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RESEARCH ARTICLE

WWOX developmental and epileptic encephalopathy: Understanding the epileptology and the mortality risk

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Abstract

Objective: *WWOX* is an autosomal recessive cause of early infantile developmental and epileptic encephalopathy (*WWOX*-DEE), also known as WOREE (*WWOX*-related epileptic encephalopathy). We analyzed the epileptology and imaging features of *WWOX*-DEE, and investigated genotype–phenotype correlations, particularly with regard to survival.

Methods: We studied 13 patients from 12 families with *WWOX*-DEE. Information regarding seizure semiology, comorbidities, facial dysmorphisms, and disease outcome were collected. Electroencephalographic (EEG) and brain magnetic resonance imaging (MRI) data were analyzed. Pathogenic *WWOX* variants from our cohort and the literature were coded as either null or missense, allowing individuals to be classified into one of three genotype classes: (1) null/null, (2) null/missense, (3) missense/missense. Differences in survival outcome were estimated using the Kaplan–Meier method.

Results: All patients experienced multiple seizure types (median onset = 5 weeks, range = 1 day–10 months), the most frequent being focal (85%), epileptic spasms (77%), and tonic seizures (69%). Ictal EEG recordings in six of 13 patients showed tonic ($n = 5$), myoclonic ($n = 2$), epileptic spasms ($n = 2$), focal ($n = 1$), and migrating focal ($n = 1$) seizures. Interictal EEGs demonstrated slow background activity with multifocal discharges, predominantly over frontal or temporo-occipital regions. Eleven of 13 patients had a movement disorder, most frequently dystonia. Brain MRIs revealed severe frontotemporal, hippocampal, and optic atrophy, thin corpus callosum, and white matter signal abnormalities. Pathogenic variants were located throughout *WWOX* and comprised both missense and null changes including five copy number variants (four deletions, one duplication). Survival analyses showed that patients with two null variants are at higher mortality risk (p-value = .0085, log-rank test).

Significance: Biallelic *WWOX* pathogenic variants cause an early infantile developmental and epileptic encephalopathy syndrome. The most common seizure types are focal seizures and epileptic spasms. Mortality risk is associated with mutation type; patients with biallelic null *WWOX* pathogenic variants have significantly lower survival probability compared to those carrying at least one presumed hypomorphic missense pathogenic variant.

KEYWORDS
early infantile developmental and epileptic encephalopathy, EIDEE, epileptic spasms, genotype–phenotype correlation, survival probability, *WWOX*

1 | INTRODUCTION

The developmental and epileptic encephalopathies (DEEs) are a group of severe early onset disorders usually characterized by multiple seizure types, abundant epileptiform activity, and developmental slowing, plateau, or regression.[1,2] The DEEs are clinically and genetically heterogeneous, with the number of genes implicated now into the hundreds.[3–5] Although de novo pathogenic variants in autosomal dominant DEE genes are most commonly implicated,[6] *WWOX* has emerged as an important, albeit rare, autosomal recessive cause.

Although *WWOX* developmental and epileptic encephalopathy (*WWOX*-DEE), also known as WOREE (*WWOX*-related epileptic encephalopathy), has been reported in 62 individuals from 45 families,[7–24] the epileptology has not been clearly defined. The median age of reported cases is 2.5 years (mean = 3.3 years), with the oldest case being 19 years, and the mortality rate is high, with death often occurring in childhood. Although the predominant pattern is of a DEE, the spectrum of epilepsy, electroencephalography (EEG), and imaging features need further delineation. The phenotypic spectrum of *WWOX* pathogenic variants extends to a milder phenotype comprising spinocerebellar ataxia (SCAR12), epilepsy, and intellectual disability.[25,26]

The *WWOX* locus at 16q23.1–q23.2 encompasses FRA16D, the second most common fragile site in the human genome. During DNA replication, fragile sites are prone to genomic instability, making them hotspots for translocations and deletions.[27] Consistent with the FRA16D site being susceptible to such chromosomal rearrangements,[28] one third of reported unrelated patients with *WWOX*-DEE carry at least one pathogenic copy number variant (CNV), with deletions being more common than duplications. This has led to the suggestion that a *WWOX* gene dosage effect may exist,[15] with the severe DEE phenotype associated more often with null loss-of-function variants (e.g., deletions), whereas the milder SCAR12 phenotype has only been reported with missense variants.

Understanding the *WWOX*-DEE phenotypic spectrum is critical for interpreting the significance of *WWOX* variants. This, in turn, informs diagnosis, management, and prognostic and genetic counseling. Here, we describe the clinical, electrophysiological, and brain magnetic resonance imaging (MRI) features of 13 patients with *WWOX*-DEE and report nine novel *WWOX* pathogenic variants. We then examine genotype–phenotype correlations, particularly regarding mortality, in all reported cases to assist prognostic counseling.

Key Points

- *WWOX*-DEE is an autosomal recessive EIDEE with profound impairment
- *WWOX*-DEE can present as infantile epileptic spasms syndrome and epilepsy in infancy with migrating focal seizures
- *WWOX*-DEE brain MRIs show severe frontotemporal, hippocampal, and optic atrophy, thin corpus callosum, and white matter signal abnormalities
- Mortality risk correlates with *WWOX* genotype; the presence of ≥1 missense variant increases 5-year survival probability from <50% to >75%
- A high proportion of *WWOX* pathogenic variants are CNVs; molecular diagnosis may require dual sequencing and chromosomal microarray approach

2 | MATERIALS AND METHODS

Through an international collaborative study, we ascertained 13 patients (12 families) with biallelic *WWOX* pathogenic variants from five epilepsy centers (Australia, France, Germany, Italy, USA), including two patients (Patients 6 and 7) briefly reported.[29,30]

2.1 | Ethics approval and patient consent

The study was approved by the Austin Health Human Research Ethics Committee (H2007/02961). Written informed consent was obtained from the legal guardians of all patients following local institutional review board requirements.

2.2 | Clinical analyses

We analyzed phenotypic data on birth and development, seizure semiology, motor symptoms, comorbidities, facial dysmorphism, treatment, disease progression, and outcome. Epileptic seizures and syndromes were classified according to the International League Against Epilepsy classification.[1,31,32] Source EEG and brain imaging data were available for all 13 patients, allowing analysis of each dataset at the cohort level.

2.3 | Genetic variants

Pathogenic variants in *WWOX* were identified by local clinical and research genetic pipelines that included a combination of high-throughput sequencing (exome/genome/gene panel) and chromosomal microarray for CNV detection. Parental segregation was performed to confirm that genetic variants were in *trans*. RNA studies were conducted to characterize the protein consequences for two novel CNVs: one intronic deletion (Patient 6) and one duplication (brothers, Patients 9 and 10; Supplementary Material).

2.4 | Genotype–phenotype correlation

All variants reported here and those associated with a DEE phenotype in the literature[7–24] were classified according to American College of Medical Genetics and Genomics guidelines[33] to ensure they met the criteria for pathogenic/likely pathogenic (see Table S1). To identify *WWOX*-DEE cases in the literature, we searched PubMed with the terms "*WWOX*" and "Epilepsy" for articles published before July 1, 2022.

Each pathogenic/likely pathogenic variant was coded as either null (i.e., frameshift, nonsense, donor/acceptor splice site, deletion) or missense. Individuals with biallelic *WWOX* pathogenic variants were then classified into three genotypic classes based on variant types: (1) null/null, (2) null/missense, (3) missense/missense. Differences in phenotypic outcome, such as seizure onset age, survival, and sex, between the three groups were estimated using the Kaplan–Meier method.[34] Statistical analyses were performed using the R Survival package (R version 4.0.2).

3 | RESULTS

3.1 | Patients

We recruited 13 patients (seven female) from 12 families with *WWOX*-DEE due to biallelic pathogenic variants in *WWOX* (Table 1). The median age at study was 6 years 9 months (range = 13 months–23 years 11 months, mean = 8 years 2 months). Three patients (Patients 5, 6, 8) were deceased.

Seizures began at a median of 5 weeks (range = 1 day–10 months, mean = 9 weeks; Table 2). The most frequently reported seizures were focal (n = 11, median onset = 2.5 months, range = 1 day–1 year), in particular, focal clonic. Epileptic spasms (ES) were reported in 10 of 13 (77%) patients; all had ES onset during the first year of life (median onset = 3.5 months, range = 2– 6 months). Tonic (n = 9, median onset = 4 months, range = 1 week–3 years) and tonic–clonic seizures (TCS) (n = 7, median onset = 3.5 months, range = 1 month–3 years) also occurred in >50% patients. Myoclonic (n = 6, median onset = 1.5 months, range = 2 days–1 year), myoclonic–atonic (n = 1, onset = 3 years), and eyelid myoclonia (n = 3, median onset = 2 months, range = 2 days–1 year) seizures were less frequent. Six patients had status epilepticus.

Epilepsy was resistant to antiseizure medications (ASMs) in all patients, except Patient 5. Different ASMs were used, single or in combination, with variable efficacy. The most frequently used drugs were levetiracetam (n = 11) and valproic acid (n = 8). Vigabatrin was used in 7 of 10 patients for the treatment of ES; Patient 2 received adrenocorticotropic hormone and Patient 11 prednisone. Only 1 of 3 individuals who started the ketogenic diet continued it. In contrast, all four patients who had cannabidiol continued that ASM.

Development was abnormal from birth in 11 of 13 patients, with 9 of 13 patients not meeting any developmental milestones at seizure onset and 2 of 13 having poor visual attention or diffuse hypotonia. Only two had no developmental concerns prior to seizure onset at 2 and 2.5 months (Patients 12 and 6, respectively).

Development was profoundly impaired in all patients at follow-up. None achieved independent walking, and only two had a single word, whereas 11 were nonverbal. All had poor or absent eye contact, consistent with visual impairment, and severe truncal hypotonia; peripheral spasticity was observed in 10 of 13. Eleven patients had movement disorders, mainly dystonia (n = 8), including three with a dyskinetic component, bradykinesia (n = 2), or hyperekplexia (n = 1). Eleven patients required a gastric tube for feeding.

Three patients (Patients 5, 6, 8) died at age 8, 11, and 6 years, respectively. Patient 6 died from respiratory complications and Patient 8 from possible sudden unexpected death in epilepsy (SUDEP), on the background of a recent respiratory tract infection (postmortem was not performed). The cause of death for Patient 5 was unknown. None of our patients had tumors, which is noteworthy, as *WWOX* is an established tumor suppressor gene.[35–37]

3.2 | Electroencephalography

All available EEG recordings for the 13 patients, aged from 1 month to 21 years, were analyzed. We rereviewed at least two EEGs for each patient, except Patient 6, for whom we had only one EEG available (Table 2). EEGs recorded throughout life were reviewed for Patients 2, 3, 9, and 12 (Table 2).

All patients had background slowing. EEG at epilepsy onset in eight patients showed background slowing, with poor regional differentiation, that persisted over time (Table 2). Six of the eight onset EEGs showed multifocal epileptiform abnormalities with slowing being maximal over the posterior quadrants. Over years, epileptiform abnormalities were maximal over frontal or temporo-occipital regions (Figure S1). Patient 2, with the longest follow-up (21 years), showed progression to a diffuse low-voltage background without epileptiform abnormalities (Figure S1).

Ictal EEGs were available for six patients and recorded ES, focal, tonic, and myoclonic seizures (Table 2). Two patients (Patients 3, 11) developed hypsarrhythmia with ES at ages 2 and 4 months, respectively (Figure 1A,B). Ictal recording of ES was characterized by a diffuse high-voltage slow wave with superimposed low-voltage fast activity. Clinically, ES were asymmetric and lasted up to 1.5 s (Figure 1B).

Focal seizures occurred in 11 patients with variable semiology. Focal motor seizures were common, with six patients having clonic attacks. Focal seizures characterized by behavioral arrest, eye deviation, cyanosis, and asymmetric upper limb stiffening were recorded. EEG showed a focal ictal rhythm limited to one hemisphere, with spread to the contralateral hemisphere (Figure 1C). In Patient 9, seizure migration between hemispheres was recorded.

Bilateral tonic seizures and myoclonic seizures were also reported (Figure 1D–F). Tonic seizures were either focal in onset (Patients 6, 7) or generalized (Patients 1, 3, 4). TCS were not captured, therefore we could not determine whether they were focal or generalized in onset.

3.3 | Epilepsy syndromes

Early infantile DEE (EIDEE) was the most frequent epilepsy syndrome, occurring in 9 of 13 patients (Table 2). Patient 11 went on to develop infantile ES syndrome (IESS). Two patients had infantile onset of their DEE, with Patient 10 evolving to IESS. The remaining 2 of 13 patients had epilepsy of infancy with migrating focal seizures (EIMFS) with seizure migration evident clinically (Patient 6)[29] or on ictal EEG (Patient 9).

3.4 | Brain imaging

A distinctive pattern was observed on the brain MRI of our 13 patients (Table 2). All demonstrated severe frontotemporal atrophy (Figure 2A). Other features included hippocampal atrophy, white matter signal abnormality, and volume loss with a very thin corpus callosum (Figure 2A,C,D). All cases demonstrated severe optic atrophy, irrespective of age, and some patients showed brainstem changes, which were mainly dorsal (Figure 2B, Figure S2). Even as early as 15 and 19 days of age, brain MRI abnormalities were observed in Patients 1 and 7 respectively; specifically, delayed myelination, a thin corpus callosum, and frontotemporal atrophy were evident for Patient 7 (Figure S3). Seven patients had serial MRI that showed progression of the abnormalities with age.

Brain fluorodeoxyglucose positron emission tomography in Patient 6 at age 6 years showed low metabolism in the temporal lobes and perisylvian regions with moderate atrophy and moderate hypometabolism in the frontal lobes (Figure S4).

3.5 | Dysmorphic features

Of the cohort, 10 of 13 (77%) patients were microcephalic. Photos were available for 11 patients, with dysmorphic features in all (Figure S5), consistent with previous reports.[7,9,11,13,16,23] Features included round face with full cheeks, a short neck, and facial hypotonia ($n = 8$). Other frequent features were hypertelorism, arched and bushy eyebrows, long eyelashes, epicanthic folds, and bitemporal narrowing ($n = 6$). Less frequently observed, in 3 of 13 (23%) patients, was low anterior hairline and/or broad nose. High forehead, depressed nasal bridge, and gingival hypertrophy were each observed in 2 of 13 patients. For Patients 9 and 11, the only dysmorphic feature was low-set and large ears (only patient 11).

3.6 | Genetic variants

Of the 12 unrelated individuals, six had homozygous and six compound heterozygous variants, with a total of 14 unique *WWOX* [NM_016373.3] pathogenic variants (Figure 3). These comprised three missense, five nonsense, one splice site, four deletions, and one duplication variant. Three were recurrent single nucleotide variants: p.Glu17Lys occurred in two of our cohort (Patients 6, 12) and in one reported patient[16]; p.Gln230Pro in three of our patients (homozygous in two; compound heterozygous in one) and was reported in six previous families from Iran, Afghanistan, France, and Morocco[14,16,23]; and homozygous p.Arg264Ter in Patient 4 and in three families from India[16] and Sicily.[13,17] Of our six patients with homozygous variants, three were known to be from consanguineous families (Patients 5, 8, 13).

Of the five CNVs, three were deletions encompassing whole exons. The remaining two were of uncertain

TABLE 1 Genetic and neurological examination features.

Patient #	1	2	3	4	5	6
Age, sex	4 y 7 m, F	23 y 11 m, M	9 y 1 m, F	12 y 3 m, M	8 y 3 m (dec.), F	11 y 7 m (dec.), F
Genetics						
WWOX (NM_016373.3) variant(s) (hg19)	c.689A > C, p.Gln230Pro (mat)/exon 7–8 deletion (pat)	c.689A > C, p.Gln230Pro (homozygous)	c.1043delT, p.Phe348SerfsTer57 (pat)/exon 7–8 deletion (mat)	c.790C > T, p.Arg264Ter (homozygous)	c.689A > C, p.Gln230Pro (homozygous)	c.49G > A, p.Glu17Lys (mat)/intron 4 deletion (pat)
Genetic combination	Missense/null	Missense/missense	Null/null	Null/null	Missense/missense	Missense/null
Country (self-identified ethnicity)	Italy (Italian)	Italy (Italian)	Italy (Italian)	Italy (Italian)	France (North African)	Australia (Anglo-Australian)
Family history for epilepsy	No	No	No	No	Yes (father's siblings)	No
Consanguineous	No	No	No	No	Yes	No
Genetic studies	GS	ES	ES/MLPA	ES	ES (gene panel)	ES, CMA
Examination						
Intellectual disability	Profound	Profound	Profound	Profound	Profound	Profound
Speech	Nonverbal	Nonverbal	Nonverbal	Nonverbal	Nonverbal	Single word "Dad"
Walking/ambulant	No	No	No	No	No	No
Facial dysmorphisms	Yes	Yes	Yes	Yes	Yes	Yes
Acquired microcephaly	Yes	Yes	Yes	Yes	Yes	Yes
Short stature[a]	Yes	No	Yes	Yes	Yes	No
Scoliosis	Yes	Yes	Yes	Yes	Yes	Yes
Feeding tube	Yes	Yes	Yes	Yes	Yes	Yes
Spasticity/limb hypertonia	Yes	Yes	Yes	Yes	Yes	Yes
Axial hypotonia	Yes	Yes	Yes	Yes	Yes	Yes
Movement disorder	Dystonic–dyskinetic movements	Dystonia	Dystonia	Dystonic–dyskinetic movements	Dystonia	Bradykinetic movement disorder
Ophthalmologic features	Poor eye contact	Absent eye contact; erratic ocular movements	Poor eye contact	Poor eye contact	Poor eye contact	Poor eye contact

Abbreviations: CMA, chromosomal microarray; dec., deceased; ES, exome sequencing; F, female; FDIU, fetal death in utero; GS, genome sequencing; M, male; m, months; mat, maternal inheritance; MLPA, multiplex-ligation dependent probe amplification; NA, not available; pat, paternal inheritance; w, weeks; y, years.

[a]Short stature defined as height = 3 SD below the mean for age.

[Correction added on 24 March 2023, after first online publication: The entries in column 9 of Table 1 for the "WWOX" and "Genetic combination" rows of the "Genetics" section have been updated.]

pathogenicity and were investigated further. Patient 6 had two paternally inherited intronic deletions involving intron 3 and intron 4. RNA sequencing followed by real-time polymerase chain reaction (RT-PCR) suggested that the intron 3 deletion was a benign variant, whereas the intron 4 variant resulted in exon 5 skipping (Supplementary Material). For brothers, Patients 9 and 10, RT-PCR suggested that their maternally inherited exon 5 duplication resulted in premature termination (Supplementary Material).

Comparing our findings with reported pathogenic variants causing *WWOX*-DEE,[7–24] no region of the gene emerged as specific for being associated with *WWOX*-DEE. Furthermore, the two missense variants associated with the rarer, milder SCAR12 phenotype are situated in close proximity to *WWOX*-DEE variants: p.Gly372Arg in exon 9 and p.Pro47Thr in exon 2. Interestingly, p.Pro47 has been associated with two pathogenic variants; the more conservative change to threonine was found in SCAR12[26]

7	8	9	10	11	12	13
4 y 9 m, F	6 y (dec.), F	6 y 10 m, M	3 y 11 m, M	2 y 11 m, M	1 y 1 m, M	10 y 10 m, F
c.864G > A, p.Trp288Ter (mat)/exon 6 deletion (pat)	Exon 5 deletion (homozygous)	c.728dupT, p.Gln244ProfsTer26 (pat)/exon 5 duplication, p.His173GlyfsTer14 (mat)		c.1087G > C, p.Ala363Pro (mat)/ c.1182_1183dupCC, p.Arg396ProfsTer11 (pat)	c.49G > A, p.Glu17Lys (mat)/exon 6 deletion (pat)	c.107 + 2_107 + 5delTAAG (homozygous)
Null/null	Null/null	Null/null		Missense/null	Missense/null	Null/null
Australia (South African/Bolivian)	Australia (Pakistani)	US (Anglo-American/ Hispanic)		Germany (Italian)	Germany (German)	Germany (Turkish)
No	Yes; sibling FDIU (34 w)	Yes (siblings)		No	No	No
No	Yes	No		No	No	Yes
ES, CMA	CMA	CMA, ES		ES (gene panel)	ES (gene panel)/ CMA	ES
Profound	Profound	Profound	Profound	Profound	Profound	Profound
Nonverbal	Nonverbal	Nonverbal	Single word "Mama"	Nonverbal	Nonverbal	Nonverbal
No	No	No	No	No	No	No
Yes	NA	Yes	Yes	Yes	Yes	NA
Yes	Yes	No	No	Yes	No	Yes
No	Yes	No	No	Yes	No	Yes
Yes	Yes	No	No	No	No	Yes
Yes	Yes	No	Yes	Yes	No	Yes
Yes	Yes	No	No	No	Yes	Yes
Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bradykinetic movement disorder; parkinsonism	Dystonia	No	No	Dystonic–dyskinetic movements	Hyperekplexia	Dystonia
Poor eye contact	Absent eye contact	Poor eye contact	Poor eye contact	Poor eye contact	Poor eye contact	Poor eye contact

compared with the arginine substitution found in *WWOX*-DEE[38] (Figure 3).

3.7 | Genotype–phenotype correlation

We compared our cohort ($n = 13$) with 62 individuals with *WWOX*-DEE from the literature[7–24] (i.e., excluding six published SCAR12 cases). We report the oldest living patient, aged 23 years 11 months. Our cohort shared similar clinical features overall with those published (Table 3); however, despite our patient group being notably older (mean = 8 years 2 months vs. 3 years 4 months), the mortality was lower (23% vs. 38%).

We examined the *WWOX*-DEE mortality–genotype relationship. We stratified all 75 cases into one of three genetic groups: (1) null/null ($n = 45$), (2) null/missense ($n = 15$), (3) missense/missense ($n = 15$). Using the Kaplan–Meier method to analyze time to death, we found that survival was much poorer for the double null

TABLE 2 Epilepsy, EEG, and brain MRI features.

Patient #	1	2	3	4	5	6
Epilepsy						
Seizure onset	2 d	34 d	2 m	7 d	1 m	2.5 m
Seizure types (at onset)	EM, ES, T, TCS, F, SE, M	M, TCS, T, ES	ES, T, F, M, TCS, SE	F clonic, ES, T, TCS, SE	M, TCS	F, TCS, HC, T, M, SE
ASMs trialed (current)	PHB, VPA, RFM, VGB, PHT	LEV, VPA, LTG, CLB, CBZ, ACTH, CLP	VGB, VPA, LEV, CLP	PHB, RFM, LEV, CBZ	VPA, LEV	CLB, TPM, CBD, MDZ, PER, PHB, LEV, CLP, OXC, VGB, LAC, ESM, LTG, DZP
Drug-resistant	Yes	Yes	Yes	Yes	No	Yes
Epilepsy syndrome	EIDEE	EIDEE	EIDEE → IESS	EIDEE	EIDEE	EIMFS
EEG						
EEG interictal	10 d (onset): slow BGA, multifocal spike and waves (mainly bilateral Fr, C-P); 3 y: slow BGA, multifocal spike and waves (mainly Te-P-O)	34 d (onset): slow BGA, multifocal spike and waves (mainly C-Te-P); 11 y: slow BGA, multifocal spike and waves; 21 y: low-voltage BGA, no epileptiform abnormalities	2 m (onset): hypsarrhythmia; 3 y: slow BGA, multifocal spike and waves (mainly Te-P-O); 7 y: slow BGA, multifocal spike and waves	2 y: slow BGA, multifocal spike and waves (mainly bilateral Fr); 9 y: slow BGA, multifocal spikes	2 m (onset): slow BGA, Fr and C spike and waves; 2 y: slow BGA, no epileptiform abnormalities	14 m: slow BGA, multifocal spike and waves (mainly Te-P-O)
EEG ictal	Tonic seizure, myoclonus	ND	Epileptic spasms, tonic seizures, myoclonus	Tonic seizure	ND	ND
Brain MRI						
MRI findings	15 d: mild perisylvian atrophy, thin CC, res diff dorsal pons; 2 y: severe Fr-Te atrophy, small HiC, WM volume loss and T2 change PVWM	2 m: delayed myelination, Fr atrophy; 3 y: poor myelination, inc T2 WM, worse Fr atrophy, OA, thin CC; 8 y: worse atrophy	2 m: Fr-Te atrophy, delayed myelination, thin CC; 19 m: very severe generalized atrophy; worse A > P, perisylvian and Fr-Te, thin CC, HiC atrophy, res diff CTT, mild vermis atrophy	13 m: moderate–severe Fr-Te atrophy, thin CC, inc T2 WM; 7 y: severe Fr-sylvian-Te atrophy, dec quantity WM inc T2 PVWM and Fr lobes, thin CC	17 m: scaphocephaly, thin CC, OA, inc T2 dorsal pons, Fr atrophy, abn T2 Fr-Te WM	6 m: dysmorphic CC, severe OA, R O platybasia, abn WM signal, delayed myelination, inc T2, res diff CTT; 2.5 y: bilateral HiC atrophy; 6 y: mild Fr atrophy, severe bitemporal atrophy (L > R) with HS, abn T2 WM, PVWM, and posterior lobar WM

Abbreviations: A > P, anterior greater than posterior; abn, abnormal; ACTH, adrenocorticotropic hormone; ASM, antiseizure medication; BG, basal ganglia; BGA, background activity; BRV, brivaracetam; C, central; CBD, cannabidiol; CBZ, carbamazepine; CC, corpus callosum; CLB, clobazam; CLP, clonazepam; CTT, central tegmental tracts; d, days; dec, decreased; DEE, developmental and epileptic encephalopathy; DZP, diazepam; EEG, electroencephalography; EIDEE, early infantile DEE; EIMFS, epilepsy of infancy with migrating focal seizures; EM, eyelid myoclonia; ES, epileptic spasms; ESM, ethosuximide; F, focal seizures; Fr, frontal; GP, globus pallidus; HC, hemiclonic; HiC, hippocampi; HS, hippocampal sclerosis; IESS, infantile epileptic spasms syndrome; inc, increased; KD, ketogenic diet; L, left; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; LV, lateral ventricle; M, myoclonic seizures; m, months; MA, myoclonic atonic seizures; MDZ, midazolam; MRI, magnetic resonance imaging; ND, not done; O, occipital; OA, optic atrophy; OXC, oxcarbazepine; P, parietal; PER, perampanel; PHB, phenobarbital; PHT, phenytoin; PRED, prednisolone; PVWM, periventricular white matter; R, right; res diff, restricted diffusion; RFM, rufinamide; SE, status epilepticus; T, tonic seizures; T2, T2-weighted signal intensity; TCS, tonic/clonic seizures; Te, temporal; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; w, weeks; WM, white matter; y, years; ZNS, zonisamide.

7	8	9	10	11	12	13
17 d	14 d	10 m	4 m	1 d	2 m	4 m
F clonic, T, ES	F clonic, T, F, ES	TCS, F, MA	F, ES	HC, ES, T, SE	EM, HC, M, ES	ES, EM, T, F, SE
LTG, ZNS, CLB, LAC, MDZ, PHT, PHB, PRED, ACTH, TPM, KD, VGB, VPA, LEV	VGB, PHB, DZP	LEV, OXC, CBD	LEV, VGB, CBD	CLB, LAC, CBD, LEV, CBZ, PRED, VGB, KD, VPA	VPA, KD, PHB, LEV, TPM, CLB, MDZ	VPA, LTG, BRV, VGB, LEV, CLB, TPM, PER
Yes	Yes	Yes	Yes	Yes	Yes	Yes
EIDEE	EIDEE	EIMFS	DEE → IESS	EIDEE → IESS	EIDEE	DEE
3 m (onset): slow BGA, no epileptiform abnormalities, bilateral C slow waves; 5 y: slow BGA, multifocal spike and waves (mainly bilateral Fr)	5 w (onset): slow BGA, multifocal spike and waves (mainly Te-P-O); 2 y: slow BGA, multifocal spike and waves	10 m (onset): slow BGA, bilateral P sharp waves; 5 y: slow BGA, no epileptiform abnormalities, bilateral P sharp waves	1 y: slow BGA, bilateral Fr–P spike and waves; 2 y: slow BGA, multifocal spike and waves (mainly Te-P-O)	1 m (onset): slow BGA, L O spike and polyspike; 4 m: hypsarrhythmia; 3 y: slow BGA multifocal spike and waves (mainly Te-P-O)	6 m: slow BGA, multifocal spike and waves (mainly Te-P-O); 9 m: slow BGA, multifocal spike and waves (mainly Te-P-O)	5 y: slow BGA, multifocal spike and waves (mainly Fr); 8 y: slow BGA, multifocal spike and waves (mainly Te-P-O)
Epileptic spasms, tonic seizures	R Fr focal seizure; tonic seizure	Migrating seizures	ND	ND	ND	ND
19 d: Fr-Te atrophy, delayed myelination, thin CC; 8 m: severe generalized atrophy with abn T2 BG, cerebellum, peduncles, brainstem, PVWM, atrophic HiC, OA, PVWM cysts incorporated into LV; 11 m: worse Fr-Te atrophy, abn T2 WM, thin CC, inc T2 GP	1 m: mild Fr-Te atrophy, abn T2 WM, tiny HiC, thin CC; 3 y: severe Fr-sylvian-Te atrophy, inc T2 WM, abn myelination, thin CC, OA, HiC atrophy, res diff posterior midbrain	12 m: moderate Fr-Te atrophy, mild ex vacuo dilatation Fr horns, OA, thin CC, WM volume loss with inc T2 PVWM and Fr lobe	14 m: severe cortical atrophy, worse A > P Fr-Te, WM inc T2 brainstem dentate nuclei, delayed myelination, thin CC, tiny HiC	1 m: very thin CC	9 w: mild Fr atrophy, borderline thin CC	6 y: thin CC, small HiC, abn WM signal, Te-Fr atrophy, OA

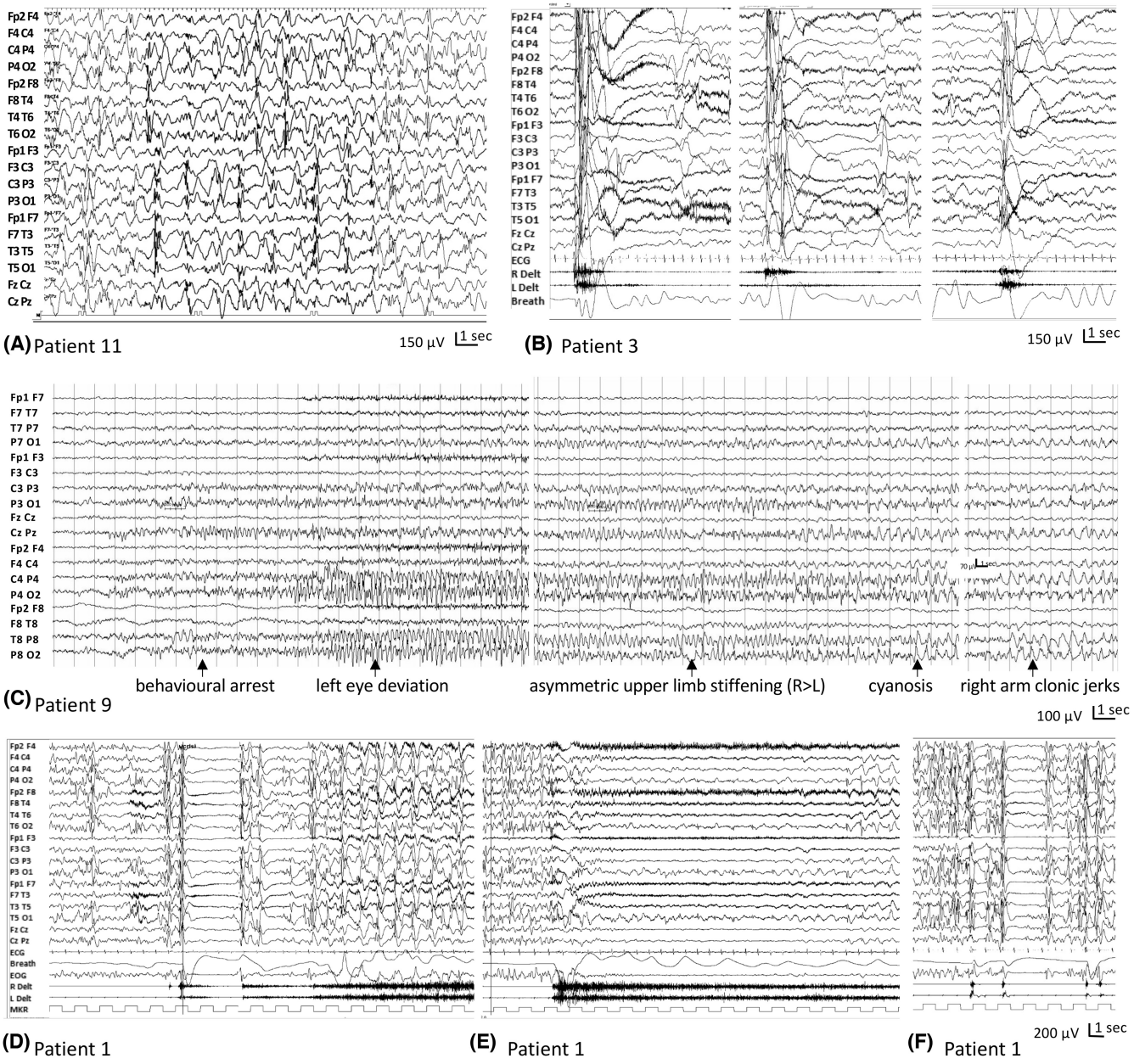

FIGURE 1 Electroencephalograms (EEGs) of patients with *WWOX* developmental and epileptic encephalopathy. (A) EEG of Patient 11 at age 4 months shows hypsarrhythmia characterized by multifocal, synchronous and asynchronous, high-amplitude spikes and delta activity. (B) EEG of a cluster of epileptic spasms with prolonged and asymmetric bilateral contraction of deltoid muscles (right > left) in a 2-month-old girl (Patient 3). The EEG shows a diffuse high-amplitude slow wave with superimposed low-voltage fast activity. (C) Focal seizure in a 10-month-old boy (Patient 9) characterized by behavioral arrest, left eye deviation, asymmetric upper limb stiffening, cyanosis, and clonic activity of the right upper limb. EEG showed a left parietal–occipital ictal rhythm characterized by theta activity increasing in amplitude and reducing in frequency, and involving the same regions of the contralateral hemisphere. The seizure lasted 70 s. (D) Epileptic spasm followed by tonic seizure in a 3-year-old girl (Patient 1) characterized by sudden contraction of both deltoids for 1.5 s followed by atonia and then prolonged bilateral symmetric upper limb contraction. The EEG shows diffuse polyspikes and waves followed, after 3 s, by diffuse electrodecremental activity, and high-amplitude spike and slow wave complexes. (E) Bilateral symmetric tonic seizures with EEG showing diffuse flattening of cerebral activity (Patient 1). (F) Three-year-old girl (Patient 1), during sleep, with EEG showing diffuse high-amplitude spikes and polyspikes associated with a clinical correlate of bilateral myoclonic seizures.

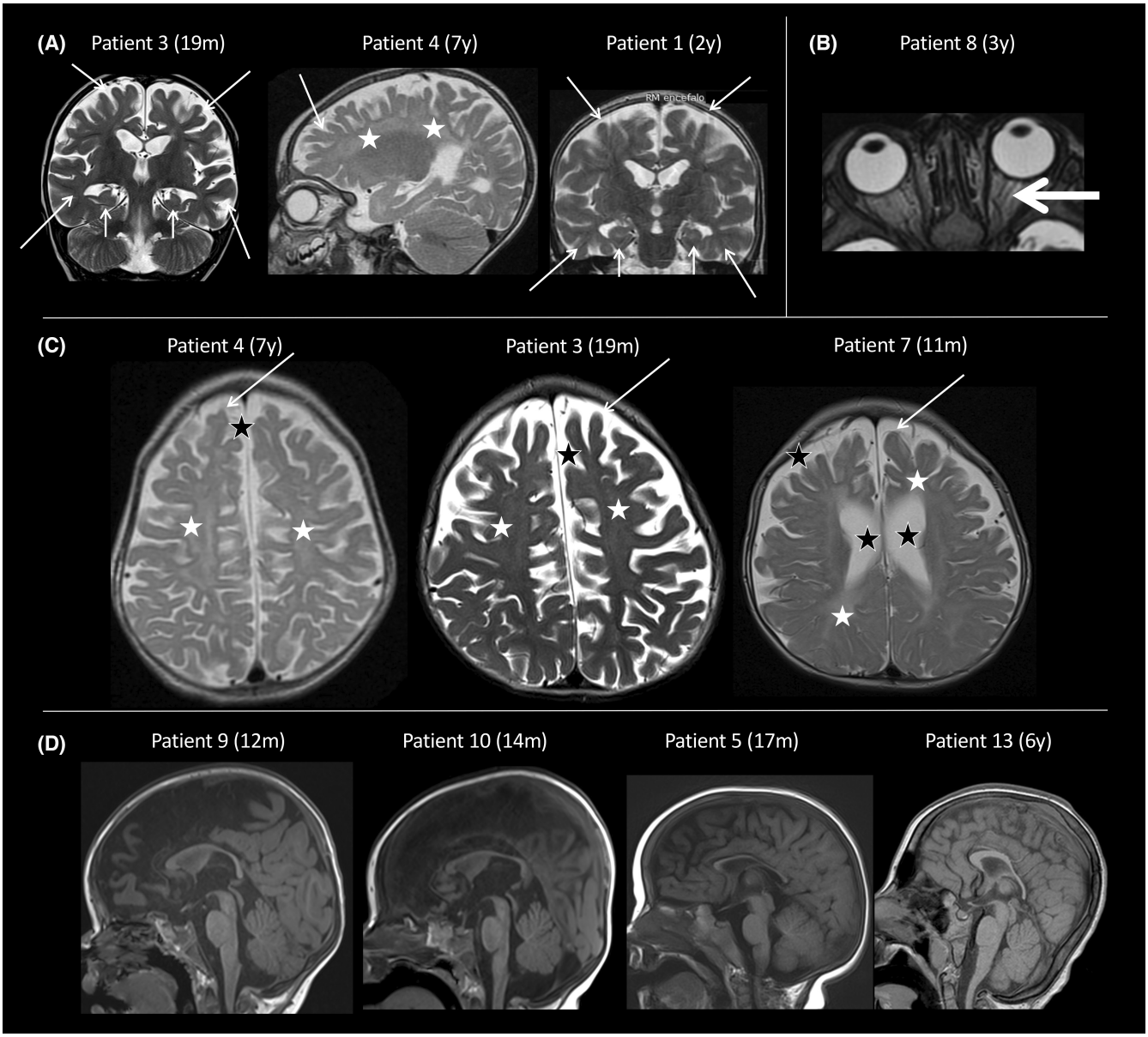

FIGURE 2 Typical brain magnetic resonance imaging (MRI) features across the cohort. (A) Extreme frontal and temporal atrophy (arrows), including hippocampal atrophy (shorter vertical arrows). White stars indicate white matter signal abnormality. (B) Severe optic atrophy (thick arrow). (C) Severe cortical atrophy (arrows), white matter atrophy with abnormal T2 signal intensity (white stars), and ex vacuo ventriculomegaly with increased size of extra axial cerebrospinal fluid spaces (black stars). (D) Thin corpus callosum and/or splenium corpus callosum. Age at the time of MRI shown is in brackets after patient number. m, months; y, years.

group compared with the patients who had at least one missense pathogenic variant (p-value = .0085, log-rank test). Probability of survival to the age of 5 years for the double null group was <50%; by comparison, it was >75% for the other two, presumably less severe, genetic groups (Figure 4A). By the age of 10 years, the gap in survival probability widened, with the null group at 25% whereas the missense groups remained somewhat steady at >60%.

By comparison, we found no difference in time to seizure onset between the three genetic groups (p-value = .65, log-rank test; Figure 4B). No sex differences were observed for either time to seizure onset or death (Figure S6).

4 | DISCUSSION

We describe the electroclinical, radiological, and genetic features of 13 patients, from 12 families, with biallelic pathogenic variants in *WWOX*. Seizure onset typically occurs in early infancy. Seizure types include focal, generalized, and ES, and are invariably resistant to ASMs. Patients present with a DEE with developmental concerns preceding seizure onset and long-term profound impairment, coupled with axial hypotonia and limb spasticity.

In terms of epilepsy syndrome, we found that eight had EIDEE, two had IESS, two had EIMFS, and one did

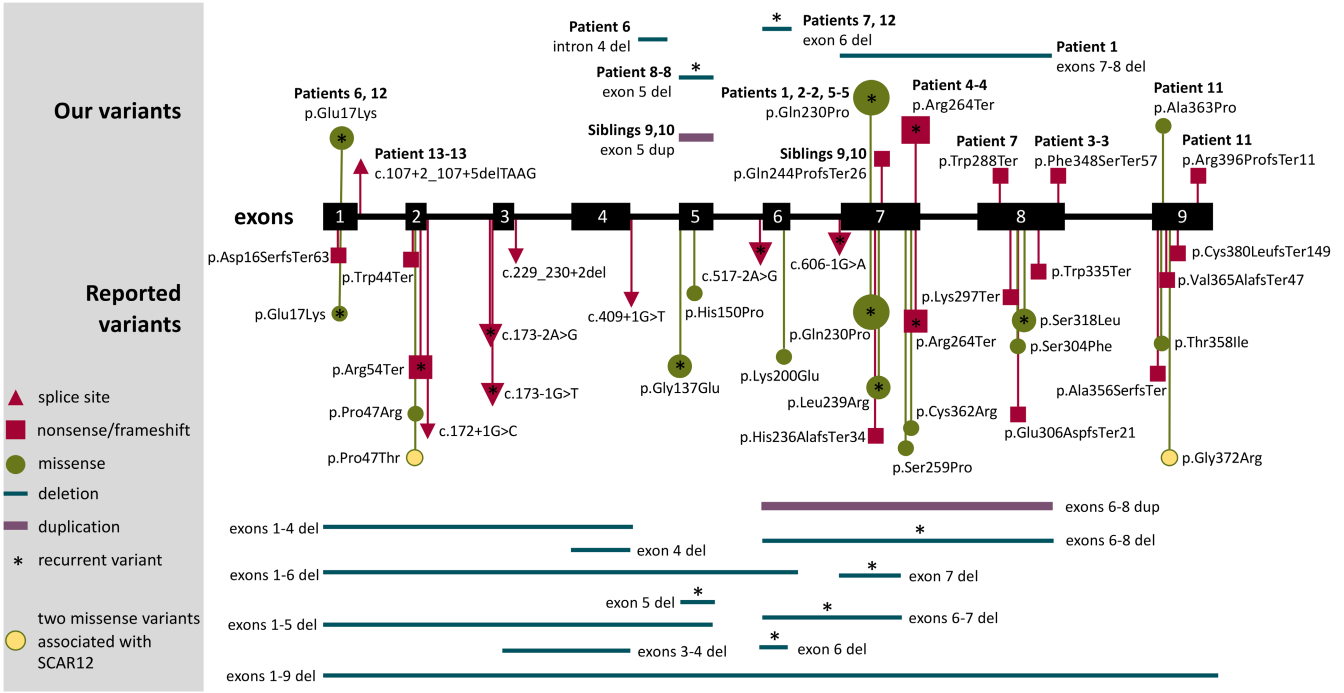

FIGURE 3 Location and type of pathogenic *WWOX* variants in our cohort (top) of 13 patients and those from the literature (bottom). Homozygous variants in our cohort are denoted by patient #-#. Size of variant symbol is commensurate with number of times reported. References and known/inferred country of origin details for reported variants are given in Table S1.

not fit into a specific epilepsy syndrome. Fewer than one quarter of the previously published cases state the epilepsy syndrome observed, which include IESS (previously West syndrome; $n = 9$)[12,14,15,19] and Lennox–Gastaut syndrome (LGS; $n = 4$).[14,16] Although our patients had multiple seizure types, they did not show the mandatory EEG hallmark of LGS of <2.5 Hz slow spike–wave,[39] excluding this syndromic diagnosis. It is notable that this EEG feature was not reported for patients previously classified as LGS.[14,16]

There are now many genetic causes of EIDEE defined by onset of a DEE in the first 3 months of life.[6,32] Many are characterized by focal seizures and ES. Examples include *CDKL5* deficiency disorder and *STXBP1*-DEE. Electroclinical features help in differentiating different genetic EIDEEs. In *CDKL5* deficiency disorder, the EEG at onset is relatively normal and seizures often remit with treatment before the appearance of ES.[40] In *STXBP1*-DEE, 30% of patients have a burst-suppression pattern at onset, which is not described in *WWOX*-DEE.[41] PEHO (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy) syndrome also shares a number of clinical features with *WWOX*-DEE, in particular, infantile onset ES and optic atrophy.[42] Although our patients did not manifest the subcutaneous limb edema typical of PEHO syndrome, it is a reasonable differential clinical diagnosis. In turn, this makes *WWOX* a plausible candidate gene for patients with PEHO or PEHO-like syndrome that remain without a genetic diagnosis.[43,44]

Previous studies provided limited details regarding MRI findings in *WWOX*-DEE, the largest reporting abnormalities in 80% of patients, with the most common features being hypoplasia of the corpus callosum and cerebral atrophy.[16] Here, we extend and refine our understanding of the MRI phenotype, highlighting that all patients had brain abnormalities. We identified a *WWOX*-DEE pattern of severe frontotemporal atrophy, hippocampal atrophy, very thin corpus callosum, optic atrophy, and white matter signal abnormalities. These findings were evident from as early as 15 days of life, with repeat MRI revealing increased cerebral atrophy over time. We found no polymicrogyria in our cohort, noting that there are three patients reported with frontoparietal or diffuse polymicrogyria.[8,19,22] All of our patients had optic nerve atrophy consistent with the visual impairment observed in *WWOX*-DEE. Dysmorphic features such as microcephaly, round face with full cheeks, short neck, short stature, and other features such as scoliosis, feeding difficulties, and hyper- and hypotonia were observed, consistent with previous reports.[7–9,11,13,15,16,18,19,23]

Our analysis shows that biallelic pathogenic variants in *WWOX* causes a severe DEE. With EIDEE, it is often difficult to ascertain whether early development is normal prior to seizure onset. In the milder *WWOX* phenotype of SCAR12, early development is slow, with seizure onset

TABLE 3 Primary *WWOX*-DEE clinical features: Our cohort versus the literature.

Clinical feature		Our cohort, $n = 13$	Published cases, $n = 62$
Sex		46% Male	39% Male
Age last known	Range	1 y 1 m–23 y 11 m	0 d–19 y
	Median	6 y 9 m	2 y 6 m
	Mean	8 y 2 m	3 y 4 m
Consanguineous		23%	42%
Genotype class	Null/null	50%	60%
	Null/missense	33%	15.5%
	Missense/missense	17%	24.5%
Deceased		23%	38%
Seizure onset age	Range	1 d–10 m	1 d–6 m
	Median	5 weeks	8.6 weeks
	Mean	9 weeks	8 weeks
Seizures		100%	100%
Drug-resistant		92%	97%
Severe–profound ID		100%	100%
Facial dysmorphisms		100%	66%
Microcephalic		77%	70%
Short stature		54%	48%
Scoliosis/kyphosis		69%	71%
Feeding problems		85%	85%
Spasticity/hypertonia		77%	86%
Hypotonia		100%	72%
Movement disorder		85%	64%
Absent or poor eye contact		100%	89%

Abbreviations: d, day; ID, intellectual disability; m, month; y, year.

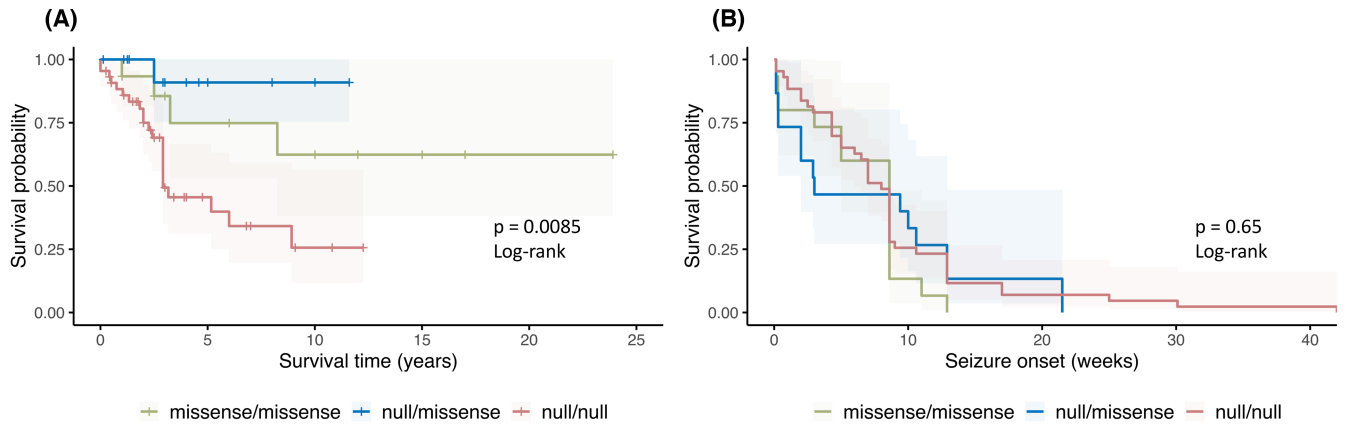

FIGURE 4 Survival analysis for 75 individuals with *WWOX* developmental and epileptic encephalopathy stratified by genetic variant group. (A) Time to death. (B) Time to seizure onset. Probability was calculated using the Kaplan–Meier method. Each vertical dash in A denotes the most recent age known to be living of each individual (censored observations). The shaded color regions define the 95% confidence intervals.

from 9 to 12 months, providing support for developmental impairment due to *WWOX* pathogenic variants.[25,26] The epileptic encephalopathy component of the disease is associated with slowing, plateau, or regression of development, with all our patients being nonambulant with profound impairment.

WWOX-DEE has a high mortality rate of 35%, with 23 of 62 individuals deceased in the literature and 3 of 13 patients here. As discussed further below, we have shown that mortality risk correlates with *WWOX* genotype, whereby the presence of at least one missense variant increases 5-year survival probability from <50% to >75%. Respiratory complications are the most frequently reported cause of death,[11,12,15,23] although one of our patients died of possible SUDEP. Alternate causes of death in the literature included status epilepticus[7] and obstructive cardiomyopathy.[22] Such a high mortality rate can be seen in patients with profound impairment and typically due to respiratory problems.

A functional gene dosage effect has been postulated for *WWOX* diseases.[15] Until recently, the severe *WWOX*-DEE phenotype had been associated with at least one loss-of-function null allele and a second missense or null allele. By contrast, the milder SCAR12 phenotype has been reported in six individuals from two families with homozygous missense pathogenic variants, suggesting that the functional impact of some missense variants may result in a hypomorphic allele compared to complete loss-of-function null variants. Functional studies would be required to support this hypothesis. Here, we, and others,[11,14,16,18] report patients with *WWOX*-DEE due to two missense pathogenic variants, noting that there is no regional predilection for missense pathogenic variants within the gene leading to *WWOX*-DEE versus SCAR12 (Figure 3).

We observed an interesting correlation that builds on the question of a milder outcome with a presumed hypomorphic pathogenic allele. We revealed that longer survival of *WWOX*-DEE is associated with the presence of at least one missense pathogenic variant, when interrogating all published cases with our cohort (Figure 4). We found no difference between individuals with one or two missense variants and therefore no evidence to support an "intermediate" phenotype, as our *WWOX*-DEE patients were as severe as those with two loss-of-function null alleles.[15] Therefore, the nature of pathogenic variants carries important prognostic implications for patients and their families. This may be a model relevant to other DEE genetic diseases, particularly those that are autosomal recessive.

WWOX deletions have been observed in various human cancer cell lines and tumors,[36,37,45] with mouse models supporting a role for *WWOX* in tumor suppression.[35] Despite this, there are no reports of *WWOX*-DEE or SCAR12 patients with tumors; however, this could simply be due to the high early mortality rate of *WWOX*-DEE. *Wwox* knockout mouse models have also recapitulated some of the clinical observations made in both *WWOX*-DEE and SCAR12, including ataxia, seizures, and early death.[26,46,47] Furthermore, the brains of *Wwox*-mutant rodents demonstrate severe hypomyelination,[13,46–48] a finding more recently observed in human WWOX-deficient brain organoids.[46] Such observations support a critical role for WWOX in neural development and may help explain the abnormal brain MRI features (e.g., cerebral atrophy) observed in patients with *WWOX*-DEE.

Our study highlights the importance of combining high-throughput sequencing and chromosomal microarray results in the molecular genetic workup of DEE. Without this dual approach, one third of our *WWOX*-DEE cases would have been missed. Although standard microarrays will often be performed as an initial investigation for a patient with a DEE, they can still miss intragenic pathogenic CNVs due to lack of probe coverage.[49] Rather, high-resolution gene-focused single nucleotide polymorphism microarrays may still be required for CNV detection in some genes.[50] Importantly, sequencing technologies are also evolving to better detect CNVs; multiexon gene panels and a move toward genome (over exome) sequencing will further enable the dual detection and interpretation of single nucleotide variants and CNVs. However, where the pathogenicity of a CNV is unclear, RNA studies may be required to confirm the deleterious effect, as was the case for two of our five CNVs. Such functional testing falls outside of the realm of standard clinical diagnostic testing and highlights the challenges in interpreting novel CNVs in clinical practice even once detected.

This multicenter cohort establishes *WWOX*-DEE as an important autosomal recessive EIDEE syndrome and expands the epilepsy syndromic spectrum from IESS and LGS to EIMFS and EIDEE. This distinguishes the profound *WWOX*-DEE from the rarer *WWOX* SCAR12 phenotype, albeit both may arise due to biallelic missense variants. Genotype–phenotype correlations revealed that although overall features are similar in all patients with *WWOX*-DEE, the presence of two null variants results in higher mortality than when at least one of the pathogenic variants is a missense change.

AUTHOR CONTRIBUTIONS

Study design: Ingrid E. Scheffer, Nicola Specchio, Karen L. Oliver, Marina Trivisano. Patient recruitment, clinical data curation, and phenotyping: Marina Trivisano, Karen L. Oliver, Christoph Hertzberg, Klaus Goldhahn, Julia Metreau, Christine Prager, Jason Pinner, Michael Cardamone, Kenneth A. Myers, Richard J. Leventer, Gaetan Lesca, Ingrid E. Scheffer, Nicola Specchio. EEG

analysis: Marina Trivisano. Brain MRI analysis: Simone A. Mandelstam. Facial dysmorphism analysis: Angela De Dominicis. Molecular genetic, bioinformatic, and statistical analysis: David I. Francis, Timothy E. Green, Alison M. Muir, Apoorva Chowdhary, Melanie Bahlo, Michael S. Hildebrand, Heather C. Mefford, Karen L. Oliver. Supervision: Ingrid E. Scheffer, Melanie Bahlo, Nicola Specchio, Michael S. Hildebrand. Initial manuscript writing: Karen L. Oliver, Marina Trivisano, Ingrid E. Scheffer. Manuscript revision: all authors.

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CONFLICT OF INTEREST STATEMENT

IES has served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, Rogcon, Takeda Pharmaceuticals, UCB, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, LivaNova, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, BioMarin, and Eisai; has served as an investigator for Anavex Life Sciences, Cerecin, Cerevel Therapeutics, Eisai, Encoded Therapeutics, EpiMinder, Epygenyx, ES-Therapeutics, GW Pharmaceuticals, Marinus, Neuren Pharmaceuticals, Neurocrine BioSciences, Ovid Therapeutics, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix, and Zynerba; has consulted for Atheneum Partners, Care Beyond Diagnosis, Epilepsy Consortium, Ovid Therapeutics, UCB, and Zynerba Pharmaceuticals; and is a nonexecutive director of Bellberry and a director of the Australian Academy of Health and Medical Sciences and the Australian Council of Learned Academies Limited. She may accrue future revenue on pending patent WO61/010176 (filed 2008): Therapeutic Compound; has a patent for SCN1A testing held by Bionomics and licensed to various diagnostic companies; and has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy (PRRT2) 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID: 2012–009). The remaining authors have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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