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RESEARCH ARTICLE - SHORT

Isolated absence epilepsy associated with a de novo *FBXW7* missense variant in the F-box domain

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Abstract

The *FBXW7* gene encodes a substrate-recognition component of the Skp1-Cul1-F-box (SCF) E3 ubiquitin ligase complex, which targets key regulatory proteins for proteasomal degradation. Recently, loss-of-function *FBXW7* variants have been associated with a novel neurodevelopmental disorder characterized by heterogeneous clinical features. Most reported pathogenic variants cluster within the WD40 domains, while variants in other regions, such as the F-box domain, remain poorly characterized. In this study, we performed trio-exome sequencing on a 3-year-old girl with Early-Onset Childhood Absence Epilepsy. We analyzed the identified *FBXW7* variant using multiple in silico tools for pathogenicity prediction and structural modeling. Clinical phenotype was compared with previously reported cases. We identified a novel de novo missense variant in *FBXW7*, c.926G>C; p.(Arg309Pro), affecting a highly conserved residue in the F-box domain. Notably, unlike prior cases predominantly associated with WD40 domain variants and severe phenotypes, our patient exhibited a much milder clinical presentation consisting of isolated, drug-responsive absence seizures without intellectual disability. Structural modeling predicted significant impairment in protein–protein binding affinity, particularly with the SCF complex component SKP1, supporting a potentially disruptive effect of the p.(Arg309Pro) substitution on complex assembly. Overall, our findings expand the genotypic and phenotypic spectrum of FBXW7-related disorders. Variants in the F-box domain may result in milder neurological phenotypes compared to those in the WD40 domains, suggesting domain-specific effects and potentially distinct pathogenic mechanisms.

Plain Language Summary: The *FBXW7* gene helps regulate the stability of many proteins essential for brain development and function. Changes in this

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gene have recently been linked to neurodevelopmental disorders with epilepsy. We identified a new *FBXW7* variant in a 3-year-old girl with early-onset absence epilepsy. Computer-based modeling suggests that this change weakens the protein's normal interactions. Our findings broaden the spectrum of *FBXW7*-related disorders and indicate that variants in different gene regions may result in variable clinical severity.

KEYWORDS

de novo, early-onset absence epilepsy, F-box, *FBXW7*, missense variant, neurodevelopmental disorder

1 | INTRODUCTION

Neurodevelopmental disorders (NDDs) are a heterogeneous group of conditions featuring impairments in motor skills, adaptive behaviors, communication, and cognition.[1] These disorders are underlain by the disruption of a variety of crucial processes involved in brain development, such as neurogenesis, neuronal migration, and axonogenesis.[2] The development of next-generation sequencing (NGS)-based technologies has significantly improved the diagnostic yield in NDDs, paving the way to the identification of many novel disease genes.[3–7] In the specific context of Early-Onset Absence Epilepsy (EOAE), recent clinical and epidemiological data suggest a genetic diagnostic yield ranging between 10% and 30%.[6–8] While *SLC2A1* mutations represent a major differential diagnosis, they appear to be infrequent in strictly defined EOAE cohorts.[9] However, the landscape of epilepsies with absence seizures and single-gene etiology has been increasingly characterized, with identified variations in genes such as *GABRG2* and *CACNA1H*.[10] Recently, de novo variants in the human *FBXW7* gene (MIM * 606278), encoding the F-box and WD40 domain protein 7 (FBXW7), have been identified as the cause of a neurodevelopmental syndrome known as Developmental Delay, Hypotonia, and Impaired Language (DEDHIL, MIM # 620012).[11] Loss of FBXW7 function causes reduced neuron formation, an increased number of astrocytes, and myelination defects.[12,13] FBXW7 controls the equilibrium between the differentiation of oligodendrocytes and Schwann cells by adjusting the Notch and mTOR signaling pathways.[13,14] Its substrates, such as mTOR and c-Jun, are linked to autism and tuberous sclerosis, and it has been implicated in neurodegenerative conditions.[14,15] FBXW7 also impacts the production of amyloid-beta and the death of neurons in Alzheimer's disease, while abnormal levels of FBXW7β affecting neuronal survival are present in patients with PARK2-related Parkinson's disease.[14,15] In Huntington's disease, FBXW7 contributes to breaking down protective proteins like HSF1 and regulates the function of mitochondria through p53.[14]

Key points

- We identified a novel de novo *FBXW7* missense variant, p.(Arg309Pro), in the F-box domain in a child with early-onset absence epilepsy.
- Unlike WD40 domain variants, this F-box variant caused a mild phenotype: drug-responsive seizures without other neurodevelopmental signs.
- Protein modeling suggests the variant impairs binding to the SKP1 component of the SCF ubiquitin ligase complex.
- This case expands the FBXW7 spectrum, suggesting that domain-specific effects influence clinical severity in DEDHIL syndrome.

So far, most disease-related *FBXW7* variants have been reported to alter the WD40 domain structure and function, impacting on protein–protein interactions.[12] Conversely, variants in other regions of the protein, especially the F-box domain, appear to be extremely rare. Affected individuals show a severe neurological phenotype featuring global developmental delay, hypotonia, and intellectual disability.[11,13] Of note, seizures have only been documented in 22.9% of patients.[11,13] Although the report of early-onset absence epilepsy (EOAE) in a single subject may suggest that epilepsy is a significant feature of *FBXW7* patients, current literature suggests that epileptic phenotypes may be an underappreciated feature of DEDHIL.[11,13]

In this study, we report a patient harboring a novel de novo missense variant localizing to the F-box domain of FBXW7 and showing a distinctive neurological phenotype,

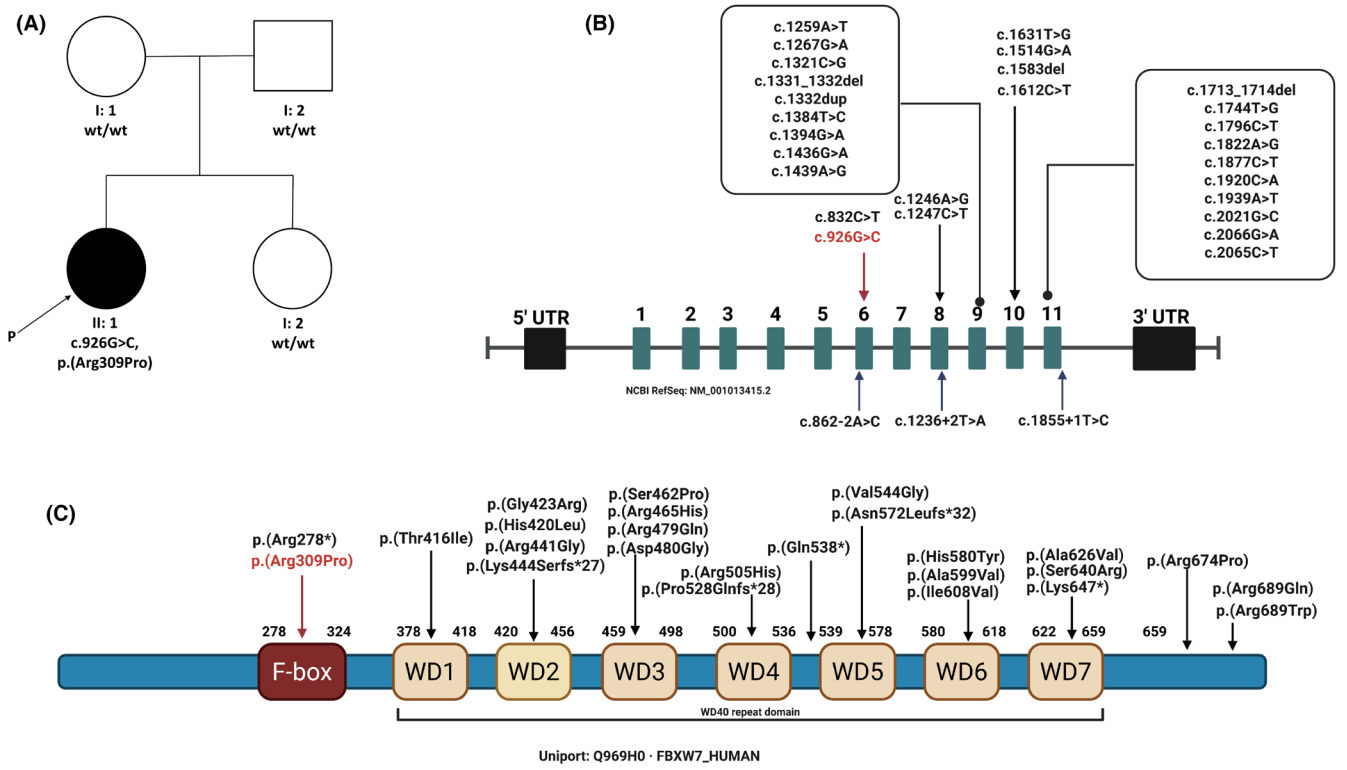

FIGURE 1 Genetic and clinical findings. (A) Pedigree of the reported family showing the segregation of the p.(Arg309Pro) variant in FBXW7 in the family. The variant occurs de novo in the proband. (B, C) Schematic representation of the *FBXW7* gene (B) and protein (C) showing the localization of the novel (red) and previously reported (black) variants associated with neurodevelopmental disorders in human patients.

consisting of drug-responsive early-onset absence seizures. This case expands the genotype–phenotype spectrum of DEDHIL, suggesting that it may be wider than expected based on previous reports.

2 | CASE PRESENTATION

This 3-year-old girl was born to unrelated healthy parents of Italian ancestry (Figure 1A). Family history was unremarkable. She was delivered at term following a physiologic pregnancy and the neonatal course was uneventful. She regularly met developmental milestones. At the age of 11 months, the patient started to suffer from brief (6–10 s) episodes of loss of contact, staring, and inconstant eyelid jerks, occasionally associated with automatisms (shoulder shrugging). These episodes occurred at a frequency of approximately four to five episodes per day. Neurological examination was unremarkable. EEG recordings revealed generalized high-amplitude spike-waves (SWs) discharges, sometimes with clinical correlates associated with a 3.5 Hz SW discharge, indicative of absence seizures (Figure 2A).

Based on the early age at onset, the characteristic seizure semiology, and the EEG pattern, her epilepsy was classified within the spectrum of early-onset childhood absence epilepsy (early-onset CAE).[6,7]

During sleep, generalized epileptiform abnormalities (sharp waves and spike waves) were organized in brief non-rhythmic discharges (Figure 2B). Her brain MRI was unremarkable. Treatment with Ethosuximide (150 mg BID increased to 200 mg BID the following year) led to marked reduction of seizure frequency to 1-2/day alternating with days without events, followed by complete seizure control at 2 years of age and EEG normalization. At the age of 3, the global developmental quotient (GDQ) resulted in 110 at Griffith's Developmental Scales. At last follow-up, performed at the age of 4 years, the patient was seizure-free; her routine wake and sleep EEG, neurological examination, and development resulted in normal except for mild dyslalia.

3 | GENETIC ASSESSMENT AND IN SILICO ANALYSIS

Trio-exome sequencing (ES) was performed on genomic DNA obtained from peripheral blood samples of the patient and the parents, as previously described. Genetic variants were evaluated according to allele frequency,

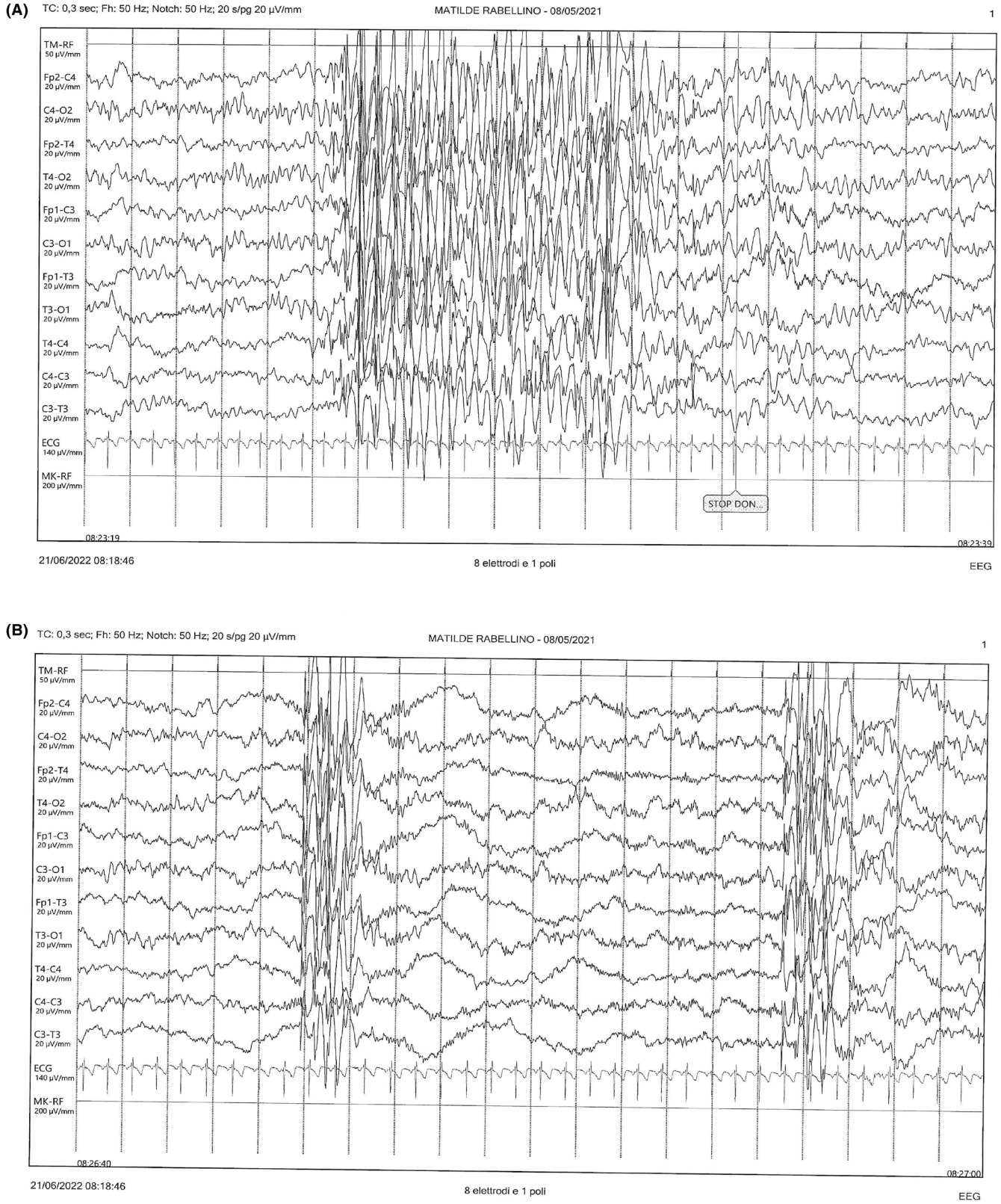

FIGURE 2 EEG findings. Wake (A) and Sleep (B) EEG performed at the age of 13 months, 2 months after seizure onset at the time of diagnosis. International system 10–20, longitudinal and transverse montage, 8-channel. HF 50 Hz, Sens 20 uv/mm. During wake: An absence seizure is recorded, with generalized spike–wave discharge at 3–3.5 Hz lasting 8 s. During sleep: Normal architecture of sleep with brief generalized discharges of spike and waves.

conservation of affected residues, and predicted impact on protein structure and function, as previously reported.[16] ES identified a de novo *FBXW7* variant NM_001349798.2: c.926G>C, p.(Arg309Pro) (Figure 1B). This variant is absent from the gnomAD database (v4.1.0). The affected gene is highly intolerant to loss-of-function variation (LOEUF = 0.149),[17] and is predicted by MutationTaster2[18] to be deleterious. According to the ACMG/AMP guidelines, the variant is classified as a variant of uncertain significance (VUS) based on criteria PM2, PP2, and PP3 (class III).[3]

4 | PROTEIN MODELING

FBXW7 is a 707-amino acid protein lacking a complete experimentally resolved 3D structure. To assess the structural impact of the p.(Arg309Pro) missense variant, we used the AlphaFold2-predicted model (AF-Q969H0-F1).[19] The Arg309 residue is located within the F-box domain, suggesting a potential role in disrupting protein–protein interactions (Figure 1C).

To evaluate the potential structural consequences of the p.(Arg309Pro) substitution, we applied two deep neural network–based predictors of protein stability: ThermoMPNN[20] and DDMut.[21] ThermoMPNN predicted a ΔΔG of −0.1896 kcal/mol, while DDMut yielded a ΔΔG of 0.15 kcal/mol. In ThermoMPNN, negative ΔΔG values indicate stabilizing effects, whereas in DDMut, positive ΔΔG values reflect stabilization. These findings suggest that the variant has negligible effects on global folding stability and is likely neutral in terms of structural stability.

To further assess the potential functional impact, we next used four complementary computational approaches–AlphaMissense,[22] SIFT,[23] PolyPhen-2,[24] and CADD.[25] AlphaMissense predicted a high pathogenicity score (0.987), SIFT a score of 0.02 (interpreted as deleterious; threshold ≤0.05), PolyPhen-2 a score of 0.998 (probably damaging; threshold >0.908), and CADD a PHRED-scaled score of 32. This CADD value places the variant within the top 0.1% of potentially deleterious single-nucleotide variants in the human genome.

Taken together, while structural modeling predicted minimal influence on protein folding, the pathogenicity algorithms yielded consistently high scores, supporting a functionally damaging effect. These data indicate that the p.(Arg309Pro) variant may impair FBXW7 activity not by destabilizing the protein, but rather by altering key interaction surfaces within the F-box domain, particularly those required for binding with the SCF complex component SKP1 (Figure S1A). To further assess functional effects, we analyzed the FBXW7–SKP1 complex (PDB: 2OVP, 2.90 Å), which provides experimental structural insight into this critical interaction. In this complex, the Arg309 residue from the full-length FBXW7 protein aligns with Arg196 in chain B of the PDB structure. This specific structure contains 20 unresolved residues, which we reconstructed using MODELER v10.6. Among 100 generated models, the one with the lowest molpdf score (124.8304) was selected.[26] The completed complex structure enabled accurate mapping of the p.(Arg309Pro) variant's position relative to the SKP1-binding interface (Figure S1B), reinforcing its potential to interfere with substrate recognition or SCF complex assembly despite limited impact on global protein stability.

To evaluate the impact of this p.(Arg309Pro) variant on binding affinity (assessed at the corresponding Arg196 position within the complex), we then used DDMut-PPI and mCSM-PPI2.[27,28] Both predicted a notable reduction in binding affinity; DDMut-PPI estimated a −3.503 kcal/mol change, while mCSM-PPI2 predicted −1.563 kcal/mol, suggesting the variant significantly weakens the FBXW7–SKP1 interaction.

5 | DISCUSSION

Deleterious variants in several *FBX* genes have been linked to neurodevelopmental disorders, including *FBXW11*, *FBXO11*, and *FBXO28*, which are associated with developmental delay, intellectual disability, behavioral abnormalities, and epilepsy.[29–31] Biallelic variants in *FBXL3* and *FBXL4* lead to syndromic forms involving dysmorphism or mitochondrial dysfunction, while *FBXL10* (*KDM2B*) variants have been associated with developmental delay and intellectual disability.[32–34] The *FBXW7* gene encodes a key component of the Skp1-Cullin1-F-box (SCF) ubiquitin ligase. This complex helps degrade oncoproteins through the ubiquitin-proteasome system and regulates cell development.[35] *FBXW7* variants are associated with a highly variable neurodevelopmental disorder (DEDHIL, OMIM #620012), presenting with global developmental delay, intellectual disability, language disorder, hypotonia, heterogeneous neurological manifestations, developmental regression, and syndromic features[11,14] (Table 1). Phenotypic variability occurs, since individuals with normal cognitive function have also been reported.

Compared to previous cases, our patient showed a distinctive neurological phenotype. Indeed, this individual presented with an isolated generalized epilepsy aligning with early-onset childhood absence epilepsy in the absence of any concomitant neurodevelopmental comorbidities. Furthermore, her seizures were responsive to treatment, and she achieved complete seizure control

TABLE 1 Clinical phenotypes in our *FBXW7* patient compared to previous cases.

	Present case	Fabienne Meier-Abt et al. PMID: 38169111	Wang et al. PMID: 39364007	Stephenson et al., 2022 PMID: 35395208	Saito et al., 2025 PMID: 39414990	Helbling et al., 2023 https://doi.org/10.1016/j.gimo.2023.100530
Gender	Female	Male	Male	26 Males/9 Females	Male	Male
Age	3 years	9 years	2 years 1 month	Ranged from 2 to 44 years	3 years 1 month	16 months
Variants (NM_001349798.2)	c.926G>C, p.(Arg309Pro)	c.862-2A>C, p.(Leu288Glyfs*13)	c.1612C>T, p.(G1n538*)	c.1331_1332del, p.(Lys444Serfs*27); c.1332dup, p.(Val445Serfs*27); c.1236+2T>A; c.1713_1714del, p.(Asn572Leufs*32); c.1939A>T, p.(Lys647*)	c.1583del, p.(Pro528Glnfs*28); c.832C>T, p.(Arg278*)	c.1855+1T>C
Neonatal course	Normal	Congenital malformations: subclavian vein thrombosis, pectus excavatum	Fever, intracranial hemorrhage, hyperbilirubinemia, infection, anemia	Normal	Normal	NA
Developmental delay	No	Yes	Yes	Yes	Yes	Yes
Intellectual disability	No	Mild	Borderline	Yes	Yes	Yes
Hypotonia	No	Yes	Yes	Yes	Yes	Yes
Dysmorphism	None	Yes	Yes	Yes	Yes	Yes
Seizures	Yes	No	No	Yes	No	No
Epilepsy type	Early-onset childhood absence epilepsy	NA	No	No	–	–
EEG abnormalities	Yes	NA	No	–	–	–
Response to antiepileptic drugs	Yes	NA	No	–	–	–
Cardiac defects	No	No	No	Yes	–	No
Brain MRI						
Thin/abnormal corpus callosum	No	NA	No	Yes	NA	NA
Delayed myelination	No	NA	No	Yes	NA	NA
Cerebellar abnormalities	No	NA	No	Yes	NA	NA
Other anomalies	No	NA	IVH, hydrocephalus	No	Macrocephaly	Macrocephaly

Abbreviations: IVH, intraventricular hemorrhage; NA, not available.

with ethosuximide, a clinical course consistent with the favorable outcome often observed in this epileptic syndrome.[6,7] While recognizing the limitations of a single case report, these findings raise the possibility that the phenotypic spectrum of *FBXW7*-related disorder may be wide and encompass mild clinical presentations. The regular psychomotor development and the absence of significant cognitive or social impairment in our patient, except for a very mild form of dyslalia, suggest that DEDHIL phenotypes might range from severe to milder presentations, including isolated, drug-responsive generalized epilepsy.

Previously reported DEDHIL cases have predominantly involved germline missense variants located within the WD40 domain of FBXW7, which is critical for substrate binding. Among 35 individuals, 28 distinct germline variants were identified, including large deletions, a splice site variant, and frameshift variants predicted to result in loss of protein function. Most missense variants clustered in the carboxy-terminal half of the protein, with the majority affecting residues within the WD40 domain.[11] These alterations likely disrupt substrate binding and may also impair protein stability, promoting degradation via the ubiquitin-proteasome system.[11] According to the current literature, variants in the F-box domain appear to be very rare. A single truncating variant has been reported, p.(Arg278*), but this substitution is a truncating change predicted to lead to severe loss of function. As such, the missense change identified in our patient is the first missense affecting the F-box domain. Although the report of additional patients harboring similar substitutions is needed to confirm this hypothesis, it is possible that such changes may be associated with less severe neurological manifestations, possibly involving distinctive pathophysiological mechanisms.

The Arg309 is a highly conserved amino acid in the F-box domain, which is critical for mediating interactions with SKP1. This is a key component of the SCF ubiquitin ligase complex, which regulates the degradation of important neuronal development and signaling proteins such as Cyclin E1/2, Notch, c-Myc, and mTOR. Structural modeling revealed that the p.(Arg309Pro) variant had minimal impact on overall FBXW7 protein stability, yet it was predicted to significantly weaken the crucial binding affinity between FBXW7 and SKP1. As a result, ubiquitin-mediated degradation of target proteins may be affected, resulting in abnormal neuronal function.[35] These findings suggest that the impairment of critical protein–protein interactions might underlie the mild phenotype observed in our patient. Substitutions in the F-box domain might induce less severe functional consequences compared to the highly disruptive loss-of-function effects of WD40 domain variants, which directly impair substrate recognition. In fact, previous studies have shown that partial loss of FBXW7 function can result in a range of phenotypic consequences depending on the affected domain and substrate specificity. More investigation is needed to determine if F-box variants may exert a specific effect on neuronal excitability, predisposing to epilepsy without broader neurodevelopmental damage.

In summary, we describe a patient harboring a novel de novo variant in *FBXW7*, affecting a highly conserved and potentially critical residue in the F-box domain. The phenotype of this subject consisted of isolated early-onset childhood absence epilepsy responsive to treatment. This case suggests that variants outside the WD repeats may affect the distinctive function of FBXW7 and lead to atypically milder phenotypes, broadening the genotype–phenotype spectrum of DEDHIL. From a clinical perspective, our findings support the potential utility of genetic evaluation in patients with early-onset absence epilepsy, even in the absence of other neurodevelopmental signs, as identifying rare single-gene etiologies can refine the diagnostic and prognostic landscape.[10]

AUTHOR CONTRIBUTIONS

AM and MSSN contributed equally to the conception and design of the study, data collection and interpretation, and drafting of the manuscript. AD performed the bioinformatic analyses and contributed to manuscript writing. FM, MMM, SF, LB, and ZHT were involved in patient evaluation, data collection, and clinical interpretation. MDO and FZ critically revised the manuscript for intellectual content. MS conceptualized and supervised the study and contributed to manuscript drafting and critical revision.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest relevant to this manuscript. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (M.S.) upon request.

ETHICS STATEMENT

This study adheres to the Declaration of Helsinki principles. The following Research Ethics Committees approved it: Gaslini Children's Hospital (Comitato Etico della Regione Liguria) (163/2018). Written informed consents were obtained from the parents or legal guardians of the enrolled subjects to publish genetic and clinical data, including clinical photographs and brain MRI images.

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SUPPORTING INFORMATION

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