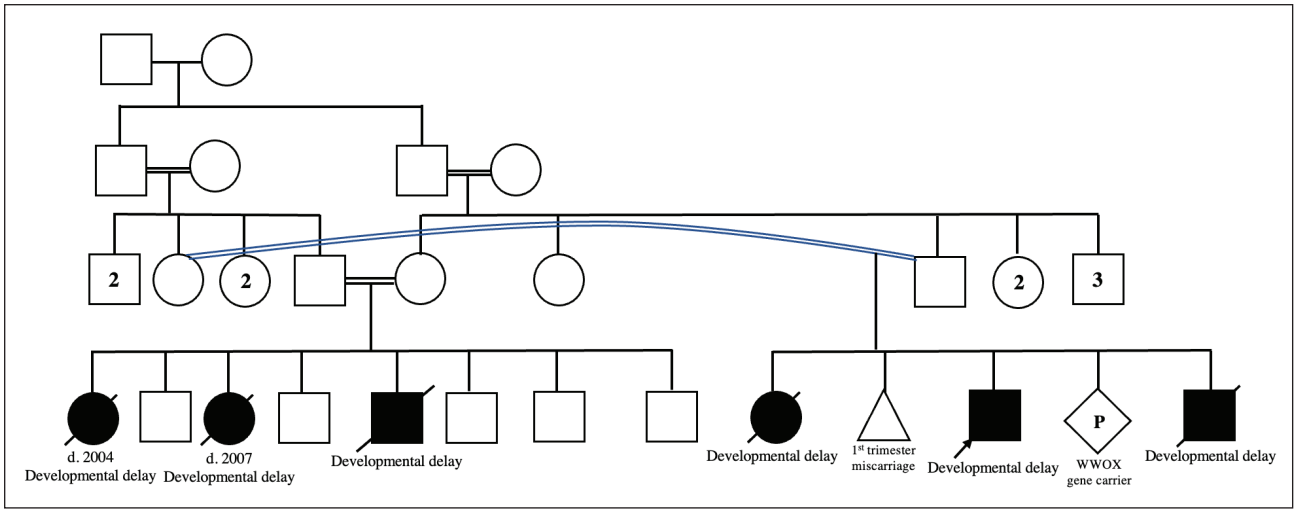

Figure 2. *Pedigree chart of the patient and the extended family.*

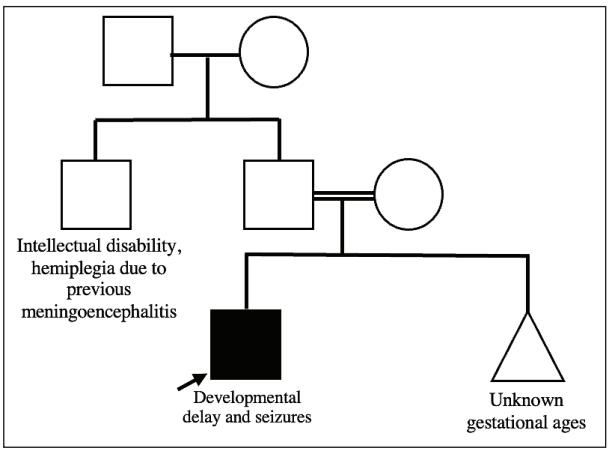

Figure 3. *Pedigree chart of the patient and the family.*

5 days to an unknown reason and had neonatal jaundice. He was well until the age of 2 months when he started having abnormal movements which were polymorphic in nature with focal seizures associated with sudden extensor spasms, alongside intermittent myoclonus, and crying. Those seizures were controlled with levetiracetam and phenobarbitone. Family history was significant for a consanguineous marriage and three previous abortions, furthermore, the child's uncle has intellectual disability, hemiplegia, and speech issues with a significant history of neonatal jaundice and meningoencephalitis as a child. On examination, his weight was 9.4 kg at the age of 2 years, the child had generalized hypotonia, microcephaly, coarse facies, micrognathia, hyperlaxity of joints, and short fingers. Abdominal examination was significant for hepatosplenomegaly.

Initial workup included EEG which showed continuous bilateral occipital epileptiform discharges and evolving epileptic encephalopathy, in addition, computed tomography scan which showed diffuse cortical atrophy and the brain MRI was not done. CGH microarray was sent as part of the genetic workup which revealed 284 Kb homozygous deletion in chromosome 16q23.1 which is the site of the *WWOX* gene. Parents were not tested to assess for carrier status. The child's condition persisted and he is currently bedridden and tracheostomized; seizures were controlled on topiramate, and levetiracetam was stopped gradually. The pedigree chart of the family is displayed in Figure 3.

Discussion

WWOX gene mutation is mainly associated with DEE28 or WOREE syndrome. Those patients usually present with refractory seizures in their first months of life along with other features such as impaired psychomotor development and severe axial hypotonia (8). As aforementioned, our patient's presentation included infantile seizures which were not resolved by medical treatment, and the patient's genetic results showed affected *WWOX* gene.

In 2014, Abdel-Salam et al. (9) reported an Egyptian girl, born to consanguineous parents, who exhibited features of neonatal growth retardation, microcephaly, retinal dystrophy, severe psychomotor delay, and intractable epileptic seizures. Brain MRI showed supratentorial atrophy with a simplified gyral pattern, hypoplasia of the hippocampus and the temporal lobe, and thin corpus callosum. The patient developed status epilepticus and died at the age of 16 months. An older sibling had died at age 3 months of a similar disorder, she developed seizures at age 40 days and did not follow objects or react to light, suggesting retinal degeneration (9).

In general, epileptic encephalopathy diseases appear to be refractory to pharmacotherapy like antiepileptic medications. Definite treatment is still not found. In 2021, Repudi et al. (10) published a paper related to *WWOX* gene therapy. They experimented on the brains of *WWOX*-null mice and used a viral vector (AAV9) to restore the *WWOX* expression, therefore, the authors believed that delivering AAV9-*WWOX* into the brain of WOREE syndrome patients could be a novel gene therapy approach that would help these patients (10). This approach to genetic treatment is displayed in Figure 4.

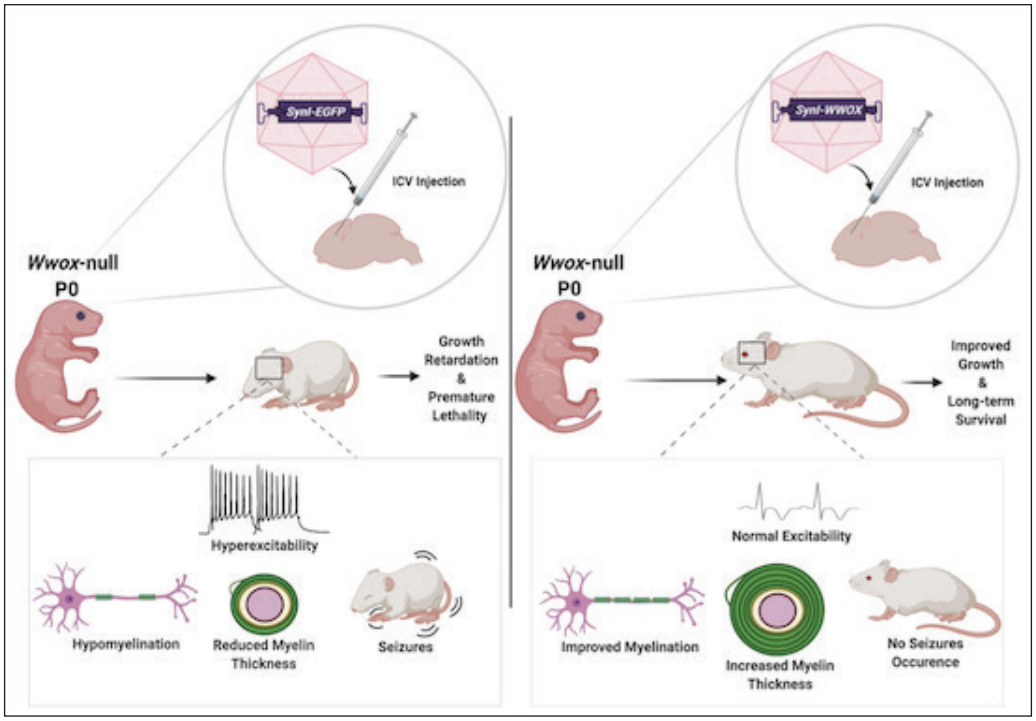

Figure 4. *Schematic diagram explaining the effect of WWOX expression in WWOX-null mice. Retrieved from Repudi et al. (10).*

In addition to that, genetic testing and counseling are essential steps for families with *WWOX* mutation to raise awareness about the disease and its implication on their lives.

Conclusion

In conclusion, *WWOX* is a gene that codes for an important protein and is involved in multiple functions. Therefore, the different affected functions can cause multiple disorders and diseases such as WOREE syndrome and SCA12. DEE28 or WOREE syndrome is a specific type of developmental and epileptic encephalopathy that is inherited as an autosomal recessive disease and can cause severe developmental delay, hypotonia, spasticity, and ataxia along with other features. Genetic testing and counseling are very important for all families with *WWOX* disease to explain to them more about the mutation and the disease and its possibilities of inheritance.

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National Genetic Center of the Sultanate of Oman.

List of Abbreviations

APGAR	Appearance, pulse, grimace, activity, and respiration
ATP8B1	ATP8B1 ATPase phospholipid transporting 8B1
CGH	Comparative genomic hybridization
CNS	Central nervous system
CT	Computed tomography
DEE28	Developmental and epileptic encephalopathy type 28
EEG	Electroencephalogram
EVC	EvC ciliary complex subunit 1
GALC	Galactosylceramidase
HGNC	HUGO Gene Nomenclature Committee
MRI	Magnetic resonance imaging
OMIM	Online mendelian inheritance in man
SCA12	Spinocerebellar ataxia 12
WES	Whole exome sequencing
WOREE	WWOX-related epileptic encephalopathy
WWOX	WW domain-containing oxidoreductase

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Declaration of conflicting interests
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Consent for publication
Due permission was obtained from the patient/parents/guardians of the patient to publish the case and the accompanying images.

Ethical approval
Ethical approval was granted by the Scientific Research Committee, Royal Hospital, Sultanate of Oman, Ministry of Health, via CR#2023/20, dated: 02 May 2023. The study conforms to recognized standards and all studies were undertaken with the understanding and consent of the parents of the child.

Author contributions
All the authors listed in this article contributed to the acquisition of data from the patient's parents, drafting and writing the manuscript along with final approval of this version to be published.

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