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Original article

Developmental and epileptic encephalopathy 56 due to *YWHAG* variants: 12 new cases and review of the literature

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ABSTRACT

Background and objectives: Developmental and epileptic encephalopathy 56 (DEE-56) is caused by pathogenic variants in *YWHAG* and is characterized by early-onset epilepsy and neurodevelopmental delay. This study reports on a cohort of DEE-56 individuals, correlating antiseizure medication usage and comorbidities, to aid in understanding disease evolution.

Methods: We analyzed data from thirty-nine individuals aged 3–40 years with *YWHAG* variants, including 12 previously unreported individuals (2 of these with recurrent distal 7q11.23 deletions) and 27 previously published cases (21 families, including 3 adult individuals reported in a family case). Our assessments encompassed clinical, radiological, and genetic evaluations. All procedures adhered to standardized protocols for patient approvals, registrations, and data collection.

Results: Individuals with *YWHAG* variants exhibited variable psychomotor delay, with the majority experiencing mild intellectual disability. Early-onset seizures, particularly febrile seizures, were common, with various seizure

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types reported. Valproic acid has emerged as an effective antiseizure medication. Movement disorders were present in a subset of individuals, primarily manifesting as ataxia and tremor. Comorbidities such as autism spectrum disorders and attention deficit-hyperreactivity disorder were observed in a proportion of individuals. We identified a novel *YWHAG* variant (c.634_645del/p.Asn212_Ser215del) and expanded the genotypic spectrum of the disease.

Conclusions: We provide insights into the clinical, radiological, and genetic features of *YWHAG*-related epileptic encephalopathy. Despite mild clinical symptoms, affected individuals face challenges in daily functioning, underscoring the need for comprehensive care. Valproic acid has been used for seizure control with variable results.

1. Introduction

The developmental and epileptic encephalopathies (DEEs) represent a severe category of epilepsies, typically starting in infancy or childhood with drug-resistant seizures, epileptiform EEG patterns, and developmental slowing or regression, leading to intellectual disability (ID). DEEs have a high mortality rate and profound morbidity; comorbidities are common, including autism spectrum disorders (ASD). With advancements in genetic diagnostic technologies, over 265 genes have been associated with DEEs, with genetic causes identified in 70–80 % of affected individuals [1]. Each genetic DEE typically presents a broad genotypic-phenotypic spectrum, influenced by the underlying pathophysiology. There is a pressing need to improve health outcomes by developing novel targeted therapies for specific genetic DEE phenotypes that not only improve seizure control but also developmental outcomes and comorbidities [2].

DEE-56 (OMIM#617665), due to pathogenic variants or deletions of the *YWHAG* gene, primarily presents with global developmental delay (DD), early-onset seizures that are frequently refractory to antiseizure medication (ASM), followed by ID, autism spectrum disorder (ASD), or neurological regression. Various seizure types have been reported in association with DEE-56, including febrile seizures, febrile seizures plus, generalized tonic-clonic seizures, myoclonus, typical and atypical absences, status epilepticus, and frontal lobe epilepsy. DD typically emerges before the age of 2, primarily impacting motor skills and language development. Behavioral, communication, and ASD features, as well as dysmorphic features, exhibit variability, with the potential occurrence of diverse movement disorders throughout the natural course of the condition [9,10].

The *YWHAG* gene, located at cytogenetic location 7q11.23, was first associated with early-onset epilepsy, including epileptic encephalopathy and ID, in 2017 with its initial description in four subjects [9]. This initial work was further supported by subsequent studies, which collectively contributed to the characterization of clinical and behavioral features associated with *YWHAG* variants [3–5,11–13]. In addition to variants in *YWHAG*, a recurring deletion within the distal 7q11.23 region, encompassing *HIP1* (Huntingtin-interacting protein 1, OMIM*601,767) and *YWHAG*, has been identified in individuals exhibiting ID, epilepsy, and neurobehavioral features.

The *YWHAG* gene encodes the protein known as tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma isoform (OMIM*605356), which is part of the 14-3-3 proteins. The 14-3-3 proteins serve as a protein kinase-dependent activator for tyrosine and tryptophan hydroxylases while also acting as an endogenous inhibitor of protein kinase C, existing in several distinct forms: beta (*YWHAB*), gamma (*YWHAG*), epsilon (*YWHAE*), zeta (*YWHAZ*), theta (*YWHAQ*), sigma (*SFN*), and eta (*YWHAH*). *YWHAG* plays a crucial role in signal transduction pathways leading to mitosis and cellular proliferation, cortical development, and neuronal migration [6].

In this study, we aim to delineate the clinical, radiological, and genetic features of 10 newly identified individuals with DEE-56 and compare them to two individuals with distal 7q11.23 region recurrent deletion (including *YWHAG* and *HIP1* genes), with a particular focus on the epileptic phenotype and their response to ASMs. Furthermore, we assess the impact of this condition on the quality of life of the individuals and seek to enhance the description of the *YWAHG* phenotype by incorporating data from existing literature.

2. Affected individuals and methods

We conducted a data collection study to investigate clinical, radiological, and video EEG characteristics in twelve previously unreported individuals from twelve families harboring pathogenic variants or deletions in *YWHAG* and compared them with 27 previously reported individuals. All the participants were identified through collaborative efforts involving sharing data with colleagues or families willing to participate. Project information was publicly displayed through advertisements on the Epicare and ERN-ITHACA websites.

2.1. Standard protocol for patient approvals, registrations, and authorizations

This study was approved by the Ethics Committee of the Sant Joan de Déu Research Institute (PIC-151-23). Written informed consent was obtained from the parents and guardians of participants to use and disclose the information obtained.

2.2. Data collection

Data was collected through a RedCap database and included demographic data, growth and neurodevelopmental parameters, epilepsy, movement disorders, feeding, social and behavioral development, autism features, dysmorphism, quality of life, treatments and treatment effectiveness, and other supplementary studies, such as video EEG recordings and brain-image studies. The assessment of the degree of ID (>6 years of age) and the severity of psychomotor developmental delay (<6 years of age) was conducted through clinical observations or, where specified, through developmental or cognitive evaluations, which were not available in all cases. Comprehensive clinical, genetic, and radiological data were collected and analyzed by each reference hospital. Data collection for each patient relies on a designated referring doctor who collects the data and also conducts assessments for movement disorders, seizure classifications, and functional abilities. Whole exome sequencing, targeted Sanger sequencing, and array-CGH were employed for genetic analysis, which had been previously conducted as part of routine diagnostics in their reference hospital. The variants were classified following the guidelines outlined by the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) for the interpretation of sequence variants [7].

2.3. Epilepsy

The information provided has been analyzed based on the ILAE operational classification of types of seizures, as well as electroencephalographic records, antiepileptic treatment, and the assessment of response.

2.4. Movement disorders

Through direct clinical examination, the characterization of movement disorders was only possible for each treating physician.

2.5. Development and intellectual quotient

Development was assessed based on information about the motor and language milestones of individuals under the age of six. Intellectual disability was assessed by the subjective impression of the clinician, and in a few cases, the intellectual quotient was formally assessed.

2.6. Severity of disease and quality of life

In this study, severity of disease and quality of life were assessed by using the CP-Child questionnaire to evaluate the quality of life among the new cohort of 12 patients, alongside the disability section of the BFMDRS (Burke-Fahn-Marsden Dystonia Rating Scale) scale and the *GNAO1* severity score [8].

The CP-Child questionnaire was used in this study to assess the impact of DEE-56 on the quality of life of patients and their families. This questionnaire was completed by parents either directly or through their healthcare providers. We focused on parental perceptions of the emotional well-being and functional abilities of their children. The adolescent version of the CP-Child questionnaire was not employed due to the predominance of younger patients and the level of impairment observed in eligible adolescents within our cohort.

Considering the absence of a specific severity scale for DEE-56 and the similarities observed with another DEE caused by *GNAO1* (DEE-17), we applied the *GNAO1* severity score [8]. The *GNAO1* severity score evaluates epilepsy, movement disorders, motor and language development, and the use of a gastrostomy, utilizing a scale from 0 to 13. Severity categories include mild (0–3.9), moderate (4–7.9), and severe [3–8]. We are currently conducting a validation study across multiple DEEs, involving international participation, to assess the utility of the score at diagnosis and during follow-up. Upon validation, we propose using this score for comparative studies pre- and post-treatment.

The disability section of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) is a straightforward scale that assesses aspects of daily life, including speech, handwriting, feeding, eating/swallowing, hygiene, dressing, and walking.

2.7. Literature review

We have carried out a detailed analysis of previously published individuals with genetic variants in the *YWHAG* gene or deletions that contain the *YWHAG* gene in association with their typical clinical and neurological history. Detailed methods are provided in the **Supplemental Data**.

2.8. Statistics

Reverse Kaplan-Meier plots were generated using R (v. 4.3.1) to visualize the age of the individuals at the onset of their first seizure, the age at onset of different types of seizures, and the age at onset of febrile versus afebrile seizures. Due to the limited sample size, comparative analyses between groups were not conducted.

3. Results

3.1. Individuals with YWHAG variants exhibit variable psychomotor delay, with the majority being mildly affected

This study population included 39 individuals (20 females, 16 males, and 3 unknowns), 28/39 of whom were from non-consanguineous families (Fig. 1A). We identified 12 novel individuals (Table 1), and 27 individuals were reported in the literature review. The median age of all individuals was 11.16 ± 0.29 years (media ±standard error (SE), range 1–40 years). 4/19 individuals experienced neonatal events, such as feeding difficulties, the need for respiratory support due to meconium aspiration, and jaundice/hyperbilirubinemia. Motor delay was identified in 27/33 individuals, with a median age at sitting of 9.66 ± 0.22 months (15 individuals, mean ± SE, range 6–20 months) and a median age at walking of 21.32 ± 0.33 months (25 individuals, mean ± SE, range 14–48 months). Language delay was observed in 14/20, with a median age at first words of 23.1 ± 0.66 years (mean ± SE, range 9–60 months).

3.2. Early seizures and diverse epileptiform patterns in individuals with DEE-56 and 7q11.23del

Seizures were identified in all individuals. The median age at seizure onset was 24.55 ± 0,96 months (mean ± SE, range 4 months–16 years) (Fig. 1D), with 29/33 individuals experiencing seizures before the age of 2 years. Various seizure types were reported, including generalized tonic-clonic seizures (21/34), febrile seizures (19/34), epileptic myoclonus (10/34), typical absence (7/34), atypical absence (2/34), focal seizure (4/34), frontal lobe seizure (3/34), and afebrile status epilepticus (5/34) (Fig. 1B). Febrile seizures were the initial seizure type in 15/34 individuals (Fig. 1E). However, the difference was not significant when comparing the age at onset of febrile versus afebrile seizures in months (Fig. 1F).

The initial videoEEG description was available for 23 individuals. VideoEEG recordings occasionally revealed a slow background in 7/23 individuals and interictal alterations such as generalized discharges in 17/23 individuals or focal bi-frontal or parieto-temporal region discharges in 6/23 individuals. The seizures reported in the VEEG studies primarily consisted of generalized tonic-clonic seizures (**Supplemental Data**).

3.3. DEE-56 and 7q11.23del individuals exhibit a broad spectrum of developmental delay/ID, including comorbidities such as ataxia, ASD, and ADHD

Movement disorders were present in 9/15, including ataxia (5/15), tremor (4/15), stereotypes (2/15), and myoclonus (1/15) (Fig. 1B). There was no status dystonicus reported. Cerebellar signs included dysmetria (3/15), abnormal Romberg test (2/15), vertigo (3/15), dysarthria (2/15), and global coordination difficulties (2/15). Other neurological signs included dysgraphia (1/15), dyspraxia (1/15), and difficulties in feeding, chewing, or swallowing (3/15).

DD was present in 27/34 individuals (mild 3/27, moderate 2/27, severe 2/27, and undetermined 20/27 individuals). ID was present in 22/30 individuals (borderline 1/22, mild 9/22, moderate 6/22, severe 1/22, undetermined 5/22). 9/39 had normal cognitive function (Fig. 1B). In our cohort, ASD was detected in 6/12 individuals, with 3/5 in level 1 (requiring support), 1/5 in level 2 (requiring substantial support), 1/5 in level 3 (requiring very substantial support), and 3/12 cases with ADHD. Literature reported 6/18 cases with ASD and 3/12 cases with ADHD.

3.4. DEE-56 and 7q11.23del individuals exhibit mild dysmorphic features with non-specific brain MRI abnormalities

Mild dysmorphias were observed in 16/25 individuals, including down-slanting or up-slating palpebral fissures (8/25), a broad nasal bridge with a prominent bulbous nose (7/25), a prominent broad forehead (5/25), a wide mouth (5/25), and low-set posteriorly rotated ears or some ear abnormality (4/25) (**Supplemental Data**). The literature only described one individual with Irlen syndrome (scotopic sensitivity syndrome) [12]. There is no available data on dysmorphic features in 14 patients.

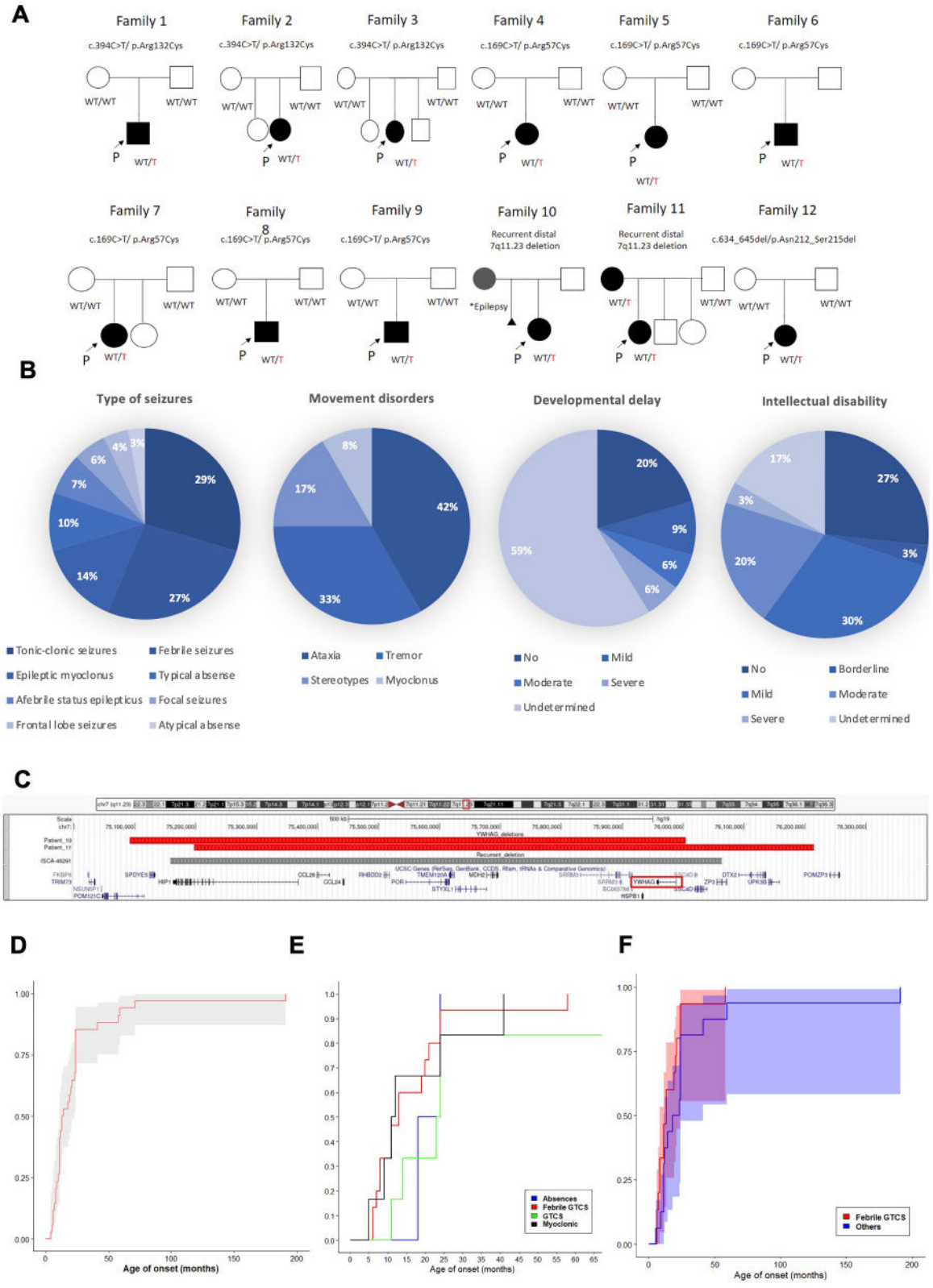

Fig. 1. **A)** presents the pedigrees of the families involved in the study and the segregation of *YWHAG* variants or 7q11.23 deletion. **B)** provides a visual representation of the distribution of individuals categorized by type of seizures (71 types across 39 patients), movement disorders (n = 12), developmental delay (n = 34), and intellectual disability (n = 30). **C)** provides the details of the 7q11.23 region deleted. Individuals with deletions described in this study are represented by red bars, while those with recurrent deletions are represented by a gray bar (breakpoint regions LCR-C and LCR-D). Genes included in the region are listed, with *YWHAG* in the red box. Reverse Kaplan-Meier plots illustrate **D)** age at onset of seizures in months; **E)** age at onset of different types of seizures in months; and **F)** age at onset of febrile versus afebrile seizures in months (log-rank test: $\chi(1) = 2.5$; $p = 0.1$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Overview of clinical, genetic, and radiological features of *YWHAG* and the distal 7q11.23 region deletion individuals.

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
Sex	M	M	F	F	F	M	F	M	F	F	M	F
Age at last follow-up (years)	4	1	12	16	5	1	2	9	1,5	8	12	16
***YWHAG* variant**	c.394C>T	c.394C>T	c.394C>T	c.169C>T	c.169C>T	c.169C>T	c.169C>T	c.169C>T	c.169C>T	*7q11.23* deletion	*7q11.23* deletion	c.634_645del
Type Variant	Missense	Missense	Missense	Missense	Missense	Missense	Missense	Missense	Missense	Gene deletion	Gene deletion	In frame microdeletion
Inheritance	De *novo*	De *novo*	De *novo*	De *novo*	De *novo*	Unknown	De *novo*	De *novo*	De *novo*	Unknown	Maternal	De *novo*
DD	Global	Global	Mild-moderate	Global	Global	Severe	Mild-moderate	Mild	Mild-moderate	Mild-moderate	Mild	Moderate-severe
ASD	No	No	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Movement disorders	Tremor, ataxia, myoclonus	No	Tremor, Ataxia	Ataxia	Ataxia, stereotypes	No	No	No	No	Ataxia, stereotypes	No	No
Age at seizure onset (months)	41	13	11	21	13	14	8	11	6	42	20	11
Onset seizure	Myoclonic	Febrile GTCS	Nocturne seizures + Startle episodes ±head falls	Febrile GTCS	Febrile GTCS	GTCS	Febrile GTCS	Myoclonic	Febrile GTCS	Febrile GTCS	Febrile GTCS	GTCS
Type of seizures	Myoclonic, febrile GTCS, GTCS	Myoclonic, febrile GTCS	Myoclonic, febrile GTCS, GTCS	Febrile GTCS, atypical absences	Febrile GTCS, GTCS, myoclonic, absences, frontal lobe seizures	GTCS	Febrile GTCS, GTCS, focal seizures	Myoclonic, tonic	Febrile GTCS, GTCS	Febrile GTCS, frontal lobe seizures	Febrile GTCS, GTCS	GTCS
Status epilepticus	No	No	No	No	No	Yes	Yes	No	Yes	No	No	Yes
Current ASM **Treatment**	ESM	VPA	VPA, RUF, Ketogenic Diet	No	VPA, LTG, LEV	VPA, LEV	VPA, LEV	LCM, cannabidiol	VPA	LTG	No	No
Brain MRI	Normal	NA	Normal	Venous anomaly	Normal	Normal	Normal	NA	Normal	CC Hypoplasia	Normal	Normal
Other findings	Hypotonia	NA	Hypotonia, feeding difficulties	Hypotonia, scoliosis	Hypotonia	Hypotonia	NA	NA	NA	Scoliosis	NA	No

ASD: autism spectrum disorders, ASM: antiseizure medication, CC: corpus callosum, DD: developmental delay, ESM: ethosuximide, GTCS: generalized tonic-clonic seizure, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, RUF: rufinamide, VPA: valproic acid.

In 20/27 individuals, brain MRI was normal. Brain MRI abnormalities include brain atrophy [9], unspecific T2W white matter hyperintensity [12,13], and corpus callosum hypoplasia (P10).

3.5. Identification of a hotspot in the YWHAG gene NM_012479.4: c.169C>T/p.Arg57Cys and a novel variant

The median age at genetic diagnosis was 7.19 ± 0.41years (12 individuals, mean ± SE, range 1–15 years). Among the 12 newly identified individuals, the pathogenic variants identified were c.394C>T/p.Arg132Cys (3/12 individuals), c.169C>T/p.Arg57Cys (6/12 individuals), c.634_645del/p.Asn212_Ser215del (1/12 individuals), and a 7q11.23 deletion, including the *YWHAG* gene (2/12 individuals). Pathogenic variants previously reported in the literature include c.394C>T/p.Arg132Cys (5/27), c.169C>T/p.Arg57Cys (2/27), c.398A>C/p.Tyr133Ser (2/27), and c.170G>A/p.Arg57His (3/27) ([14–16]). The remaining variants, namely c.395G>A/p.Arg132His, c.44A>T/p.Glu15Ala, c.619G>A/p.Glu207Lys, c.387C>G/p.Asp129Glu, c.532A>G/p.Asn178Asp, c.529C>A/p.Leu1777Ile, c.148A>C/p.Lys50Gln, c.373A>G/p.Arg125His, and c.304del/p.Ser102Alafs*7, each account for (1/27). Lastly, the variant c.124C>T/p.Arg42Ter represents (6/27) individuals, corresponding to a family case with six affected members. Considering all individuals, missense variants were observed in 29/39, while truncating variants or in-frame microdeletion were present in 10/39. Regarding inheritance patterns, 29/39 variants were *de novo*, 8/39 were inherited from either the maternal or paternal side, and 2/39 had an unknown inheritance pattern.

We aim to highlight a case of particular significance due to its novel mutation. The individual with a novel *YWHAG* in-frame intragenic deletion (c.634_645del/p.Asn212_Ser215del) was a 16-year-old girl who has exhibited abnormal psychomotor development since the age of 3 months. Epilepsy onset occurred at 11 months, presenting with generalized tonic-clonic seizures and subsequent status epilepticus. Despite a normal brain MRI, EEG findings revealed burst diffuse waves. Treatment with valproic acid (VPA) initially provided partial seizure control, necessitating the addition of clonazepam for adequate seizure management. Following three years of treatment, seizures were controlled and videoEEG normalized. Upon discontinuation of antiseizure medications at 4 years old, no seizure recurrence was observed. She did not present with movement disorders or dyskinetic crises and exhibited joint hyperlaxity without dysmorphic features. Gait function is currently independent but moderately abnormal, accompanied by a moderate ID and associated ASD. Significant academic support is required due to severe learning disabilities.

3.6. Individuals with recurrent distal 7q11.23 deletions exhibited shared characteristics with DEE-56 individuals

We have included two individuals for analysis due to the involvement of *YWHAG* in the clinical features observed in individuals with recurrent deletions in the distal 7q11.23 region (Fig. 1C). It is noteworthy to mention that three individuals have been reported in the literature to have distal 7q11.23 region deletions affecting solely the *HIP1* gene, without any involvement of *YWHAG*. This indicates that the induction of a neurological phenotype might be achievable through the deletion of *HIP1* alone [17].

P10, a child with recurrent distal 7q11.23 deletion (arr(GRCh38) 7q11.23(75462614_76374545)x1 of 912 kb, including both *HIP1* and *YWHAG*), experienced an uncomplicated febrile seizure at 3.5 years old, followed by another at 4 years and 10 months old. Despite a history of normal development until 12 months old, she exhibited mild DD and delayed language skills by age 3. Additionally, EEG recordings revealed spike and wave discharges, predominantly on the right side. Although she required ASM adjustment, no further seizure events occurred. She had a family history of epilepsy (and her mother used VPA during pregnancy), but segregation studies have not been performed yet. Neurologically, she presented with mild intellectual disability, dysmorphic features, ataxia, and coordination disturbances at 6 years and 9 months old, along with ASD (**Supplemental Data**).

P11, born to healthy, unrelated parents, experienced an uneventful pregnancy and was delivered at 36 GW with normal anthropometric measurements. Although the neonatal period required phototherapy for jaundice, initial motor and speech development were typical. Epilepsy onset occurred at 20 months with febrile seizures, leading to VPA treatment after the fourth episode. Discontinuation of VPA due to poor tolerance was followed by seizure recurrence at age 3 during an upper respiratory tract infection. The reintroduction of VPA successfully controlled seizures. ASD, dysmorphic features, and moderate ID were present, with notable dysmorphisms including additional hair whorl, convergent strabismus, and enlarged interphalangeal joints. Genetic testing identified a deletion involving the *HIP1* and the *YWHAG* genes ((arr[GRCh37] 7q11.23(75197465_76214077)x1 of 1,01 Mb), inherited from a healthy mother.

3.7. The majority of individuals required ASMs, with VPA being the most effective

28/34 individuals required ASM to control seizures, 6/34 did not require treatment (all individuals previously reported), and 5 individuals lacked information (Table 2). 12/28 required one ASM, 8/28 two ASM, and 8/28 three or more. The most effective ASM was valproic acid (VPA) (13/28) (**Supplemental Data**). Additionally, we assessed whether there were patients who, after a seizure-free period, were able to discontinue medication without the need to reintroduce ASMs. In this case, we were only able to evaluate the cohort of 12 newly reported patients. Of these, 5 out of 12 individuals successfully discontinued ASMs without experiencing a recurrence of epileptic seizures. The ketogenic diet was used in three individuals, with partial improvement in two and non-effectiveness in the other. Vagal nerve stimulation (VNS), or epilepsy surgery, was not performed on any individual. For other combinations of ASMs reported in the literature, see the **Supplemental Data.**

3.8. Parent-reported quality of life in DEE-56 and 7q11.23del individuals is perceived as favorable despite mild to moderate severity

Parent-reported quality of life among individuals with DEE-56, as assessed by the CP-Child questionnaire, revealed varying perceptions despite mild to moderate clinical severity (**Supplemental Data**). Specifically, responses were obtained from 7 out of 12 families, indicating fair to excellent quality of life ratings (fair for 1/7 individuals, good for 2/7 individuals, very good for 2/7 individuals, and excellent for 1/7 individuals). Other data from the CP-Child questionnaire is available in the **Supplemental Data**. This limited but insightful dataset provides a foundational understanding of familial perspectives on quality of life, highlighting discrepancies between subjective reports and clinical assessments.

Considering the absence of a specific scale for DEE that could be used to assess the severity of individuals with *YWAHG*, we applied the *GNAO1* severity scale, recently developed by our group [8]. This decision was made due to the similarity of *YWHAG* to another DEE due to *GNAO1* (DEE-17) and their shared characteristics. This severity scale evaluates aspects of epilepsy, movement disorders, motor and language development, and the presence of dysphagia or the use of a gastrostomy. The scale ranges from 0 to 13, with individuals scoring 0–3.9 considered mild, 4–7.9 moderate, and 8–13 severe. 11/12 individuals with *YWHAG* were classified as mild, and 1/12 as moderate (Table 3). To assess the

Table 2
Treatment of the twelve *YWHAG* and the distal 7q11.23 region deletion individuals.

Patient	Variant	Treatment effective	Treatment partially effective	Treatment not effective	Combination and order Antiepileptic Drugs. (Example: 1. LEV 2. LEV + CBZ 3. LEV + CBZ + DC …. 4. None)	Amount of ASMs (0/1/2/ >3)	Most effective monotherapy	Most effective combinations of ASMs	No treatment needed or free seizure period	Currently without treatment
P1	c.394C>T/p. Arg132Cys	VPA KD ETM	LTG[a]	LCM	1. VPA, 2. VPA + LTG, 3. LCM + VPA, 4. LCM + VPA + KD, 5.VPA + ESM + KD, 6.ESM	>3	ESM	VPA + ESM + KD	None	Yes
P2	c.394C>T/p. Arg132Cys	VPA	LEV[a]	None	1. LEV, but only for 3–4 weeks due to side effects, 2. VPA	2	VPA	No need	48 months (4 years)	No
P3	c.394C>T/p. Arg132Cys	RUF CZP KD	VPA LTG	LEV - ETM TPM - OXC ZNS	1. VPA, 2. VPA + RUF, 3.VPA + RUF + LTG, 4. LEV, ESM, TPM, OXC and ZNS was indicated, 5. VPA + RUF + CZP + KD, 6. VPA + RUF + KD	>3	RUF	VPA + RUF + KD CZP + KD	None	Yes
P4	c.169C>T/p. Arg57Cys	VPA	None	None	1. VPA from 3 to 5 years	1	VPA	No need	No ASM since 5 years old (>120)	No
P5	c.169C>T/p. Arg57Cys	LEV VPA LTG	CZP	None	1. LEV, 2. LEV + VPA, 3. VPA + LTG, 4. VPA + LTG + LEV, ***CZP during short periods of multiples seizures	>3	None	VPA + LEV + LTG	12 months	Yes
P6	c.169C>T/p. Arg57Cys	None	LEV VPA	None	1.LEV + VPA	2	None	VPA + LEV	NA	Yes
P7	c.169C>T/p. Arg57Cys	VPA	LEV	None	1. LEV, 2. LEV + VPA	2	None	VPA + LEV	8 months	Yes
P8	c.169C>T/p. Arg57Cys	None	LCM CBD	ETM - LTG LEV - VPA KD	ESM, LTG, LEV, VPA, KD, and other ASMs were tried, with poor or partial response. Current combination: LCM + CBD. LTG progressively withdrawn, since the introduction of LCM to avoid 2 Sodium channel blockers). No KD currently.	>3	None	LCM + CBD	NA	Yes
P9	c.169C>T/p. Arg57Cys	None	VPA	None	1. VPA	1	VPA	None	NA	Yes
P10	7q11.23 deletion	LTG	None	None	1. LTG, 2. None	1	LTG	No need	36 months	No
P11	7q11.23 deletion	VPA[b]	None	None	1. VPA, 2. None	1	VPA	No need	108 months (9 years)	No
P12	c.634_645del/p. Asn212_Ser215del	CZP	VPA	None	1. VPA, 2. VPA + CZP, 3. None	2	None	VPA + CZP	168 months(14 years)	No

CBD: cannabidiol, CBZ: carbamazepine, CZP: clonazepam, ESM: Ethosuximide, KD: ketogenic diet, LCM: lacosamide, LEV: levetiracetam, LTG: Lamotrigine, OXC: oxcarbazepine, PHT: phenytoin, RUF: rufinamide, STP: stiripentol, TPM: topiramate, VPA: valproic acid, ZNS: zonisamide.
[a] Suspended because of side effects.
[b] Poor tolerance.

disability of these individuals, we used the disability part of the Burke-Farsh-Marden Dystonia Rating Scale (BFMDRS), which considers the following aspects: speech, handwriting, feeding, eating/swallowing, hygiene, dressing, and walking. This scale ranges from 0 to 30 points, with all categories weighted equally except for walking, which has a higher relative weight. In this scale, 5 individuals scored <10 points (mild), 5 individuals scored <20 points (moderate), and only 1 individual scored a maximum of 22 points (severe) (**Supplemental Data**).

4. Discussion

In this study, we investigated the clinical, radiological, and genetic features of twelve previously unreported individuals with *YWHAG*

Table 3
GNAO1 severity score applied to individuals with *YWHAG* and the distal 7q11.23 region deletion. Severity categories include mild (0–3.9), moderate (4–7.9), and severe [3–8].

Severity Score	Frequency	Intensity/ Duration	Falls/ Injuries	Amount ASMs	Epilepsy total	Frequency	Intensity/ Duration	Falls/ Injuries	Medication/ therapy	Movement disorders total	Gross motor development	Language development	Feeding	Total
P1	3	1	1	2	1,75	0	0	0	0	0	0	1	0	2,75
P2	0	0	0	1	0,25	0	0	0	0	0	0	0	0	0,25
P3	2	2	1	2	1,75	0	0	0	0	0	0	0	0	1,75
P4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P5	0	0	0	3	0,75	0	0	0	0	0	0	1	0	1,75
P6	1	3	2	2	2	0	0	0	0	0	0	1	0	3
P7	1	3	3	2	2,25	0	0	0	0	0	0	1	0	3,25
P8	3	1	1	3	2	0	0	0	0	0	2	1	0	5
P9	1	1	1	1	1	0	0	0	1	0,25	0	0	0	1,25
P10	0	0	0	1	0,25	1	0	0	0	0,25	0	0	0	0,50
P11	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P12	0	0	0	0	0	0	0	0	0	0	0	1	0	1

pathogenic variants or deletions, with a particular focus on the epileptic phenotype and their response to ASM. Our results indicate that individuals with *YWHAG* exhibit a delay in global psychomotor development preceding the onset of epileptic seizures, often initially febrile, followed by epileptic myoclonus, generalized tonic-clonic seizures, etc. These individuals present a mild impairment of intellectual capacity with relatively minor severity and impact on their activities of daily living. VPA is an effective medication for the treatment of epilepsy in these individuals.

Genetic epilepsy with febrile seizures plus (GEFS+) constitutes a familial epilepsy syndrome characterized by a spectrum of seizure types. Affected individuals typically manifest with various phenotypes, including simple and complex febrile seizures (FS), which generally carry a favorable prognosis. More severe manifestations can include FS+ and a range of epileptic seizures, including absence seizures, myoclonic seizures, atonic seizures, and occasionally myoclonic-astatic epilepsy. In rare cases, there may be overlap with severe epileptic encephalopathy [18,19]. Inheritance patterns include autosomal dominant genes or *de novo* cases. Associated genes include *SCN1A*, *SCN1B*, *CHRNA4*, *GABRD*, and *GABRG2*. Given the clinical features observed in *YWHAG* individuals, we propose including this gene in the differential diagnosis of GEFS+. The initial presentation of epilepsy in affected individuals often involves febrile seizures. Furthermore, the frequent episodes of decompensation during febrile episodes suggest a susceptibility to fever-induced exacerbations. Therefore, *YWHAG* should be recognized as a significant contributor to the spectrum of GEFS+, emphasizing its relevance in the differential diagnosis of such conditions.

A growing number of DEEs have been associated with movement disorders, such as genetic disorders affecting G protein-coupled receptors and cAMP signaling [20], including severe conditions like status dystonicus or dyskinetic crises. In contrast, only a small proportion of individuals with *YWHAG*-related disorders exhibited movement disorders, with the most common symptoms being ataxia, tremor, and stereotypies. While these movement disorders contribute to the clinical picture, they do not dominate it as much as neurodevelopmental disorders and epilepsy do. Additionally, the movement disorders observed in these individuals are typically mild and often do not require specific pharmacological treatment.

We have expanded the genotypic spectrum of the disease by describing a novel mutation, c.634_645del/p.Asn212_Ser215del, in the *YWHAG* gene. The individual harboring this variant, a 16-year-old girl, has displayed abnormal psychomotor development since 3 months of age, with epilepsy onset at 11 months, the absence of movement disorders or dyskinetic crises, and a moderate intellectual disability with associated autism features. Importantly, the clinical picture of this individual does not differ significantly from that of other typical *YWHAG* individuals.

From a genetic point of view, our study included two individuals with recurrent distal 7q11.23 deletions, supporting the clinical phenotype described in this recurrent microdeletion. 7q11.23 deletions were characterized in 2010 in 26 individuals with variable expression and/or incomplete penetrance of epilepsy, learning difficulties, ID, and/or neurobehavioral abnormalities [6,17]. Several genes, including *MAGI2* (OMIM*606,382), *HIP1* (OMIM*601,767), and *YWHAG*, have been posited as potential contributors to these atypical features. Earlier studies have already indicated that a smaller, shorter region of overlap containing only *HIP1* could disrupt neuronal homeostasis, leading to focal and generalized epilepsies, as well as cognitive impairment. Nevertheless, their findings do not preclude the possibility that *YWHAG* loss of function alone could induce neurological phenotypes [17]. *YWHAG* haploinsufficiency has also been proposed as a potential factor in the onset of infantile spasms in individuals with Williams-Beuren syndrome, harboring a deletion of the 7q11.23 region. As observed in other deletion cases, these individuals typically exhibit more severe phenotypes compared to those caused solely by mutations in the *YWHAG* gene, due to the involvement of adjacent genes. It is also

important to note that in recurrent distal 7q11.23 deletions, there is intrafamilial variability with incomplete penetrance [6]. Particularly remarkable is the case of the mother of P11, who, as far as we know, is the first carrier of the recurrent deletion that remains entirely healthy. This suggests the possibility of incomplete penetrance, a phenomenon that has been observed in other genetic syndromes involving chromosomal deletions, such as 22q11.2 deletion syndrome [21] and 16p11.2 deletion syndrome [22], where carriers may exhibit no clinical symptoms. The variability in phenotypic expression could be influenced by genetic background, epigenetic factors, or the presence of protective compensatory mechanisms.

Brain MRI revealed no abnormalities in most individuals, indicating the absence of common structural brain anomalies seen in epileptic encephalopathies [23]. However, one patient exhibited cerebral atrophy, three patients displayed non-specific white matter lesions, and one patient from this study had hypoplasia of the corpus callosum, all of which are non-specific findings. Furthermore, the individuals exhibited mild and non-specific dysmorphic characteristics, making this disorder not easily recognizable and adding complexity to the diagnostic process. Despite the clinical presentation aligning with features commonly observed in *YWHAG*-related epileptic encephalopathy, such as febrile seizure association, no other distinctive clinical characteristics directly pointed to involvement of the *YWHAG* gene. This lack of specific clinical markers beyond febrile seizure association underscores the challenge of diagnosing *YWHAG*-related epileptic encephalopathy solely based on clinical presentation.

From a clinical symptomatology perspective and considering their impact on their activities of daily living, individuals with *YWHAG* exhibit mild clinical symptoms with a moderate repercussion on their ADLs. The majority of these individuals scored mild on the *GNAO1* severity scale, and while a small proportion showed moderate disability on the BFMDRS, it highlights the moderate impact of their condition on their daily functioning. Despite the mild clinical symptoms, these individuals encounter difficulties in their functional abilities and independence in daily life. However, these findings differ significantly from those seen in other DEEs such as *GNAO1* [8] and *STXBP1* [24], which present a more severe impact, resulting in greater disability and impairment in ADLs.

In our cohort and as reported in the literature, VPA has frequently been used as a first-line ASM treatment, particularly for managing myoclonic and generalized seizures. While VPA has demonstrated effectiveness in some patients, often in combination therapies with other ASMs, the variability in the responses of these individuals suggests caution in proclaiming it as the definite drug of choice. Furthermore, alternative therapies, such as the ketogenic diet, have been utilized as adjunctive therapies in a subset of our cohort. Given these considerations, while acknowledging the potential for toxic side effects, our findings suggest that VPA may offer benefits to selected individuals with *YWHAG*-associated epilepsy.

In our study, as well as in other cases reported in the literature, the discontinuation of ASM was observed in five patients (P2, P4, P10, P11, and P12). This decision was made through shared decision-making between the pediatric neurologist and the families of the patients, based on an individualized assessment of each case. This finding suggests several implications for understanding the cessation of ASM in these patients. Firstly, it may indicate that these patients exhibit a milder form of DEE compared to other subtypes. This variability in DEE severity could be linked to the nature of epileptic seizures, which may have been predominantly febrile and more likely to decrease with age. While discontinuation of ASM without performing routine video-EEG monitoring may raise concerns about undetected subclinical epileptiform activity, particularly in the context of continuous spike-wave in sleep (CSWS), clinical practice tends to prioritize the observation of clinical seizures over routine EEG follow-up in patients who remain seizure-free. In these cases, despite the absence of regular video-EEG monitoring, close attention was paid to the patients' cognitive and behavioral outcomes, which were stable and showed no signs suggestive of subclinical seizure activity or CSWS. It is important to emphasize that an abnormal EEG alone, in the absence of clinical seizures, would not necessarily warrant the reintroduction of ASM. The patients did not present with clinical seizures or behavior regression after the discontinuation of ASM, which supports the decision not to reintroduce treatment in these cases.

Despite the comprehensive analysis conducted in this study, there are several limitations that should be acknowledged. The sample size of our cohort, while rather substantial for a rare genetic condition, may still be inadequate to fully reflect the range of clinical heterogeneity associated with *YWHAG*-related epileptic encephalopathy. The retrospective design of the study and reliance on medical records and individual-reported data may introduce biases and limits in data collection and interpretation. The absence of standardized evaluation techniques for certain features of the condition, like intellectual quotient, might have impacted the precision and uniformity of our results. The participation of individuals from various geographic regions and healthcare contexts may have led to differences in diagnostic criteria, treatment methods, and follow-up procedures.

In conclusion, our study sheds light on the clinical, radiological, and genetic features of *YWHAG*-related epileptic encephalopathy. We observed a diverse clinical presentation characterized by variable psychomotor delay, early-onset seizures, and mild to moderate intellectual disability. In these individuals, febrile seizures frequently marked the onset of epilepsy. VPA emerged as a commonly used first-line treatment, demonstrating efficacy in seizure control. The identification of a novel mutation in the *YWHAG* gene expands our understanding of the disease spectrum. Importantly, our findings underscore the challenges in diagnosing *YWHAG*-related epileptic encephalopathy based solely on clinical features, emphasizing the necessity of comprehensive genetic testing for accurate diagnosis.

Author contribution

Juan Darío Ortigoza-Escobar planned and designed the study, interpreted the data and revised the manuscript. Maria Eugenia Amato drafted and revised the manuscript. Sol Balsells performed the statistical analyses. Loreto Martorell, Adrián Alcalá San Martín, Karen Ansell, Malene Landbo Børresen, Heather Johnson, Christian Korff, Stephanie Garcia-Tarodo, Jeremie Lefranc, Anne-Sophie Denommé-Pichon, Elisabeth Sarrazin, Nora Zsuzsanna Szabo, Jorge M. Saraiva, Dorota Wicher, Anne Goverde, Karen G.C.B. Bindels-de Heus, and Tahsin Stefan Barakat, acquired and interpreted the data, and revised the manuscript. All authors approved the final submitted version.

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Declaration of competing interest

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2024.10.005.

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