

# STXBP1 encephalopathy

A neurodevelopmental disorder including epilepsy

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## ABSTRACT

**Objective:** To give a comprehensive overview of the phenotypic and genetic spectrum of *STXBP1* encephalopathy (*STXBP1*-E) by systematically reviewing newly diagnosed and previously reported patients.

**Methods:** We recruited newly diagnosed patients with *STXBP1* mutations through an international network of clinicians and geneticists. Furthermore, we performed a systematic literature search to review the phenotypes of all previously reported patients.

**Results:** We describe the phenotypic features of 147 patients with *STXBP1*-E including 45 previously unreported patients with 33 novel *STXBP1* mutations. All patients have intellectual disability (ID), which is mostly severe to profound (88%). Ninety-five percent of patients have epilepsy. While one-third of patients presented with Ohtahara syndrome (21%) or West syndrome (9.5%), the majority has a nonsyndromic early-onset epilepsy and encephalopathy (53%) with epileptic spasms or tonic seizures as main seizure type. We found no correlation between severity of seizures and severity of ID or between mutation type and seizure characteristics or cognitive outcome. Neurologic comorbidities including autistic features and movement disorders are frequent. We also report 2 previously unreported adult patients with prominent extrapyramidal features.

**Conclusion:** De novo *STXBP1* mutations are among the most frequent causes of epilepsy and encephalopathy. Most patients have severe to profound ID with little correlation among seizure onset, seizure severity, and the degree of ID. Accordingly, we hypothesize that seizure severity and ID present 2 independent dimensions of the *STXBP1*-E phenotype. *STXBP1*-E may be conceptualized as a complex neurodevelopmental disorder rather than a primary epileptic encephalopathy. *Neurology*® 2016;86:954-962

## GLOSSARY

**AED** = antiepileptic drugs; **EOEE** = early-onset epilepsy and encephalopathy; **ID** = intellectual disability; **ILAE** = International League Against Epilepsy; **STXBP1** = syntaxin-binding protein 1; **STXBP1-E** = *STXBP1* encephalopathy.

Syntaxin-binding protein 1 (*STXBP1*) (also known as *MUNC18-1*) is a protein of the *SEC1* family of membrane trafficking proteins predominantly expressed in the brain, which plays an important role in synaptic vesicle docking and fusion.<sup>1,2</sup> Through interaction with both vesicle-associated (synaptobrevin 2 or vesicle-associated membrane protein 2) and target-associated (syntaxin-1 and synaptosomal-associated protein 25) soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) proteins, *STXBP1* modulates the presynaptic vesicular fusion reaction.<sup>3,4</sup> *STXBP1* is encoded by the *STXBP1* gene (NM\_003165.3), consisting of 20 exons and located on chromosome 9q34.11.<sup>2,5</sup>

In 2008, Saitsu et al.<sup>6</sup> described de novo *STXBP1* mutations in 5 patients with Ohtahara syndrome. Subsequently, mutations in *STXBP1*, including missense, frameshift, splice site, and nonsense mutations, and intragenic and whole gene deletions have been described in different patient cohorts, broadening the phenotypic spectrum of *STXBP1* mutations to West syndrome, unclassified early-onset epileptic encephalopathy, Dravet syndrome, nonsyndromic epilepsy and intellectual disability, and autism.<sup>5,7-41</sup>

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Go to [Neurology.org](http://Neurology.org) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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**Supplemental data  
at Neurology.org**

In this study, we aimed to provide a comprehensive picture of the phenotypic spectrum of *STXBPI* encephalopathy (*STXBPI*-E). We report 45 previously unreported patients with *STXBPI*-E, carrying 33 unreported mutations, and summarize all *STXBPI* mutations reported to date. We further discuss future treatment options and pitfalls in the genetic diagnosis of *STXBPI*-E.

**METHODS** **Characterization of novel patients with *STXBPI*-E.** Forty-five previously unreported patients with a *STXBPI* mutation were included in this study. All patients were referred through a network of collaborating clinicians and geneticists. Mutations in *STXBPI* were identified in research or diagnostic laboratories. Referring physicians were provided a standardized phenotyping sheet to assess relevant clinical characteristics, EEG, and neuroimaging findings. International League Against Epilepsy (ILAE) criteria were used for epilepsy syndrome classification, meaning that the diagnosis of Ohtahara syndrome, Dravet syndrome, West syndrome, or Lennox-Gastaut syndrome was only made when all criteria for seizure, developmental, and EEG characteristics were present. For the purpose of this review, we classified patients with frequent seizures and intellectual disability (ID), both with onset in the first 2 years of life but not fulfilling ILAE criteria for any specific syndrome, as early-onset epilepsy and encephalopathy (EOEE; see Discussion). In case of preexisting developmental delay or ID with epilepsy onset after age 2 years, a diagnosis of ID and nonsyndromic epilepsy was made.

**Standard protocol approvals, registrations, and patient consents.** Written informed consent for participation in the study was obtained. The study was approved by the Commission of Medical Ethics of the University of Antwerp and the Ethics Committee of Western Zealand, Denmark.

**Review of patients reported in literature.** We performed a PubMed search for *STXBPI*. Articles not available in English were excluded. We also included microdeletions involving multiple genes in addition to *STXBPI* even though we recognize that in these patients, deletions of other genes than *STXBPI* might influence the phenotype.

We classified all patients as explained above, based on clinical information in the publication. For patients for whom no or little clinical information was reported, we listed the phenotype mentioned in the respective publications, but they were not included in summary statistics.

**Statistical analyses.** A  $\chi^2$  test was used to compare mutation type (missense vs truncating) and cognitive outcome (mild to moderate ID vs severe to profound) and cognitive outcome and seizure outcome (seizure-free vs not seizure-free). A Fisher exact test was used in case any of the cells had an expected count below 5. A nonparametric Mann-Whitney *U* test was used to look for a difference in age at seizure onset, age when seizure-free, and duration of seizures between the groups with truncating mutations and missense mutations and between the groups with mild to moderate ID and severe to profound ID. Statistical analyses were performed with SPSS Statistics 22 (IBM, Armonk, NY).

To estimate the frequency of *STXBPI*-E in the general population, we used the electronic population databases of National Statistics at the Statens Serum Institute (Denmark) to calculate

the birth cohort from 2001 to 2010. The Danish Epilepsy Centre is the only tertiary hospital in Denmark specialized in the treatment of epilepsy, and the majority of patients with intractable epilepsy are referred to this center. To ensure that all Danish patients diagnosed with *STXBPI*-E were included, including patients with mild or no epilepsy, we contacted all major Danish pediatric departments and clinical genetics departments for *STXBPI*-E patients treated locally.

**RESULTS** ***STXBPI*: The phenotypic spectrum.** In total, we reviewed the phenotypic features of 147 patients with *STXBPI*-E, including 45 previously unreported patients described in this article (tables e-1, e-2, and e-3 on the *Neurology*<sup>®</sup> Web site at Neurology.org). Age at inclusion ranged from 6 months to 56 years (median 5.75 years). At onset, the majority of patients had a clinical diagnosis of EOEE (*n* = 71; 53%) or Ohtahara syndrome (*n* = 28, 20.9%), 27 of whom showed evolution to West syndrome over time. *STXBPI* mutations were also identified in patients initially presenting with West syndrome (*n* = 13; 9.7%), ID with nonsyndromic epilepsy (*n* = 8; 6%), ID without epilepsy (*n* = 9; 6.7%), or Dravet syndrome (*n* = 3; 2.2%). One patient had early myoclonic encephalopathy and 1 patient had ID with 2 possible seizures. For 13 patients, no clinical description was available. Four of the 9 patients with ID without epilepsy were identified in the group of previously unreported patients.

**Seizures in *STXBPI*-E.** If present, epilepsy onset in *STXBPI*-E tends to be early in life, with a median onset age of 6 weeks (range 1 day–12 years). Childhood-onset epilepsy has been described in 8 patients with first seizures occurring at up to 12 years of age.

A broad spectrum of seizure types is seen in patients with *STXBPI*-E. Most frequently, epileptic spasms occur at some stage during the disease course (65.3%). Other frequent seizure types are focal seizures (57.9%) and tonic seizures (41.3%).

Treatment of seizures is often difficult early in the disease. Fifty-six of 104 (53.8%) patients for whom this information was available were treated with more than 3 antiepileptic drugs (AEDs) (steroid treatment and ACTH included). At last follow-up, 29 of 101 patients (28.7%) for whom information was available still had frequent seizures (more than once a week) despite treatment. Forty-six patients out of 105 for whom information was available (43.8%) nevertheless became seizure-free between the ages of 1 month and 4 years with a median age of 8 months. One patient became seizure-free after corpus callosotomy; in another patient, epilepsy surgery with resection of a focal cortical dysplasia greatly reduced seizure frequency.<sup>10,18</sup>

For the 40 newly diagnosed patients with epilepsy, different combinations of AEDs led to seizure

freedom. Although numbers are small, the AEDs most frequently reported to be effective were valproic acid, which led to seizure freedom in 4 patients (patients 4, 9, 32, and 39), levetiracetam in 3 patients (patients 2, 36, and 43), and vigabatrin in 2 patients (patients 28 and 41). In 8 out of 14 patients who became seizure-free, treatment with AEDs eventually could be discontinued. It should be noted that epilepsy relapse after a longer period of seizure freedom has been reported in 6 older patients with *STXBPI* mutations.<sup>5,12,16</sup>

**EEG and MRI characteristics.** In most patients with *STXBPI*-E, focal or multifocal epileptic activity on EEG was described (64.1%). A burst-suppression pattern was present at some point in disease history in 42 patients (35.9%) and hypsarrhythmia in 44 patients (40%).

Following the recent description of MRI characteristics in patients with *STXBPI*-E by Barcia et al.,<sup>25</sup> we reviewed all patients for the presence of cerebral atrophy, thin corpus callosum, and an aberrant myelination pattern on brain MRI. Information on MRI was present in 117 patients. Atrophic changes were described in 39 (33.3%) patients and thin corpus callosum or hypomyelination/delayed myelination in 19 patients each (16.2%). In 55 patients (47%), MRI was reported as normal.

**Development, behavior, and neurologic features.** All patients had some degree of ID, and in 107 out of 121 patients (88.4%) for whom information was available severe to profound ID was reported. In only 1 patient with a de novo p.Asp285Tyr mutation, cognitive impairment was limited to learning difficulties.<sup>27</sup> More detailed information regarding development was available for all 45 of our previously unreported patients: of the 28 patients with epilepsy onset after the neonatal period (after 30 days), 18 (64.3%) had preexisting developmental delay (information of early development not available in 1 patient). Out of all 45 unreported patients, 4 showed developmental regression (patients 1, 16, 34, and 37). In one patient (patient 34), regression occurred prior to epilepsy onset. Twenty-one out of 45 patients obtained the ability to walk (some steps) independently, acquiring this skill between the ages of 14 months and 6 years. Two learned to walk and then lost this ability later. Seven patients were able to speak more than a few words, allowing for some degree of verbal communication.

Autism or autistic features have been reported in 25 of the 147 patients reviewed. Fourteen of these patients (31.1% out of 45 patients) were identified in our cohort of previously unreported patients where this feature was specifically addressed in the questionnaire. Stereotypies have been described in 31 out of 147 patients. Other behavioral problems mentioned

were hyperactivity (n = 6) and acting out or aggressive behavior (n = 5).

Finally, a number of neurologic symptoms have been associated with *STXBPI*-E, including pyramidal, extrapyramidal, and cerebellar features suggesting involvement of various neurologic systems. The most frequent findings were (axial) hypotonia (n = 39), ataxia or ataxic gait (n = 34), (intentional) tremor (n = 31), spasticity (n = 20), dyskinesia (n = 17), and dystonia (n = 14). Following a recent report of a patient with *STXBPI*-E and juvenile-onset parkinsonism, we reviewed all new patients for features of parkinsonism.<sup>30</sup> We identified 2 adult patients (both aged 20 years; 2/12 patients older than 12 years) with prominent extrapyramidal features; 2 additional patients had only hypomimic facies.

Table 1 and figure 1 provide a summary of the phenotypic features associated with *STXBPI*-E.

**Mutation spectrum and inheritance.** Table e-2 provides an overview of all 147 *STXBPI* mutations reported to date, accounting for 123 different mutations including 33 previously unreported mutations. Out of 147 mutations, 56 (38.1%) were missense mutations (figure 2), and 91 (61.9%) were truncating mutations including nonsense (n = 21), splice site (n = 24), and frameshift mutations (n = 19), partial and whole gene deletions, and larger microdeletions including *STXBPI* (n = 25) (figure e-1). One patient (patient 28 of the new cohort) had a de novo synonymous mutation in an essential splice site, predicted to lead to a loss of the donor splice site (Human Splice Finder), and one patient had a small in-frame deletion. None of the mutations was present in the ExAC database (<http://exac.broadinstitute.org/>). Forty-one missense mutations were predicted deleterious or possibly/probably damaging by both SIFT and PolyPhen-2, 14 only by SIFT, and 1 was predicted benign by both tools (de novo p.His445Pro mutation in a patient with Dravet syndrome). Out of all mutations, 124 (84.4%) mutations were demonstrated to be de novo. One *STXBPI* mutation was inherited from a father carrying a mosaic mutation.<sup>9</sup> Two mutations were absent in the mother and for 20 mutations information on inheritance was not available, including 6 mutations of previously unreported patients. Five of these 6 mutations were truncating and thus considered to be pathogenic. The sixth mutation (patient 25) was a recurrent missense mutation, absent in the mother, and proven to occur de novo in 2 other unrelated patients.

In total, 13 recurrent mutations have been reported, including the missense mutations p.Arg406His in 7 patients and p.Arg551Cys in 4 patients. Seven recurrent mutations occurred at CpG dinucleotides leading to the substitution of an arginine residue.

**Table 1** Clinical features of *STXBP1* encephalopathy

Epilepsy	
Approximately 95% of patients	
Most frequent seizure types are epileptic spasms (65.3%), focal seizures (57.9%), and tonic seizures (41.3%)	
Seizure freedom is achieved in more than 1 in 3 patients, almost 1 in 3 remain therapy-resistant	
EEG	
>60% have focal or multifocal epileptic activity	
Burst suppression (35.9%) and hypsarrhythmia (40%) are frequent EEG findings	
Intellectual disability	
All patients; the majority has severe to profound intellectual disability (88.4%)	
Behavioral problems	
Autism or autistic features are seen in almost 1 in 5 patients	
Motor features	
(Axial) hypotonia, ataxia or ataxic gait, (intentional) tremor, spasticity and dyskinesia, or dystonia are frequently seen	
Imaging (brain MRI)	
Normal in almost 1/2	
Cerebral atrophy (33.3%), thin corpus callosum (16.2%), and hypomyelination or delayed myelination (16.2%) are frequent (age related) findings	

There was no obvious clustering of mutations in any of the 3 *STXBP1* domains (figure 2, figure e-1).

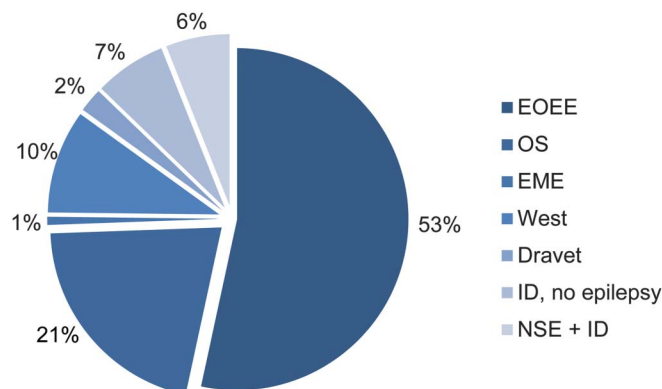
**Genotype–phenotype correlations.** We examined whether truncating mutations are associated with a more severe phenotype than missense mutations, and whether recurrent mutations lead to similar phenotypes. Forty-one of 45 patients with missense mutations for whom information on cognition was available had severe to profound ID (91.1%), compared to 66 out of 76 in patients with truncating mutations (86.8%). Out of the 9 patients without epilepsy, 3 carried missense mutations and 6 carried truncating mutations. In the group of 31 patients

who became seizure-free within 1 year after seizure onset, 9 carried missense mutations and 22 truncating mutations. These data suggest that truncating mutations do not necessarily lead to a more severe phenotype. The 7 patients with the most frequent recurrent mutation p.Arg406His all had onset of epilepsy in the first 2.5 months of life with severe to profound ID while the seizure phenotype and cognitive outcome was more variable for the other recurrent mutations including p.Arg292Cys, p.Arg292His, and p.Arg551Cys.

We next performed a statistical analysis of phenotype–genotype relationships (e-Methods and e-Results). No significant correlation was found between mutation type (missense vs truncating) and cognitive outcome (learning difficulties, mild to moderate ID, vs severe to profound ID;  $\chi^2$ , 2-sided  $p = 0.478$ ) or between mutation type and seizure outcome (seizure-free vs not seizure-free;  $\chi^2$ , 2-sided  $p = 0.127$ ). There was also no significant difference between the different mutation types regarding age at seizure onset (Mann-Whitney  $U$ , 2-tailed  $p = 0.333$ ) or age at seizure freedom (Mann-Whitney  $U$ , 2-tailed  $p = 0.225$ , figure e-2). Furthermore, there was no significant correlation between seizure outcome and cognitive outcome (Fisher exact, 2-sided  $p = 0.486$ ), and no statistical difference between the groups with learning difficulties, mild or moderate ID, and severe to profound ID with regard to age at seizure onset (Mann-Whitney  $U$ , 2-tailed  $p = 0.393$ ), age at seizure freedom (Mann-Whitney  $U$ , 2-tailed  $p = 0.603$ , figure e-3), and duration of seizures (time between seizure onset and seizure freedom or age at inclusion; Mann-Whitney  $U$ , 2-tailed  $p = 0.809$ ).

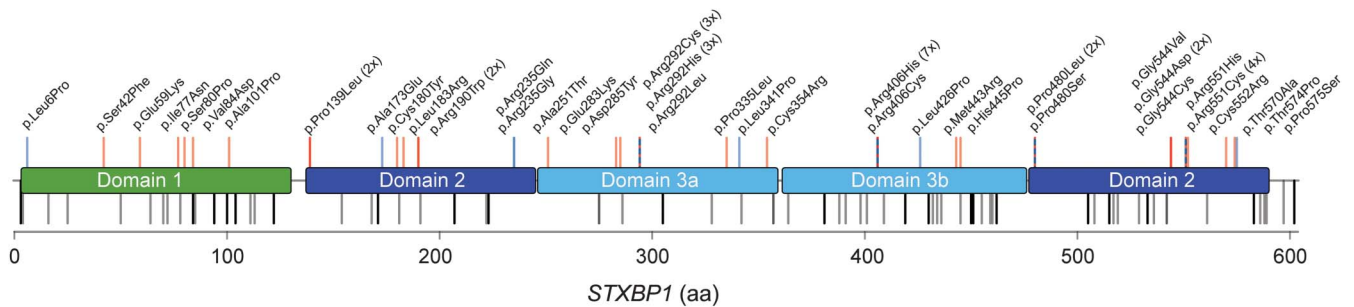
**Frequency of *STXBP1*-E.** Seven Danish children born between 2001 and 2010 were referred to the Danish Epilepsy Centre and diagnosed with *STXBP1*-E. None was treated outside the Epilepsy Centre. According to the 10-year Danish birth cohort from 2001 to 2010, the number of live births in Denmark in this period was 643,039. Based on these numbers, we estimated that the frequency of *STXBP1*-E in the Danish population is at least 1: 91,862.

**DISCUSSION** *STXBP1* plays an important role in vesicular docking and fusion, a necessary mechanism for neurotransmitter secretion. An *STXBP1* knockout mouse model showed that total disruption of *STXBP1* leads to a complete loss of neurotransmitter secretion from synaptic vesicles. *STXBP1* knockout mice further showed neurodegeneration after an initially normal brain assembly, indicating that neurotransmitter secretion, and thus functional *STXBP1*, is important for the maintenance of neuronal synapses.<sup>42</sup> Reduced *STXBP1* expression was further shown to

**Figure 1** Spectrum of *STXBP1*-associated phenotypes

Epilepsy syndrome classification made as of age at onset of seizures. EME = early myoclonic encephalopathy; EOEE = early-onset epilepsy and encephalopathy; ID = intellectual disability; NSE + ID = nonsyndromic epilepsy and intellectual disability; OS = Ohtahara syndrome.

**Figure 2** *STXBP1* missense mutations



*STXBP1* missense mutations located on the protein that consists of 3 domains. There is no obvious clustering in either of the domains. The blue bars represent the previously unreported mutations, the red bars the already published mutations, and the red and blue bars the mutations seen in newly diagnosed and previously reported patients. The gray bars represent the ExAC missense variants reported once, the black the missense variants reported more than once. None of the mutations reported in patients with *STXBP1* encephalopathy is seen in ExAC.

increase synaptic depression at both GABAergic and glutamatergic synapses with a greater impact on GABAergic interneurons.<sup>43</sup> This might result in a net hyperexcitability and epileptic activity in case of *STXBP1* haploinsufficiency.

Over recent years, the phenotypic spectrum of patients with *STXBP1* mutations has expanded. One goal of our study was to assess the phenotypic spectrum of *STXBP1*-E. We found that ID and epilepsy present the 2 major, independent, phenotypic dimensions of *STXBP1*-E. All patients with *STXBP1*-E have some degree of ID, which is severe to profound in almost 90% of patients. Ninety-five percent of patients have epilepsy, although a recruitment bias towards patients with epilepsy might be present in many articles that were reviewed for our study.

Although stagnation of development can be seen at seizure onset, some degree of developmental delay is already present prior to seizure onset in many patients. Regression is rarely seen, and does not always seem to be related to seizure activity. We did not find a relationship between the age at onset or duration of seizures and the degree of intellectual impairment, although the power of our analyses was limited. This reinforces the notion that *STXBP1* plays an important role in many aspects of neurodevelopment and that *STXBP1*-E is not a pure epileptic encephalopathy. A similar, but less evident, observation has been made in other severe genetic epilepsies such as Dravet syndrome.<sup>44</sup> For the purpose of this article, we therefore chose to define EOEE as early-onset epilepsy and encephalopathy, rather than early-onset epileptic encephalopathy.

With regards to the epilepsy phenotype, about one-third of patients present with either Ohtahara or West syndrome. Approximately one-quarter of patients with EOEE or Ohtahara syndrome evolve to West syndrome over time. While most patients do not fulfill precise ILAE criteria for these particular electroclinical syndromes, the majority of the patients

with epilepsy have epileptic spasms or tonic seizures at some point in their disease history. Accordingly, this constellation may be considered the core seizure phenotype of *STXBP1*-E. More than one-third of the patients eventually become seizure-free; however, in some patients, epilepsy remains difficult to control.

The main EEG finding is (multi)focal epileptic activity, while burst-suppression or hypsarrhythmia are seen in approximately one-third of patients. MRI of the brain is normal in almost half of the patients. Nevertheless, cortical atrophy, delayed myelination, and thin corpus callosum are recurrent findings. Since MRI features are partially age-dependent, aberrant MRI findings might be underreported because of the young age of some of the patients reported.

Most patients with *STXBP1*-E present with additional neurologic features after infancy besides ID and epilepsy. Autism or autistic features are present in almost 20% of published cases, but might also be underreported due to the focus of most studies on the epilepsy phenotype. The combination of stereotypes, autistic features, and regression in some patients explains the identification of *STXBP1* mutations in a few patients with atypical Rett syndrome.<sup>37,38</sup> Furthermore, patients with *STXBP1*-E frequently have additional neurologic features, including dyskinesia, dystonia, tremor, (axial) hypotonia, and ataxia, which suggest an impairment of various neurologic systems. Moreover, in our cohort of previously unreported patients, we identified 2 patients with extrapyramidal features at age 20 years. Levodopa-responsive parkinsonism has been described in adult patients with Dravet syndrome.<sup>45</sup> Further studies in adult patients with *STXBP1*-E are warranted to establish the prevalence of parkinsonism at older age, and to study the effect of treatment with levodopa.

Treatment of *STXBP1*-E warrants a multidisciplinary approach, and currently consists of symptomatic treatment of seizures and behavioral and locomotor

problems with physical therapy and occupational therapy to maximize the developmental potential. A good response of epileptic spasms to vigabatrin has been reported in several studies,<sup>7,12,13,19,24,25,37</sup> as has a good effect of valproic acid<sup>12,25</sup> and levetiracetam.<sup>40,46</sup> The latter is an interesting observation given that levetiracetam acts through modulation of synaptic vesicle release.<sup>40,47</sup> However, these beneficial effects are only seen in some selected patients and larger prospective studies are needed to identify the most favorable anti-epileptic treatment regimen for *STXBPI-E*. Improvement of prognosis on both seizure and cognitive outcome may further come from the development of a targeted disease-modifying treatment. For example, protein–protein interaction inhibition has been suggested as a possible therapeutic strategy in *STXBPI* haploinsufficiency.<sup>48</sup> Finally, *STXBPI* was recently shown to play a role in endothelial granule exocytosis, and a significantly impaired histamine and stimulated von Willebrand Factor secretion was observed in a patient with *STXBPI-E*.<sup>49</sup> Although this was insufficient to result in clinical symptoms, this decrease might be a good biomarker to monitor the effect of future targeted therapies.

Both de novo missense mutations and truncating mutations or deletions can lead to *STXBPI-E*. In our analyses, we did not find any correlation between mutation type and the presence of seizures, age at seizure onset, or cognitive outcome. Also taking into account the phenotypic variability seen in patients with some of the recurrent de novo mutations, other factors such as genetic background or environmental factors may play a role in defining the eventual phenotype.

Confirming a pathogenic mutation and making a diagnosis of *STXBPI-E* is not always straightforward. Truncating mutations in *STXBPI* are generally considered to be pathogenic. However, different truncating variants have been described in the ExAC database. All are located at the end of the last exon, outside the last domain 2, while all causative *STXBPI* truncating mutations are positioned prior to this region (figure e-1). Possibly, the truncating ExAC variants escape nonsense-mediated decay and may lead to a functional protein. Moreover, it remains unclear whether the 6 individuals carrying any of the 4 truncating variants are healthy controls or derived from cohorts with late-onset neuropsychiatric disorders who were recruited for ExAC.

Missense variants can be found in both healthy individuals and patients with *STXBPI-E*. Four of the 21 *STXBPI* missense variants occurring more than once in the ExAC database are predicted deleterious by both SIFT and PolyPhen-2 (figure 2), demonstrating the limitations of in silico prediction tools alone for clinical interpretation of missense variants. On the

other hand, one missense mutation, p.His445Pro, identified in a patient with Dravet syndrome, was predicted benign by both SIFT and PolyPhen-2.<sup>27</sup> This variant was classified as pathogenic based on its de novo status. Therefore, interpretation of novel *STXBPI* missense variants will remain challenging in the absence of segregation data.

In this study, we describe 45 previously unreported patients with *STXBPI-E*, resulting in a total of 147 reported patients. These numbers suggest that *STXBPI* mutations are among the most frequent causative mutations in patients with epilepsy and ID next to genes like *SCN1A*, *CDKL5*, *MECP2*, and *KCNQ2*. We estimate a frequency of 1:91,862 in a Danish birth cohort, but this number might be an underestimate since *STXBPI-E* is a heterogeneous condition and some patients may be undiagnosed. We illustrate the phenotypic spectrum of *STXBPI-E* and hypothesize that *STXBPI-E* should be considered a complex neurodevelopmental disorder rather than a primary epileptic encephalopathy.

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## DISCLOSURE

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