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NLM Citation: Mercimek-Andrews S. *STXBP1* Encephalopathy with Epilepsy. 2016 Dec 1 [Updated 2023 Sep 28]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

STXBP1 Encephalopathy with Epilepsy

Synonyms: Early-Infantile Epileptic Encephalopathy 4 (EIEE4), *STXBP1* Epileptic Encephalopathy, *STXBP1*-Related Developmental and Epileptic Encephalopathy (*STXBP1*-DEE)

Saadet Mercimek-Andrews, MD, PhD, FCCMG, FRCPC[1]

Created: December 1, 2016; Updated: September 28, 2023.

Summary

Clinical characteristics

STXBP1 encephalopathy with epilepsy is characterized by early-onset developmental delay, intellectual disability or cognitive dysfunction, and epilepsy. The median age of onset of seizures is six weeks (range: 1 day to 13 years). Seizure types can include infantile spasms; generalized tonic-clonic, clonic, or tonic seizures; and myoclonic, atonic, absence, and focal seizures. EEG abnormalities can include focal epileptic activity, burst suppression, hypsarrhythmia, or generalized spike-and-slow waves. Other neurologic findings include abnormal tone, movement disorders (especially ataxia and dystonia), and behavioral issues and autism spectrum disorder. Feeding difficulties are common.

Diagnosis/testing

The diagnosis is established in a proband with a heterozygous *STXBP1* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatments for developmental, cognitive, and neurobehavioral issues. The most commonly used anti-seizure medications (ASMs) are phenobarbital, valproic acid, and vigabatrin. About 20% of individuals require more than one ASM and approximately 25% are refractory to ASM therapy. Severe dystonia, dyskinesia, and choreoathetosis can be treated with monoamine-depleting or dopaminergic agents. Treatment per orthopedics, physical medicine and rehabilitation, physical therapy, and occupational therapy to help avoid contractures and falls, with positioning and mobility devices as needed. Feeding difficulties and constipation are managed per standard protocols. Social work support and care coordination as needed.

Author Affiliation: 1 Department of Medical Genetics, Faculty of Medicine and Dentistry, University of Alberta, Alberta Health Services, Edmonton, Alberta, Canada; Email: saadet@ualberta.ca.

Surveillance: Monitor developmental progress and educational needs, seizures, changes in tone, movement disorders, behavioral issues, growth and nutritional status, evidence of constipation, and family needs at each visit; follow-up EEG as needed; occupational and physical therapy assessments as needed.

Genetic counseling

STXBP1 encephalopathy with epilepsy is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Most individuals reported to date represent simplex cases (i.e., the only family member known to be affected) and have the disorder as the result of a *de novo STXBP1* pathogenic variant. Individuals with *STXBP1* encephalopathy with epilepsy are not known to reproduce. Once the *STXBP1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are available.

Diagnosis

Suggestive Findings

STXBP1 encephalopathy with epilepsy **should be considered** in individuals with early-onset refractory seizures, developmental delay, and intellectual disability or cognitive dysfunction, particularly those with the following epilepsy features and seizure types.

Epilepsy features

- Median age of onset six weeks (range: 1 day to 13 years)
- EEG characterized by focal epileptic activity, burst suppression, hypsarrhythmia, or generalized spike-and-slow waves

Seizure types

- Infantile spasms
- Generalized tonic-clonic, clonic, or tonic seizures
- Myoclonic seizures
- Atonic seizures
- Absence seizures
- Focal seizures

Other features

- Mild-to-profound intellectual disability
- Tone abnormalities: spasticity, hypotonia
- Movement disorders including ataxia, dystonia, dyskinesia, tremor, or choreoathetosis
- Behavioral issues
- Autism spectrum disorder

Establishing the Diagnosis

The diagnosis of *STXBP1* encephalopathy with epilepsy **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *STXBP1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is

understood to include likely pathogenic variants. (2) Identification of a heterozygous *STXBP1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: Single-gene testing (sequence analysis of *STXBP1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A multigene panel that includes *STXBP1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *STXBP1* Encephalopathy with Epilepsy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
STXBP1	Sequence analysis [3]	<95% [4]
	Gene-targeted deletion/duplication analysis [5]	>5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

STXBP1 encephalopathy with epilepsy is characterized by developmental delay, intellectual disability or cognitive dysfunction, and epilepsy. To date, about 500 affected individuals have been reported [Vatta et al 2012, Allen et al 2013, Tucker et al 2014, Di Meglio et al 2015, Ehret et al 2015, Kwong et al 2015, Allen et al 2016, Dilena et al 2016, Guacci et al 2016, Helbig 2016, Lopes et al 2016, Marchese et al 2016, Nambot et al 2016, Yamamoto et al 2016, Xian et al 2022].

Table 2. *STXBP1* Encephalopathy with Epilepsy: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Developmental delay	100%	Mild to profound
Intellectual disability / cognitive dysfunction	≥90%	Mild to profound
Seizures	70%-95%	
Movement disorders	≥87%	Hypomimia, bradykinesia, tremor, ataxia, dyskinesia, dystonia, or choreoathetosis
Neurobehavioral disorders	~65%	Autism spectrum disorder, autistic-like features, hyperactivity, & self-aggressive behaviors

Developmental delay. Generalized hypotonia or absence of head control was reported in fewer than 50% of affected individuals. Developmental trajectories of 48 individuals with *STXBP1* encephalopathy with epilepsy showed evidence of early developmental delays in gross motor, fine motor, and speech in most individuals [Balagura et al 2022]. Later seizure onset correlated in general with better developmental outcomes, whereas there was no significant correlation between neurodevelopmental outcomes and age at seizure remission.

In a natural history study of adults with *STXBP1* encephalopathy with epilepsy, 71% of adults were nonverbal. Only 50% of adults were walking independently, and 39% were wheelchair bound. The first signs of developmental delay were present in the first year of life in 76% of adults. All adults were dependent on caregivers for most of their activities of daily living [Stamberger et al 2022].

Episodic developmental regression was reported in 59% of adults with *STXBP1* encephalopathy with epilepsy but did not always correlate with increased seizure frequency.

Intellectual disability / cognitive dysfunction is present in all individuals with *STXBP1* encephalopathy with epilepsy. In 48 individuals with *STXBP1* encephalopathy with epilepsy, intellectual disability ranged from severe to profound in 87% of individuals, and mild intellectual disability was reported in 13% [Balagura et al 2022]. In a separate study, intellectual disability was reported in 90% of individuals older than age 11 years; 64% of individuals had severe or profound intellectual disability and 2% had mild intellectual disability. Additionally, about 38% of individuals were nonverbal [Xian et al 2022]. In the natural history study of adults with *STXBP1* encephalopathy with epilepsy, 87% of adults had severe or profound intellectual disability [Stamberger et al 2022].

Seizures. Age of seizure onset ranges from six hours of life to age 13 years [Milh et al 2011, Di Meglio et al 2015]. In two large studies of individuals with *STXBP1* encephalopathy with epilepsy, seizure onset was within the first year of life in 84.7%-89% of individuals [Xian et al 2022, Xian et al 2023].

Focal-onset seizures, generalized-onset seizures, and infantile spasms were the most common seizure types [Xian et al 2022]. Focal-onset seizures were reported in 66.6% of individuals and infantile spasms in 40.3%-50% [Xian et al 2022, Xian et al 2023]. In a small number of individuals, simple febrile seizures, myoclonic atonic

seizures, typical absence seizures, and hemiclonic seizures were reported [Xian et al 2022]. More than 60% of affected individuals had more than one seizure type during their lifetime.

Epilepsy course was reported for 48 individuals with *STXBP1* encephalopathy with epilepsy. The number of anti-seizure medications (ASMs) used to treat each individual ranged from one to eight different ASMs and included phenobarbital (50%), valproic acid (42%), vigabatrin (31%), ACTH (27%), pyridoxine (31%), levetiracetam (31%), benzodiazepines (23%), topiramate (23%), and carbamazepine (23%). In more than 20% of individuals, two or more ASMs were used in combination. About 25% of affected individuals were refractory to ASM therapy [Balagura et al 2022]. In individuals who became seizure-free, ASMs were discontinued between one month and 5.5 years after treatment began [Deprez et al 2010, Romaniello et al 2015, Sampaio et al 2015]. The longest seizure-free period after discontinuation of ASMs was approximately 11 years [Deprez et al 2010].

In about 1% of affected individuals, the ketogenic diet was used for seizure management. Response to the ketogenic diet ranged from a mild reduction in seizure frequency to no response in early studies [Saitsu et al 2011, Weckhuysen et al 2013]. In a recent study, effects of the ketogenic diet were reported in 12 individuals with *STXBP1* encephalopathy with epilepsy. Complete or near complete seizure freedom was reported in 33% of those individuals [Nam et al 2022].

Epilepsy surgery was the treatment of choice in two affected individuals: one became seizure-free following corpuscallosotomy [Otsuka et al 2010]; and the other had a significant reduction in seizure frequency following resection of focal cortical dysplasia [Weckhuysen et al 2013]. In another study, epilepsy surgery was performed in one individual with significant improvements in seizures [Balagura et al 2022].

In 30 adults with *STXBP1* encephalopathy with epilepsy, 80% had refractory seizures and 37% had long periods without seizures [Stamberger et al 2022].

Epilepsy or electroclinical syndromes. Historically, several electroclinical syndromes have been reported in association with pathogenic variants in *STXBP1*. In a large study of 534 individuals with *STXBP1* encephalopathy with epilepsy, 26% of individuals had specific electroclinical syndromes, including infantile spasms syndrome (previously termed West syndrome, 15%), Ohtahara syndrome (9%), and Rett syndrome phenotype (2%) [Xian et al 2022].

- **Ohtahara syndrome** is characterized by frequent generalized tonic refractory seizures and burst suppression patterns on EEG. Age of seizure onset is typically during the neonatal or early infantile period. Approximately 20% of individuals with a *STXBP1* pathogenic variant were reported to have features consistent with Ohtahara syndrome [Otsuka et al 2010, Saitsu et al 2012, Kodera et al 2013, Weckhuysen et al 2013, Tso et al 2014, Di Meglio et al 2015, Allen et al 2016, Stamberger et al 2016].
- **Infantile spasms syndrome** is characterized by tonic spasms with clustering, arrest of psychomotor development, and hypsarrhythmia on EEG. Five of 192 individuals with infantile spasms had *STXBP1* encephalopathy with epilepsy [Otsuka et al 2010, Allen et al 2013]. Thirteen individuals with a *STXBP1* pathogenic variant were reported with a clinical phenotype of infantile spasms, either as single case reports or small cohorts of epileptic encephalopathy [Saitsu et al 2008, Deprez et al 2010, Saitsu et al 2010, Weckhuysen et al 2013, Di Meglio et al 2015, Romaniello et al 2015, Lopes et al 2016].
- **Early myoclonic epileptic encephalopathy,** characterized by myoclonic seizures and burst suppression pattern in sleep on EEG, was identified in two individuals with *STXBP1* encephalopathy with epilepsy [Saitsu et al 2012, Kodera et al 2013].
- **Dravet syndrome** is characterized by fever-induced refractory seizures with age of onset usually within the first year of life. EEG patterns typically show generalized spike-wave activity as seizures progress. Three of 80 individuals with Dravet syndrome were identified with *STXBP1* encephalopathy with epilepsy [Carvill et al 2014].

- **Lennox-Gastaut syndrome** is characterized by multiple seizure types, particularly tonic and myoclonic refractory epilepsy. EEG shows slow background and spike-wave bursts at frequencies less than 2.5 per second. One of 115 individuals with Lennox-Gastaut syndrome was identified with *STXBP1* encephalopathy with epilepsy [Allen et al 2013].
- **Rett syndrome phenotype.** Three individuals with Rett syndrome phenotype have been identified with an *STXBP1* pathogenic variant [Olson et al 2015, Romaniello et al 2015, Lopes et al 2016]. Rett syndrome, a progressive neurodevelopmental disorder, is characterized by apparently normal motor and cognitive development during the first six to 18 months of life, followed by a short period of developmental stagnation, then rapid regression in language and motor skills, followed by long-term stability. During the phase of rapid regression, repetitive and stereotypic hand movements replace purposeful hand use. Additional findings include fits of screaming and inconsolable crying, autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, seizures, and acquired microcephaly.

Electroencephalography (EEG) abnormalities have been reported in the majority of affected individuals. The two most common EEG abnormalities were burst suppression pattern (42 affected individuals) and hypsarrhythmia (37 affected individuals) [Saitsu et al 2012, Allen et al 2013, Kim et al 2013, Di Meglio et al 2015, Sampaio et al 2015, Allen et al 2016, Guacci et al 2016, Yamamoto et al 2016].

Other EEG abnormalities included focal and multifocal discharges, spike-and-slow waves, polyspike waves, theta and delta waves, paroxysmal activity, and low-amplitude fast rhythms. Background activity was frequently described as slow or poorly organized.

Movement disorders. Reported movement disorders in individuals with *STXBP1* encephalopathy with epilepsy include hypomimia, bradykinesia, tremor, ataxia, dyskinesia, dystonia, or choreoathetosis. In 30 adults, movement disorders were present in 87%. The most common types were hypomimia (83%), bradykinesia (63%), and tremor (56%) [Stamberger et al 2022]. Tremor and ataxia were present in about 40% of individuals older than age 11 years [Xian et al 2022].

Neurobehavioral disorders include autism spectrum disorder, autistic-like features, hyperactivity, and self-aggressive behaviors. In a natural history study of adults with *STXBP1* encephalopathy with epilepsy, significant behavioral issues were reported in 65% of adults, including aggressive behavior, hyperactivity, self-mutilation, compulsive symptoms, and (rarely) psychotic episodes. Autism spectrum disorder or autistic features were present in 42% of adults [Stamberger et al 2022]. Significant sleep problems have included either problems with initiation or maintenance of sleep in 20% of individuals [Stamberger et al 2022].

Gastrointestinal manifestations. In 47% of individuals gastrointestinal manifestations were reported, including constipation, poor weight gain, and gastroesophageal reflux disease. Gastrostomy tube feeding was needed in 13% of individuals [Stamberger et al 2022].

Microcephaly was reported in fewer than ten individuals [Kwong et al 2015, Allen et al 2016, Stamberger et al 2016, Yamamoto et al 2016].

Other

- Scoliosis (4 individuals) [Stamberger et al 2022]
- Joint laxity (3 individuals) [Stamberger et al 2022]
- Strabismus (2 individuals) [Boutry-Kryza et al 2015, Dilena et al 2016]

Brain MRI findings were reported in more than 75% of affected individuals. In about half of these individuals, brain MRI showed various abnormalities, including diffuse cerebral atrophy, delayed myelination, or thinning of the corpus callosum. Brain MRI findings in 29 individuals with *STXBP1* encephalopathy with epilepsy showed 76% had normal brain MRIs. Cerebral atrophy was present in 14% of individuals. Nonspecific brain MRI

features were found such as right parietal gyral asymmetry and FLAIR hyperintensities (n=1), a small infarction (n=1), small hippocampi with incomplete rotation (n=1), and suspected temporal myelination defect (n=1). One adult had a normal brain MRI at age four years and age 13 years, but mild cerebral atrophy was identified in adulthood [Stamberger et al 2022].

Genotype-Phenotype Correlations

In more than 50 individuals with *STXBP1* encephalopathy with epilepsy, no correlation was found between phenotype and the type of pathogenic variant (including splice, nonsense, deletion/duplication, or missense variant) [Carvill et al 2014]. In 147 individuals, no correlation between the severity of cognitive dysfunction or response to ASM and the type of pathogenic variant (missense or truncating) was identified [Stamberger et al 2016].

In a study of recurrent pathogenic variants (p.Arg406His/Cys, p.Arg292Cys/His/Leu, p.Arg551Cys/Gly/His/Leu, p.Pro139Leu, p.Arg190Trp) identified in more than ten individuals with *STXBP1* encephalopathy with epilepsy, there were no identifiable genotype-phenotype correlations for these variants. Individuals with protein-truncating variants and deletions in *STXBP1* showed significant phenotypic similarities. Individuals with protein-truncating variants and deletions had West syndrome (odds ratio [OR] = 1.6, 95% confidence interval [CI] = 0.95-2.73) and infantile spasms and ataxia (OR = 1.59, 95% CI = 1.08-2.35). Individuals with missense variants had a developmental epileptic encephalopathy phenotype (OR = 2.05, 95% CI = 1.28-3.32). However, there were no phenotypic similarities between individuals with the recurrent variants in *STXBP1* [Xian et al 2022].

Penetrance

STXBP1 encephalopathy with epilepsy is expected to be completely penetrant.

Prevalence

More than 500 individuals with an *STXBP1* encephalopathy with epilepsy have been reported in a recent study [Xian et al 2022]. Stamberger et al [2016] estimated the prevalence of *STXBP1* encephalopathy with epilepsy to be 1:91,862 individuals in the Danish population.

Costain et al [2019] reported that *STXBP1* encephalopathy with epilepsy was one of the most common causes of developmental epileptic encephalopathy.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *STXBP1*.

Contiguous gene deletions (≤4 Mb) encompassing *STXBP1* along with as many as 92 contiguous genes have been reported in 20 individuals [Saitsu et al 2008, Mignot et al 2011, Campbell et al 2012, Saitsu et al 2012, Mastrangelo et al 2013, Barcia et al 2014, Matsumoto et al 2014, Di Meglio et al 2015, Ehret et al 2015, Nicita et al 2015, Nambot et al 2016, Stamberger et al 2016]. In addition to features reported in individuals with genetic alternations involving *STXBP1* only (e.g., intellectual disability, refractory seizures, and ongoing epileptiform activity), findings reported in individuals with contiguous gene deletions include:

- Absent thumbnails and hypoplastic second fingernails (1 individual) [Mignot et al 2011]
- Cleft lip and palate, ventricular septal defect, overlapping fingers, small penis (1 individual) [Saitsu et al 2012]
- Short and broad fingers and broad feet [Campbell et al 2012]

- Dysplastic right kidney, ureterocele, umbilical hernia (1 individual) [Matsumoto et al 2014]
- Cleft lip/palate, umbilical hernia, mild dysmorphic facial features, dilated renal pelvis, microcephaly (1 individual) [Nicita et al 2015]

Differential Diagnosis

The phenotypic features (both clinical and electrophysiologic) associated with *STXBP1* encephalopathy with epilepsy are not sufficient to diagnose this condition. All genes known to be associated with developmental and epileptic encephalopathy (>100 have been identified; see OMIM Phenotypic Series) should be included in the differential diagnosis.

Treatable neurometabolic disorders causing early infantile-onset epileptic encephalopathy should be included in the differential diagnosis. These disorders include:

- Vitamin B_6-dependent epilepsies (See Pyridoxine-Dependent Epilepsy – *ALDH7A1*, PNPO Deficiency, and PLPBP Deficiency.)
- Biotinidase deficiency
- Glucose transporter 1 deficiency syndrome
- Creatine deficiency disorders (i.e., the creatine biosynthesis disorders guanidinoacetate methyltransferase deficiency and L-arginine:glycine amidinotransferase deficiency, and creatine transporter deficiency)
- Holocarboxylase synthetase deficiency (OMIM 253270)
- Serine deficiency disorders with infantile, juvenile, or adult onset

Management

No clinical practice guidelines for *STXBP1* encephalopathy with epilepsy have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *STXBP1* encephalopathy with epilepsy, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. *STXBP1* Encephalopathy with Epilepsy: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Movement disorders	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl findings suggestive of ASD, ADHD, aggressive behavior, psychosis, &/or sleep disturbances
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *STXBP1* encephalopathy w/epilepsy to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *STXBP1* encephalopathy with epilepsy. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *STXBP1* Encephalopathy with Epilepsy: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	• Treatment by experienced neurologist. Options incl ASMs, ketogenic diet, & epilepsy surgery. • Education of parents/caregivers [1]	• Response to vigabatrin, carbamazepine, phenobarbital, or valproic acid & levetiracetam have been reported. [2] • Response to phenobarbital (focal seizures), ACTH (infantile spasms), clobazam, & ketogenic diet have also been reported. [3] • ≥2 ASMs were used in ≥20% of affected persons. ~25% were refractory to ASM therapy.
Movement disorder	• Severe dystonia, dyskinesia, or choreoathetosis can be treated w/ monoamine-depleting or dopaminergic agents. • Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Gastrointestinal/ Feeding	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical manifestations of dysphagia
Bowel dysfunction	Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Hamdan et al [2009], Deprez et al [2010], Saitsu et al [2010], Mignot et al [2011], Weckhuysen et al [2013], Barcia et al [2014], Romaniello et al [2014], Keogh et al [2015], Romaniello et al [2015], Dilena et al [2016], Yamamoto et al [2016]
3. Xian et al [2022]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

There are no published guidelines for surveillance of individuals diagnosed with *STXBP1* encephalopathy with epilepsy. The following assessments and investigations can be performed as needed [Stamberger et al 2022].

Table 5. *STXBP1* Encephalopathy with Epilepsy: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
	OT & PT assessments to optimize functional outcomes	As needed
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, [1] changes in tone, or movement disorders.	At each visit
	EEG	As needed
Neurobehavioral/ Psychiatric	Behavioral assessment for ASD, ADHD, aggression, self-injury, & sleep disturbances	At each visit
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Gastrointestinal	Assess for constipation.	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy
1. 38% of individuals who became seizure-free in childhood or adolescence had seizure recurrence later in life.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

STXBP1 encephalopathy with epilepsy is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most individuals reported to date with *STXBP1* encephalopathy with epilepsy represent simplex cases (i.e., the only family member known to be affected) and have the disorder as the result of a *de novo STXBP1* pathogenic variant.

- Rarely, a proband with *STXBP1* encephalopathy with epilepsy has the disorder as the result of an *STXBP1* pathogenic variant inherited from an asymptomatic parent with germline (or somatic and germline) mosaicism [Saitsu et al 2011, Møller et al 2019, Stamberger et al 2022].
  - Parental somatic and germline mosaicism was reported in the asymptomatic father of a child diagnosed with Ohtahara syndrome [Saitsu et al 2011].
  - Presumed parental germline mosaicism was reported in a family in which the *STXBP1* pathogenic variant identified in two affected sibs was not identified in parental leukocyte DNA [Stamberger et al 2022].
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Saitsu et al 2011, Møller et al 2019, Stamberger et al 2022]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *STXBP1* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *STXBP1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental mosaicism [Saitsu et al 2011, Møller et al 2019, Stamberger et al 2022].
- If the parents have not been tested for the *STXBP1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low but still increased for *STXBP1* encephalopathy with epilepsy because of the possibility of parental mosaicism.

Offspring of a proband. Individuals with *STXBP1* encephalopathy with epilepsy are not known to reproduce.

Other family members. Given that most probands with *STXBP1* encephalopathy with epilepsy reported to date have the disorder as a result of a *de novo* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *STXBP1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *STXBP1* encephalopathy with epilepsy are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **STXBP1 Foundation**
  Email: info@stxbp1disorders.org
  www.stxbp1disorders.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  www.epilepsy.ca
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **MedlinePlus**
  Intellectual Disability
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page
- **STXBP1 Registry at Simons Searchlight**
  Join the Simons Searchlight Study

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. STXBP1 Encephalopathy with Epilepsy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
STXBP1	9q34.11	Syntaxin-binding protein 1	STXBP1 database	STXBP1	STXBP1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for STXBP1 Encephalopathy with Epilepsy (View All in OMIM)

602926	SYNTAXIN-BINDING PROTEIN 1; STXBP1
612164	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 4; DEE4

Molecular Pathogenesis

STXBP1 encodes syntaxin-binding protein 1 (STXBP1 or MUNC18-1), a member of the SEC1 family of membrane-trafficking proteins. STXBP1 is expressed in neurons and plays an important role in synaptic vesicle docking and fusion [Pevsner et al 1994, Swanson et al 1998]. It is necessary for neurotransmitter release in the brain [Verhage et al 2000]. Specifically, STXBP1 modulates the presynaptic vesicular fusion reaction by interacting with vesicle- and target-associated SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins [Shen et al 2007, Gerber et al 2008].

Mechanism of disease causation. Loss of function. Pathogenic variants of *STXBP1* likely impair neurotransmitter release, specifically in GABAergic interneurons, resulting in uncontrolled firing of excitatory neurons [Hussain 2014].

Table 6. *STXBP1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_003165.6 NP_003156.1	c.416C>T	p.Pro139Leu	Recurrent variants (See Genotype-Phenotype Correlations.)
	c.568C>T	p.Arg190Trp	
	c.874C>T	p.Arg292Cys	
	c.875G>A	p.Arg292His	
	c.875G>T	p.Arg292Leu	
	c.1216C>T	p.Arg406Cys	
	c.1217G>A	p.Arg406His	
	c.1651C>T	p.Arg551Cys	
	c.1651C>G	p.Arg551Gly	
	c.1652G>A	p.Arg551His	
	c.1652G>T	p.Arg551Leu	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Saadet Mercimek-Andrews's areas of focus are neurometabolic disorders, epilepsy genetics, and neurogenetics. See:

- www.ualberta.ca/medical-genetics/people/faculty/saadet-andrews.html
- www.wchri.org/members-and-trainees/find-a-researcher/saadet-andrews

Author History

Saadet Mercimek-Andrews, MD, PhD, FCCMG, FRCPC (2016-present)

Yannay Khaikin, BSc; The Hospital for Sick Children (2016-2023)

Revision History

- 28 September 2023 (sw) Comprehensive update posted live
- 1 December 2016 (bp) Review posted live
- 23 February 2016 (smm) Original submission

References

Literature Cited

Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR, et al. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217-21. PubMed PMID: 23934111.

Allen NM, Conroy J, Shahwan A, Lynch B, Correa RG, Pena SD, McCreary D, Magalhaes TR, Ennis S, Lynch SA, King MD. Unexplained early onset epileptic encephalopathy: exome screening and phenotype expansion. Epilepsia. 2016;57:e12-7. PubMed PMID: 26648591.

Balagura G, Xian J, Riva A, Marchese F, Ben Zeev B, Rios L, Sirsi D, Accorsi P, Amadori E, Astrea G, Baldassari S, Beccaria F, Boni A, Budetta M, Cantalupo G, Capovilla G, Cesaroni E, Chiesa V, Coppola A, Dilena R, Faggioli R, Ferrari A, Fiorini E, Madia F, Gennaro E, Giacomini T, Giordano L, Iacomino M, Lattanzi S, Marini C, Mancardi MM, Mastrangelo M, Messana T, Minetti C, Nobili L, Papa A, Parmeggiani A, Pisano T, Russo A, Salpietro V, Savasta S, Scala M, Accogli A, Scelsa B, Scudieri P, Spalice A, Specchio N, Trivisano M, Tzadok M, Valeriani M, Vari MS, Verrotti A, Vigevano F, Vignoli A, Toonen R, Zara F, Helbig I, Striano P. Epilepsy course and developmental trajectories in STXBP1-DEE. Neurol Genet. 2022;8:e676. PubMed PMID: 35655584.

Barcia G, Chemaly N, Gobin S, Milh M, Van Bogaert P, Barnerias C, Kaminska A, Dulac O, Desguerre I, Cormier V, Boddaert N, Nabbout R. Early epileptic encephalopathies associated with STXBP1 mutations: Could we better delineate the phenotype? Eur J Med Genet. 2014;57:15-20. PubMed PMID: 24189369.

Boutry-Kryza N, Labalme A, Ville D, de Bellescize J, Touraine R, Prieur F, Dimassi S, Poulat AL, Till M, Rossi M, Bourel-Ponchel E, Delignieres A, Le Moing AG, Rivier C, des Portes V, Edery P, Calender A, Sanlaville D, Lesca G. Molecular characterization of a cohort of 73 patients with infantile spasms syndrome. Eur J Med Genet. 2015;58:51-8. PubMed PMID: 25497044.

Campbell IM, Yatsenko SA, Hixson P, Reimschisel T, Thomas M, Wilson W, Dayal U, Wheless JW, Crunk A, Curry C, Parkinson N, Fishman L, Riviello JJ, Nowaczyk MJ, Zeesman S, Rosenfeld JA, Bejjani BA, Shaffer LG, Cheung SW, Lupski JR, Stankiewicz P, Scaglia F. Novel 9q34.11 gene deletions encompassing combinations of four Mendelian disease genes: STXBP1, SPTAN1, ENG, and TOR1A. Genet Med. 2012;14:868-76. PubMed PMID: 22722545.

Carvill GL, Weckhuysen S, McMahon JM, Hartmann C, Moller RS, Hjalgrim H, Cook J, Geraghty E, O'Roak BJ, Petrou S, Clarke A, Gill D, Sadleir LG, Muhle H, von Spiczak S, Nikanorova M, Hodgson BL, Gazina EV, Suls A, Shendure J, Dibbens LM, De Jonghe P, Helbig I, Berkovic SF, Scheffer IE, Mefford HC. GABRA1 and STXBP1: novel genetic causes of Dravet syndrome. Neurology. 2014;82:1245-53. PubMed PMID: 24623842.

Costain G, Cordeiro D, Matviychuk D, Mercimek-Andrews S. Clinical application of targeted next-generation sequencing panels and whole exome sequencing in childhood epilepsy. Neuroscience. 2019;418:291-310. PubMed PMID: 31487502.

Deprez L, Weckhuysen S, Holmgren P, Suls A, Van Dyck T, Goossens D, Del-Favero J, Jansen A, Verhaert K, Lagae L, Jordanova A, Van Coster R, Yendle S, Berkovic SF, Scheffer I, Ceulemans B, De Jonghe P. Clinical spectrum of early-onset epileptic encephalopathies associated with STXBP1 mutations. Neurology. 2010;75:1159-65. PubMed PMID: 20876469.

Dilena R, Striano P, Traverso M, Viri M, Cristofori G, Tadini L, Barbieri S, Romeo A, Zara F. Dramatic effect of levetiracetam in early-onset epileptic encephalopathy due to STXBP1 mutation. Brain Dev. 2016;38:128-31. PubMed PMID: 26212315.

Di Meglio C, Lesca G, Villeneuve N, Lacoste C, Abidi A, Cacciagli P, Altuzarra C, Roubertie A, Afenjar A, Renaldo-Robin F, Isidor B, Gautier A, Husson M, Cances C, Metreau J, Laroche C, Chouchane M, Ville D, Marignier S, Rougeot C, Lebrun M, de Saint Martin A, Perez A, Riquet A, Badens C, Missirian C, Philip N, Chabrol B, Villard L, Milh M. Epileptic patients with de novo STXBP1 mutations: key clinical features based on 24 cases. Epilepsia. 2015;56:1931-40. PubMed PMID: 26514728.

Ehret JK, Engels H, Cremer K, Becker J, Zimmermann JP, Wohlleber E, Grasshoff U, Rossier E, Bonin M, Mangold E, Bevot A, Schon S, Heilmann-Heimbach S, Dennert N, Mathieu-Dramard M, Lacaze E, Plessis G, de Broca A, Jedraszak G, Rothlisberger B, Miny P, Filges I, Dufke A, Andrieux J, Lee JA, Zink AM. Microdeletions in 9q33.3-q34.11 in five patients with intellectual disability, microcephaly, and seizures of incomplete penetrance: is STXBP1 not the only causative gene? Mol Cytogenet. 2015;8:72 PubMed PMID: 26421060.

Gerber SH, Rah JC, Min SW, Liu X, de Wit H, Dulubova I, Meyer AC, Rizo J, Arancillo M, Hammer RE, Verhage M, Rosenmund C, Südhof TC. Conformational switch of syntaxin-1 controls synaptic vesicle fusion. Science. 2008; 321:1507–10. PubMed PMID: 18703708.

Guacci A, Chetta M, Rizzo F, Marchese G, De Filippo MR, Giurato G, Nassa G, Ravo M, Tarallo R, Rocco T, Operto FF, Weisz A, Coppola G. Phenytoin neurotoxicity in a child carrying new STXBP1 and CYP2C9 gene mutations. Seizure. 2016;34:26-8. PubMed PMID: 26658169.

Hamdan FF, Piton A, Gauthier J, Lortie A, Dubeau F, Dobrzeniecka S, Spiegelman D, Noreau A, Pellerin S, Cote M, Henrion E, Fombonne E, Mottron L, Marineau C, Drapeau P, Lafreniere RG, Lacaille JC, Rouleau GA, Michaud JL. De novo STXBP1 mutations in mental retardation and nonsyndromic epilepsy. Ann Neurol. 2009;65:748-53. PubMed PMID: 19557857.

Helbig KL, Farwell Hagman, Shinde DN, Mroske C, Powis Z, Li S, Tang S, Helbig I. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016;18:898-905. PubMed PMID: 26795593.

Hussain S. Developing a PPI inhibitor-based therapy for STXBP1 haploinsufficiency-associated epileptic disorders. Front Mol Neurosci. 2014;7:6. PubMed PMID: 24550774.

Keogh MJ, Daud D, Pyle A, Duff J, Griffin H, He L, Alston CL, Steele H, Taggart S, Basu AP, Taylor RW, Horvath R, Ramesh V, Chinnery PF. A novel de novo STXBP1 mutation is associated with mitochondrial complex I deficiency and late-onset juvenile-onset parkinsonism. Neurogenetics. 2015;16:65-7. PubMed PMID: 25418441.

Kim YO, Korff CM, Villaluz MM, Suls A, Weckhuysen S, De Jonghe P, Scheffer IE. Head stereotypies in STXBP1 encephalopathy. Dev Med Child Neurol. 2013;55:769-72. PubMed PMID: 23763664.

Kodera H, Kato M, Nord AS, Walsh T, Lee M, Yamanaka G, Tohyama J, Nakamura K, Nakagawa E, Ikeda T, Ben-Zeev B, Lev D, Lerman-Sagie T, Straussberg R, Tanabe S, Ueda K, Amamoto M, Ohta S, Nonoda Y, Nishiyama K, Tsurusaki Y, Nakashima M, Miyake N, Hayasaka K, King MC, Matsumoto N, Saitsu H. Targeted capture and sequencing for detection of mutations causing early onset epileptic encephalopathy. Epilepsia. 2013;54:1262-9. PubMed PMID: 23662938.

Kwong AK, Ho AC, Fung CW, Wong VC. Analysis of mutations in 7 genes associated with neuronal excitability and synaptic transmission in a cohort of children with non-syndromic infantile epileptic encephalopathy. PLoS One. 2015;10:e0126446. PubMed PMID: 25951140.

Lopes F, Barbosa M, Ameur A, Soares G, de Sá J, Dias AI, Oliveira G, Cabral P, Temudo T, Calado E, Cruz IF, Vieira JP, Oliveira R, Esteves S, Sauer S, Jonasson I, Syvänen AC, Gyllensten U, Pinto D, Maciel P. Identification of novel genetic causes of Rett syndrome-like phenotypes. J Med Genet. 2016;53:190-9. PubMed PMID: 26740508.

Marchese M, Valvo G, Moro F, Sicca F, Santorelli FM. Targeted gene resequencing (Astrochip) to explore the tripartite synapse in autism-epilepsy phenotype with macrocephaly. Neuromolecular Med. 2016;18:69-80. PubMed PMID: 26537360.

Mastrangelo M, Peron A, Spaccini L, Novara F, Scelsa B, Introvini P, Raviglione F, Faiola S, Zuffardi O. Neonatal suppression-burst without epileptic seizures: expanding the electroclinical phenotype of STXBP1-related, early-onset encephalopathy. Epileptic Disord. 2013;15:55-61. PubMed PMID: 23531706.

Matsumoto H, Zaha K, Nakamura Y, Hayashi S, Inazawa J, Nonoyama S. Chromosome 9q33q34 microdeletion with early infantile epileptic encephalopathy, severe dystonia, abnormal eye movements, and nephroureteral malformations. Pediatr Neurol. 2014;51:170-5. PubMed PMID: 24938147.

Mignot C, Moutard ML, Trouillard O, Gourfinkel-An I, Jacquette A, Arveiler B, Morice-Picard F, Lacombe D, Chiron C, Ville D, Charles P, LeGuern E, Depienne C, Heron D. STXBP1-related encephalopathy presenting as infantile spasms and generalized tremor in three patients. Epilepsia. 2011;52:1820-7. PubMed PMID: 21762454.

Milh M, Villeneuve N, Chouchane M, Kaminska A, Laroche C, Barthez MA, Gitiaux C, Bartoli C, Borges-Correia A, Cacciagli P, Mignon-Ravix C, Cuberos H, Chabrol B, Villard L. Epileptic and nonepileptic features in patients with early onset epileptic encephalopathy and STXBP1 mutations. Epilepsia. 2011;52:1828-34. PubMed PMID: 21770924.

Møller RS, Liebmann N, Larsen LHG, Stiller M, Hentschel J, Kako N, Abdin D, Di Donato N, Pal DK, Zacher P, Syrbe S, Dahl HA, Lemke JR. Parental mosaicism in epilepsies due to alleged de novo variants. Epilepsia. 2019;60:e63-e66. PubMed PMID: 31077350.

Nam JY, Teng LY, Cho K, Kang HC, Lee JS, Kim HD, Kim SH. Effects of the ketogenic diet therapy in patients with STXBP1-related encephalopathy. Epilepsy Res. 2022;186:106993. PubMed PMID: 35998430.

Nambot S, Masurel A, El Chehadeh S, Mosca-Boidron AL, Thauvin-Robinet C, Lefebvre M, Marle N, Thevenon J, Perez-Martin S, Dulieu V, Huet F, Plessis G, Andrieux J, Jouk PS, Billy-Lopez G, Coutton C, Morice-Picard F, Delrue MA, Heron D, Rooryck C, Goldenberg A, Saugier-Veber P, Joly-Hélas G, Calenda P, Kuentz P, Manouvrier-Hanu S, Dupuis-Girod S, Callier P, Faivre L1,3. 9q33.3q34.11 microdeletion: new contiguous gene syndrome encompassing STXBP1, LMX1B and ENG genes assessed using reverse phenotyping. Eur J Hum Genet. 2016;24:830-7. PubMed PMID: 26395556.

Nicita F, Ulgiati F, Bernardini L, Garone G, Papetti L, Novelli A, Spalice A. Early myoclonic encephalopathy in 9q33-q34 deletion encompassing STXBP1 and SPTAN1. Ann Hum Genet. 2015;79:209-17. PubMed PMID: 25779878.

Olson HE, Tambunan D, LaCoursiere C, Goldenberg M, Pinsky R, Martin E, Ho E, Khwaja O, Kaufmann WE, Poduri A. Mutations in epilepsy and intellectual disability genes in patients with features of Rett syndrome. Am J Med Genet A. 2015;167A:2017-25. PubMed PMID: 25914188.

Otsuka M, Oguni H, Liang JS, Ikeda H, Imai K, Hirasawa K, Imai K, Tachikawa E, Shimojima K, Osawa M, Yamamoto T. STXBP1 mutations cause not only Ohtahara syndrome but also West syndrome--result of Japanese cohort study. Epilepsia. 2010;51:2449-52. PubMed PMID: 21204804.

Pevsner J, Hsu SC, Scheller RH. N-Sec1: a neural-specific syntaxin-binding protein. Proc Natl Acad Sci U S A. 1994; 91:1445-9. PubMed PMID: 8108429.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Romaniello R, Saettini F, Panzeri E, Arrigoni F, Bassi MT, Borgatti R. A de-novo STXBP1 gene mutation in a patient showing the Rett syndrome phenotype. Neuroreport. 2015;26:254-7. PubMed PMID: 25714420.

Romaniello R, Zucca C, Tenderini E, Arrigoni F, Ragona F, Zorzi G, Bassi MT, Borgatti R. A novel mutation in STXBP1 gene in a child with epileptic encephalopathy and an atypical electroclinical pattern. J Child Neurol. 2014;29:249-53. PubMed PMID: 24170257.

Saitsu H, Hoshino H, Kato M, Nishiyama K, Okada I, Yoneda Y, Tsurusaki Y, Doi H, Miyake N, Kubota M, Hayasaka K, Matsumoto N. Paternal mosaicism of an STXBP1 mutation in OS. Clin Genet. 2011;80:484-8. PubMed PMID: 21062273.

Saitsu H, Kato M, Mizuguchi T, Hamada K, Osaka H, Tohyama J, Uruno K, Kumada S, Nishiyama K, Nishimura A, Okada I, Yoshimura Y, Hirai S, Kumada T, Hayasaka K, Fukuda A, Ogata K, Matsumoto N. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet. 2008;40:782-8. PubMed PMID: 18469812.

Saitsu H, Kato M, Okada I, Orii KE, Higuchi T, Hoshino H, Kubota M, Arai H, Tagawa T, Kimura S, Sudo A, Miyama S, Takami Y, Watanabe T, Nishimura A, Nishiyama K, Miyake N, Wada T, Osaka H, Kondo N, Hayasaka K, Matsumoto N. STXBP1 mutations in early infantile epileptic encephalopathy with suppression-burst pattern. Epilepsia. 2010;51:2397-405. PubMed PMID: 20887364.

Saitsu H, Kato M, Shimono M, Senju A, Tanabe S, Kimura T, Nishiyama K, Yoneda Y, Kondo Y, Tsurusaki Y, Doi H, Miyake N, Hayasaka K, Matsumoto N. Association of genomic deletions in the STXBP1 gene with Ohtahara syndrome. Clin Genet. 2012;81:399-402. PubMed PMID: 22211739.

Sampaio M, Rocha R, Biskup S, Leao M. Novel STXBP1 mutations in 2 patients with early infantile epileptic encephalopathy. J Child Neurol. 2015;30:622-4. PubMed PMID: 23533165.

Shen J, Tareste DC, Paumet F, Rothman JE, Melia TJ. Selective activation of cognate SNAREpins by Sec1/Munc18 proteins. Cell. 2007;128:183-95. PubMed PMID: 17218264.

Stamberger H, Crosiers D, Balagura G, Bonardi CM, Basu A, Cantalupo G, Chiesa V, Christensen J, Dalla Bernardina B, Ellis CA, Furia F, Gardiner F, Giron C, Guerrini R, Klein KM, Korff C, Krijtova H, Leffler M, Lerche H, Lesca G, Lewis-Smith D, Marini C, Marjanovic D, Mazzola L, McKeown Ruggiero S, Mochel F, Ramond F, Reif PS, Richard-Mornas A, Rosenow F, Schropp C, Thomas RH, Vignoli A, Weber Y, Palmer E, Helbig I, Scheffer IE, Striano P, Møller RS, Gardella E, Weckhuysen S. Natural history study of STXBP1-developmental and epileptic encephalopathy into adulthood. Neurology. 2022;99:e221-e233. PubMed PMID: 35851549.

Stamberger H, Nikanorova M, Willemsen MH, Accorsi P, Angriman M, Baier H, Benkel-Herrenbrueck I, Benoit V, Budetta M, Caliebe A, Cantalupo G, Capovilla G, Casara G, Courage C, Deprez M, Destrée A, Dilena R, Erasmus CE, Fannemel M, Fjær R, Giordano L, Helbig KL, Heyne HO, Klepper J, Kluger GJ, Lederer D, Lodi M, Maier O, Merkenschlager A, Michelberger N, Minetti C, Muhle H, Phalin J, Ramsey K, Romeo A, Schallner J, Schanze I, Shinawi M, Sleegers K, Sterbova K, Syrbe S, Traverso M, Tzschach A, Uldall P, Van Coster R, Verhelst H, Viri M, Winter S, Wolff M, Zenker M, Zoccante L, De Jonghe P, Helbig I, Striano P, Lemke JR, Møller RS, Weckhuysen S. STXBP1 encephalopathy: A neurodevelopmental disorder including epilepsy. Neurology. 2016;86:954-62. PubMed PMID: 26865513.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Swanson DA, Steel JM, Valle D. Identification and characterization of the human ortholog of rat STXBP1, a protein implicated in vesicle trafficking and neurotransmitter release. Genomics. 1998;48:373-6. PubMed PMID: 9545644.

Tso WW, Kwong AK, Fung CW, Wong VC. Folinic acid responsive epilepsy in Ohtahara syndrome caused by STXBP1 mutation. Pediatr Neurol. 2014;50:177-80. PubMed PMID: 24315539.

Tucker T, Zahir FR, Griffith M, Delaney A, Chai D, Tsang E, Lemyre E, Dobrzeniecka S, Marra M, Eydoux P, Langlois S, Hamdan FF, Michaud JL, Friedman JM. Single exon-resolution targeted chromosomal microarray analysis of known and candidate intellectual disability genes. Eur J Hum Genet. 2014;22:792-800. PubMed PMID: 24253858.

Vatta M, Tennison MB, Aylsworth AS, Turcott CM, Guerra MP, Eng CM, Yang Y. A novel STXBP1 mutation causes focal seizures with neonatal onset. J Child Neurol. 2012;27:811-4. PubMed PMID: 22596016.

Verhage M, Maia AS, Plomp JJ, Brussaard AB, Heeroma JH, Vermeer H, Toonen RF, Hammer RE, van den Berg TK, Missler M, Geuze HJ, Südhof TC. Synaptic assembly of the brain in the absence of neurotransmitter secretion. Science. 2000;287:864-9. PubMed PMID: 10657302.

Weckhuysen S, Holmgren P, Hendrickx R, Jansen AC, Hasaerts D, Dielman C, de Bellescize J, Boutry-Kryza N, Lesca G, Von Spiczak S, Helbig I, Gill D, Yendle S, Moller RS, Klitten L, Korff C, Godfraind C, Van Rijckevorsel K, De Jonghe P, Hjalgrim H, Scheffer IE, Suls A. Reduction of seizure frequency after epilepsy surgery in a patient with STXBP1 encephalopathy and clinical description of six novel mutation carriers. Epilepsia. 2013;54:e74-80. PubMed PMID: 23409955.

Xian J, Parthasarathy S, Ruggiero SM, Balagura G, Fitch E, Helbig K, Gan J, Ganesan S, Kaufman MC, Ellis CA, Lewis-Smith D, Galer P, Cunningham K, O'Brien M, Cosico M, Baker K, Darling A, Veiga de Goes F, El Achkar CM, Doering JH, Furia F, García-Cazorla Á, Gardella E, Geertjens L, Klein C, Kolesnik-Taylor A, Lammertse H, Lee J, Mackie A, Misra-Isrie M, Olson H, Sexton E, Sheidley B, Smith L, Sotero L, Stamberger H, Syrbe S, Thalwitzer KM, van Berkel A, van Haelst M, Yuskaitis C, Weckhuysen S, Prosser B, Son Rigby C, Demarest S, Pierce S, Zhang Y, Møller RS, Bruining H, Poduri A, Zara F, Verhage M, Striano P, Helbig I. Assessing the landscape of STXBP1-related disorders in 534 individuals. Brain. 2022;145:1668-83. PubMed PMID: 35190816.

Xian J, Thalwitzer KM, McKee J, Sullivan KT, Brimble E, F Eryn Fitch, Toib J, Kaufman MC, deCampo D, Cunningham K, Pierce SR, JGoss J, Rigby CS, Syrbe S, Boland M, Prosser B, Fitter N, Ruggiero SM, Helbig I. Delineating clinical and developmental outcomes in STXBP1-related disorders. medRxiv 2023:2023.05.10.23289776.

Yamamoto T, Shimojima K, Yano T, Ueda Y, Takayama R, Ikeda H, Imai K. Loss-of-function mutations of STXBP1 in patients with epileptic encephalopathy. Brain Dev. 2016;38:280-4. PubMed PMID: 26384463.

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