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CASE REPORT

Diagnosis of developmental and epileptic encephalopathies in the era of precision medicine - a case report

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ABSTRACT

Background: Developmental and epileptic encephalopathies (DEEs) are severe disorders marked by refractory seizures and developmental delay. Pathogenic variants in the syntaxin-binding protein 1 (STXBP1) gene are among the top five genetic causes of DEE and impair neurotransmitter release, especially in GABAergic interneurons. The clinical presentation is highly variable, and diagnosis depends on molecular genetic testing. Precision medicine is key for diagnosis, treatment, follow-up, prognosis, and hereditary risk reduction.

Case Presentation: We present a male patient with drug-resistant epilepsy, polypharmacy, and cognitive impairment, without significant family or perinatal risk factors. Given the clinical complexity and strong suspicion of genetic cause, a molecular study using next-generation sequencing of epilepsy-related genes and copy number variation analysis was performed. A heterozygous pathogenic variant in STXBP1, c.1652G>A (p.Arg551His), was identified, associated with early infantile epileptic encephalopathy type type 4, also known as STXBP1-DEE (MONDO:0012812 - orphanet identifier (ORPHA):599373], with autosomal dominant inheritance.

Conclusion: STXBP1-DEE represents a heterogeneous spectrum of neurodevelopmental disorders with refractory epilepsy, developmental delay, and intellectual disability. Diagnosis requires clinical suspicion, imaging, laboratory tests, and molecular confirmation. While current treatments are limited, promising approaches are under investigation. The lack of genotype-phenotype correlation and wide phenotypic variability complicate management, but advances in precision medicine support more individualized treatment strategies. Although most variants are *de novo*, genetic counseling remains crucial to assess recurrence risk. Preclinical studies show potential for novel therapies, yet clinical trials are needed to confirm their efficacy in affected individuals.

Keywords: Developmental and epileptic encephalopathies, STXBP1 gene, drug-resistant epilepsy, *de novo* variants, gene therapy, precision medicine, case report.

Introduction

Developmental and epileptic encephalopathies (DEE) represent the most severe spectrum of epilepsies. These are rare disorders characterized by refractory seizures that manifest in infancy or early childhood, accompanied by developmental delay or regression [1,2].

In recent years, genetic causes have been identified in the majority of epileptic encephalopathies. These genetic variants contribute to developmental impairment independently, and this is further exacerbated by the epileptic encephalopathy itself [2].

Pathogenic variants in the SCN2A, KCNQ2, or syntaxin-binding protein 1 (STXBP1) genes frequently cause neonatal-onset DEE. In these cases, the onset of symptoms is so early that it may be challenging to discern whether the developmental disorder arises primarily from epileptic seizures or the underlying genetic variant itself [2].

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Among the most frequent genetic causes of pediatric epilepsy and neurodevelopmental disorders are heterozygous pathogenic variants in the STXBP1 gene [3]. These variants result in genetic epilepsies and neurodevelopmental disorders with an estimated incidence of 3.30 to 3.81 per 100,000 live births [4,5]. The clinical significance of STXBP1 variants was first recognized in 2008 in patients diagnosed with Ohtahara syndrome. However, its phenotypic spectrum extends beyond this entity [4,6],including other DEE subtypes such as West syndrome, Lennox-Gastaut syndrome, early-onset epileptic encephalopathy, and neurodevelopmental disorders with infrequent or absent seizures [6].

The STXBP1 gene encodes STXBP1, also known as Sec1/Munc18-1, located on chromosome 9q34.11 [4,7]. This protein is predominantly expressed in neurons and is crucial in regulating synaptic vesicle docking and fusion by interacting with soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE proteins). The proper function of STXBP1 is essential for neurotransmitter release across all synapses and is critical for neuronal survival [3,6,8].

The primary pathogenic mechanism proposed for STXBP1-DEE is haploinsufficiency or loss of function. Pathogenic STXBP1 variants impair neurotransmitter release, affecting GABAergic/glycinergic interneurons, leading to hyperactivation of excitatory neurons [3,9]. This is supported by the fact that more than 50% of reported pathogenic variants are protein-truncating variants, splice-site variants, or small and large insertions/deletions.

STXBP1-DEE is an autosomal dominant disorder typically caused by a *de novo* heterozygous variant. Most reported cases to date are sporadic. However, STXBP1-DEE has been documented less frequently due to a pathogenic STXBP1 variant inherited from an asymptomatic parent with germline mosaicism [6,9].

These disorders exhibit extensive clinical heterogeneity, making phenotype definition challenging. Up to 95% of individuals present with neurodevelopmental delay, while more than 80% develop epilepsy, with a median seizure onset of six weeks (range: 1 day to 13 years) [9]. The seizure types observed include infantile spasms, generalized tonic-clonic, and focal seizures. Electroencephalogram (EEG)abnormalities may include focal epileptiform activity, burst suppression, or hypsarrhythmia [9]. Intellectual disability (ID) or cognitive dysfunction is a common feature of STXBP1-DEE, often accompanied by movement disorders, such as tremors and ataxia. Additionally, behavioral problems and autism spectrum disorder (ASD) are frequently reported [5,6]. The severity of ID is age-dependent, with nearly 90% of individuals over 11 years old affected; among them, 64% have severe or profound ID, whereas only 2% exhibit mild ID [4].

Diagnosis of STXBP1-DEE is confirmed by identifying a pathogenic variant through molecular genetic testing [9]. Next-generation sequencing (NGS) technologies, including gene panels, whole-exome sequencing (WES), and whole-genome sequencing, have become a routine component of the diagnostic evaluation for children with DEE, expanding the known genotypic spectrum of this condition. Early NGS studies reported high diagnostic yields, identifying pathogenic variants in up to 28% of pediatric epilepsy cohorts, facilitating precise therapeutic interventions and improving neurodevelopmental outcomes [10].

Treatment for STXBP1-DEE focuses on seizure control, though drug resistance is common; over 50% require polytherapy, and 25% remain refractory [8,9]. No antiepileptic drug has proven effective in modulating STXBP1 function [11]. Intellectual, motor, and behavioral symptoms lack targeted therapies [8,10]. Severe movement disorders may respond to dopaminergic or monoamine-depleting agents. Multidisciplinary care is essential [3,9].

Clinical Case

A 22-year-old male patient with an infantile-onset clinical presentation, diagnosed with refractory epilepsy of structural origin in the left temporal lobe, severe ID, and severe behavioral disorder.

The patient was born at term from a first pregnancy, via an uncomplicated vaginal delivery, with no reported parental consanguinity. On physical examination, the patient was eutrophic, presenting facial dysmorphisms, including a small forehead and thick lips, along with notable cognitive and behavioral alterations.

During adolescence, the patient exhibited global neurodevelopmental delay, multiple dyslexia, incomplete language acquisition, difficulty in word articulation, and deficits in sensorium, judgment, reasoning, and introspection. The patient was managed by a multidisciplinary team, including neurology, gastroenterology, orthopedics, general surgery, psychology, psychiatry, nutrition, occupational therapy, language therapy, and medical genetics.

At the age of 19 years, the patient sustained a left acetabular fracture that required surgical reduction and fixation, followed by physical therapy. That same year, he was diagnosed with cholelithiasis without immediate indication for surgery, and non-erosive gastritis. He also presented functional constipation, managed through dietary modifications and fiber supplementation.

Neuroimaging studies, including non-contrast cranial computed tomography and brain magnetic resonance imaging, were reported as normal. However, an EEG revealed baseline cortical dysfunction with alternating epileptiform activity predominantly in the left hemisphere, with secondary generalization. With paraclinical assessments including renal, hepatic, and metabolic evaluations aimed at excluding Inherited metabolic disorders, the only notable finding was a moderate elevation of transaminases (225 U/L), with no hepatic imaging abnormalities, which was attributed to polypharmacy.

In early adulthood, given the clinical complexity, disease progression, with severe cognitive and behavioral dysfunction and drug-resistance, along with no relevant family or personal history, to facilitate the implementation of targeted therapeutic strategies and

to rule out an underlying genetic cause, comprehensive molecular testing was requested, including NGS of genes associated with refractory epilepsy and copy number variation (CNV) analysis. A heterozygous pathogenic variant in STXBP1, c.1652G>A (p.Arg551His), was identified, associated with epileptic encephalopathy type 4 (EIEE4). Currently at age 22, the patient remains in stable condition under multidisciplinary follow-up.

Results

WES, encompassing the entire coding region of the genome, was performed using a DNB-SEQ400 next-generation massive parallel sequencer targeting epilepsy-associated genes through NGS methodology and CNV analysis. This analysis identified a heterozygous pathogenic variant in the STXBP1 gene, which results in the substitution of a guanine by an adenine at position 1652 of the cDNA, located in exon 18/20 of the gene (c.1652G>A). At the protein level, this missense variant leads to the replacement of an arginine by a histidine at amino acid position 551 (p.Arg551His), a residue that is evolutionarily conserved. This variant has been classified as pathogenic and likely pathogenic in ClinVar (VarID: 566474). Furthermore, the Human Gene Mutation Database has recorded this variant in association with STXBP1-related encephalopathy (Accession: CM162502), alongside two additional missense variants affecting glycine and proline residues, which have been linked to ID, epilepsy, and/or neurodevelopmental disorders (Entries: CM1513639, CM1820834) (Table 1). In the Leiden Open Variation Database, there is a single entry classifying this variant as pathogenic (ID: STXBP1_000104). A review of the scientific literature has documented multiple cases of individuals carrying this variant who presented with early-onset seizures (PMID: 26865513, 31255830). Additionally, evidence suggests that other amino acid substitutions at the same position also result in disease (PMID: 23409955, 26865513, 27069701).

The allelic frequency of this variant in the general population (gnomAD v4.1) is currently unknown. In silico meta-predictors, including REVEL and BayesDel, predict that this variant has a deleterious effect on the protein (Figure 1).

Considering the available evidence regarding the implications of this variant in disease and following the American College of Medical Genetics and Genomics guidelines for variant classification, along with subsequent updates, this variant is classified as pathogenic based on the criteria PS2, PS4, PM2, PM5, and PP3.

Discussion

This case describes a male patient with clinical manifestations suggestive of a neurocognitive-behavioral disorder of genetic origin. Molecular analysis identified a *de novo* heterozygous pathogenic variant in the STXBP1 gene c.1652G>A (p.Arg551His), associated with EIEE4, also referred to as STXBP1-DEE, MONDO:0012812 - ORPHA:599373.

Table 1. *Diseases associated with pathogenic variants in the STXBP1 gene. Self-compiled data sourced from Human Phenotype Ontology, Orphanet, MONDO, and Online Mendelian Inheritance in Man (OMIM). Available at: https://hpo.jax.org/browse/gene/NCBIGene:6812*

Identifier	Disease	Inheritance	Phenotype
OMIM:612164 MONDO:0012812	Developmental and epileptic encephalopathy 4	Autosomal dominant and autosomal recessive	Spastic paraplegia-quadriplegia, hypotonia, choreoathetosis, hypsarrhythmia, status epilepticus, hypoplasia of the corpus callosum, developmental regression, severe ID, severe global developmental delay, epileptic spasms, generalized myoclonic seizures, bilateral tonic-clonic seizures, epileptic encephalopathy, cerebral atrophy
ORPHA:495818 MONDO:0044641	9q33.3q34.11 microdeletion syndrome Monosomy 9q33.3q34.11	Not applicable	Microcephaly, prominent forehead, round face, arched eyebrows, upslanting palpebral fissures, strabismus, short nose, and thin upper lip Epilepsy, ataxia, ID, developmental delay, axial hypotonia, dysphagia, bone malformations, in particular patellar abnormalities, epistaxis, and cutaneous-mucous telangiectasias
ORPHA:599373 MONDO:0012812	STXBP1-related encephalopathy	Autosomal dominant	Severe ID, developmental delay, and early-onset epilepsy Motor disturbances include ataxia, hypotonia, dystonia, tremor, spasticity, and dyskinesia Autism/autistic-like features, signs of parkinsonism, including tremor, bradykinesia, and antecollis

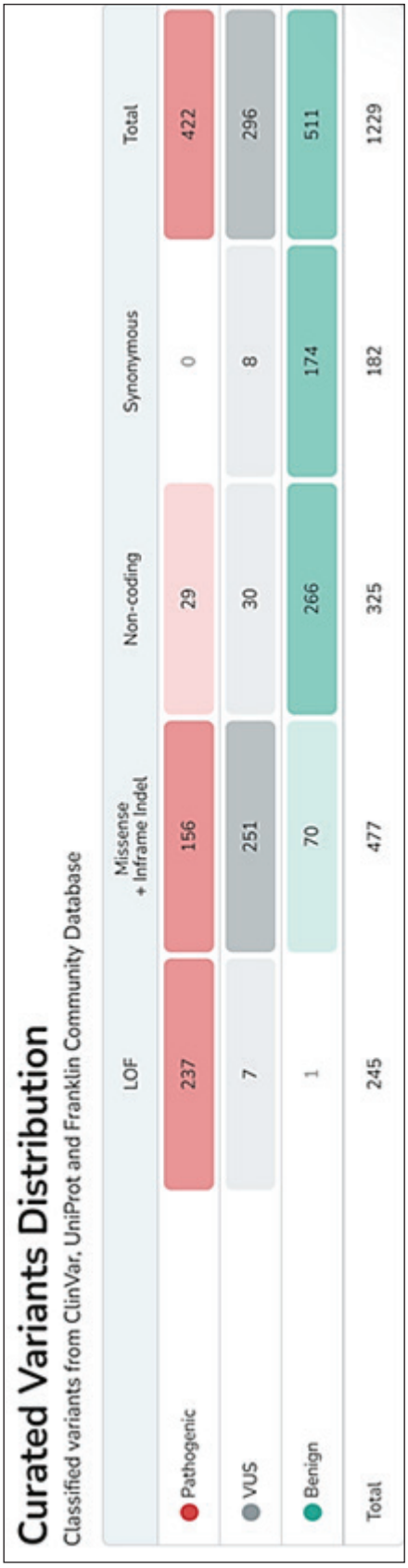

Figure 1. *Curated variants sistribution in the STXBP1 gene, classified according to ClinVar, UniProt, and Franklin community database. Source: Genoox Franklin. Available at: https://franklin.genoox.com/clinical-db/gene/hg19/STXBP1*

The STXBP1 gene encodes STXBP1, a key regulator of synaptic vesicle fusion and neurotransmitter release. Pathogenic variants in this gene, including the one identified in this case, disrupt neurotransmitter release, particularly within GABAergic interneurons, leading to neuronal hyperexcitability and refractory seizures [3,5].

The patient presents with intractable left bitemporal focal epilepsy, ASD, severe behavioral impairment, and cognitive disability, which coincides with previous descriptions of patients with this pathogenic variant [5,6,9] (Figure 2).

As demonstrated in the present case, the identification of the pathogenic variant in the STXBP1 gene via NGS confirms the DEE diagnosis and underlines the importance of these technologies in identifying patients with this condition. Genetic testing not only supports clinical diagnosis but also opens pathways for further research and the development of targeted therapies.

Currently, several neurodevelopmental genetic disorders, including STXBP1-DEE gene variants, have become key targets for the development of gene therapies and genetic regulation strategies. However, the significant phenotypic variability observed in these patients, including our case, presents major challenges in defining optimal outcome measures and therapeutic windows [11].

Recently, innovative therapeutic approaches have been explored, such as the use of chemical chaperones (trehalose, sorbitol, and 4-phenylbutyrate), which have demonstrated potential in restoring STXBP1 protein levels and rescuing synaptic deficits in animal models. These molecules could represent a promising option for patients like the one described in this case; however, further studies in heterozygous models are required to confirm their efficacy in humans [9,12].

There are several reasons why research into STXBP1-related disorders faces obstacles. First, the overall phenotypic spectrum of these disorders is broad and includes a wide range of epilepsy presentations and neurological features. Second, to date, no clear genotype-phenotype correlations have been identified; a study by Xian et al. [4] examined recurrent pathogenic variants (p.Arg406His/Cys, p.Arg292Cys/His/Leu, p.Arg551Cys/Gly/His/Leu, p.Pro139Leu, p.Arg190Trp) identified in more than 10 individuals with STXBP1 encephalopathy with epilepsy. The results revealed no identifiable genotype-phenotype correlations for these variants. Third, since STXBP1 encodes a synaptic protein, the pathogenic mechanism linking impaired synaptic vesicle release to neurological features remains less precise than, for example, channelopathy-associated disorders [13,14].

Furthermore, adeno-associated virus (AAV)-based gene therapies are currently being investigated as potential treatments for monogenic conditions, including STXBP1-related encephalopathies. In 2023, Capsida Biotherapeutics reported promising preclinical results using a next-generation capsid to deliver STXBP1 in murine models, showing improvements in seizures, motor deficits, and cognitive impairments that persisted for at least 12 months' post-treatment [15]. These advancements may open new therapeutic possibilities for patients similar to the case described.

Regarding prognosis, there are limited data on life expectancy in patients with STXBP1-EED. In the 2022 study by Stamberger et al. [6], the oldest reported patient was a 58-year-old woman. In the case of our patient, who is currently 22 years old, life expectancy must be

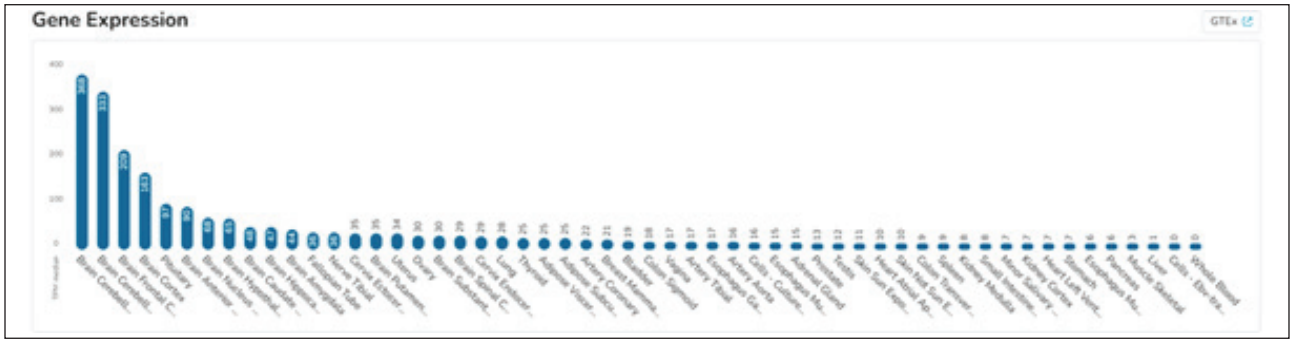

Figure 2. *STXBP1 gene expression across different tissues, based on the GTEx dataset. Source: Genoox Franklin. Available at: https://franklin.genoox.com/clinical-db/gene/hg19/STXBP1*

considered multifactorial, influenced by seizure severity and the presence of comorbidities.

Conclusion

Pathogenic heterozygous variants in the STXBP1 gene are among the most common causes of DEE. The clinical presentation is highly heterogeneous, making both diagnosis and therapeutic management challenging. Advances in NGS technologies have become a key tool for identifying these variants, allowing precise diagnoses and facilitating targeted therapeutic interventions.

Genetic counseling is essential for affected families, providing an understanding of the sporadic nature of most pathogenic variants and the low but present risk of mosaicism. In addition, genetic testing of parents is recommended to facilitate an estimate of recurrence risk and to make informed reproductive decisions.

In the era of precision medicine, identifying the underlying genetic etiology can have critical therapeutic and prognostic implications. Genetic testing should be strongly considered in children where no definitive cause of DEE can be identified based on clinical examination and neuroimaging. Although current treatments are limited, innovative therapeutic strategies are being explored, including chemical chaperones and gene therapy using AAV vectors.

However, the substantial phenotypic variability observed in STXBP1-EED patients, and the lack of clear genotype-phenotype correlations make it difficult to predict disease progression and individual therapeutic responses. Future research directions should focus on advancing these therapeutic options into clinical trials, ensuring that they evolve into viable, safe, and effective treatments that control symptoms and modify disease progression. The long-term goal is to develop innovative therapies that significantly improve the quality of life for patients affected by STXBP1-EED.

List of abbreviations:

AAV	adeno-associated virus
ASD	autism spectrum disorder
CNV	copy number variation
DEE	developmental and epileptic encephalopathies
EEG	electroencephalogram
EIEE4	early infantile epileptic encephalopathy type 4
GABA	gamma-aminobutyric acid
GABAergic	related to GABA-producing neurons
ID	intellectual disability
NGS	next-generation sequencing
OMIM	Online Mendelian Inheritance in Man
ORPHA	orphanet identifier
SNARE	soluble NSF attachment protein receptor
STXBP1	syntaxin binding protein 1
WES	whole-exome sequencing

Conflict of interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent to participate

Informed consent was obtained from the legal guardians of all individual participants included in the study and signed consent regarding publishing their data (and/or photographs).

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author contribution

María Martínez: conceptualization, writing – original draft, writing – reviewing and editing. José Goméz: conceptualization, writing – original draft, writing – reviewing and editing. Lina Moreno: visualization, resources, supervision, writing –reviewing and editing.

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