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Delineation of epileptic and neurodevelopmental phenotypes associated with variants in *STX1B*

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ABSTRACT

Objective: To further delineate the clinical and genetic spectrum of epileptic and neurodevelopmental conditions associated with variants in *STX1B*.
Methods: We screened our diagnostic in-house database (comprising >20,000 exome sequencing datasets) for pathogenic and likely pathogenic variants in*STX1B*. The detected cases were phenotyped in detail, and the findings were compared to previously published case reports.
Results: We identified four unrelated individuals with pathogenic or likely pathogenic variants in *STX1B* (one missense and three loss-of-function variants). All patients displayed epileptic phenotypes, including epileptiform discharges on electroencephalography (without apparent seizures), developmental and epileptic encephalopathy and focal epilepsy. Three of the four patients had developmental delay. Febrile seizures occurred in two individuals. One patient with focal epilepsy underwent epilepsy surgery without lasting improvement. The neuropathological workup of brain tissue revealed a mild malformation of cortical development without alterations of cortical lamination or dysplastic neurons.
Conclusions: Our findings confirm the wide clinical range of*STX1B*-related epileptic conditions and highlight the necessity of genetic testing prior to epilepsy surgery in cases with monogenic epilepsy. The identification of loss-of-function variants in very differently affected individuals suggests that no clear genotype-phenotype correlation can be established.

1. Introduction

Monogenic epilepsies represent a clinically and genetically heterogeneous group of disorders. While initial gene discoveries mainly implicated ion channel dysfunction, the advent of genomic screening led to the identification of additional mechanisms, including molecular defects of synaptic transmission [1].

One of the involved genes, *STX1B* (MIM: *601485), encodes a presynaptic protein (syntaxin-1B) which is part of the SNARE (soluble N-ethylmaleimide-sensitive-factor attachment receptor) complex and therefore crucially involved in calcium-dependent vesicle release [2].

Inherited and *de novo* variants in *STX1B* were first identified in pedigrees with fever-associated epilepsy syndromes, either presenting as genetic epilepsies with febrile seizures plus (GEFS+) or as developmental and epileptic encephalopathies (DEE) [3]. Subsequently, one patient with myoclonic-astatic epilepsy (MAE) and intellectual disability was reported [4]. A recently published analysis of 23 families (a total of 49 patients) ascribed four phenotypic subgroups of epileptic disorders to

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pathogenic variation in *STX1B*. The spectrum comprised (1) GEFS+, (2) genetic generalized epilepsy (GGE), (3) DEE with moderate to severe developmental delay, and in rare cases (4) focal epilepsy. Moreover, it has been suggested that (mostly *de novo*) missense variants may be associated with more severe neurodevelopmental and epileptic phenotypes, while truncating (loss-of-function) variants may rather lead to benign epilepsies [5].

Given the heterogeneous clinical spectrum of *STX1B*-related epilepsy, the number of published patients is still too low to fully appreciate its complexity. With the aim to stepwise delineate the wide range of associated phenotypes, we here describe the detailed clinical and genetic findings of four unrelated individuals with epileptic disorders related to causative variants in *STX1B*.

2. Patients and methods

2.1. Probands and samples

All patients (Patients 1–4) were examined by neurologists or neuropediatricians at the respective referring sites. The clinical work-up comprised a neurological examination, brain magnetic resonance imaging (MRI) and electroencephalography (EEG) recordings. Patient 3 underwent epilepsy surgery with a subsequent neuropathological workup of resected brain tissue (right temporal lobe). The same patient was also included in a previously published diagnostic exome sequencing (ES) study [6].

Patients or their legal guardians signed written informed consent for genetic analyses and the publication of findings. The study was conducted according to the declaration of Helsinki and approved by the ethics committee of the Technical University Munich, Germany.

2.2. Exome sequencing

Exome sequencing was performed at the Institute of Human Genetics of the Helmholtz Center Munich, Germany, as reported previously [7]. In brief, exonic regions were captured and enriched using a *SureSelect Human All Exon* V6 (60Mb) Kit (Agilent, Santa Clara, California, USA). DNA fragments were sequenced as 100bp paired-ends runs on *Illumina* HiSeq 4000 or NovaSeq 6000 systems (Illumina, San Diego, California, USA). Mean average coverage was at least 100-fold in all samples with (likely) pathogenic variants in *STX1B*. Variants were filtered based on minor allele frequency (MAF), which was estimated using our in-house database comprising >20,000 exome datasets and confirmed using the gnomAD database [8]. The standard criteria of the American College of Medical Genetics and Genomics (ACMG) were applied for variant interpretation [9].

3. Results

3.1. Clinical findings

Two patients displayed a DEE phenotype with multiple seizure types and global developmental plateauing or regression, one had treatment-refractory temporal lobe epilepsy (TLE) without any developmental abnormalities, and one had a neurodevelopmental disorder with epileptiform EEG findings but no reported epileptic seizures. Fever- or infection-related seizures were present in two of four patients (one with DEE and one with TLE). Age of seizure onset ranged from 3 to 9 years. Three of the four individuals (Patients 2–4) experienced epileptic seizures that were refractory to multiple treatment trials, including antiseizure medications (ASM), modified Atkins diet, steroid treatment, epilepsy surgery and deep brain stimulation (DBS). Apart from temporal pole/lobe hypoplasia in the patient with TLE, no MRI abnormalities were detected in our cohort. However, two individuals (Patients 1 and 4) had additional neurological features, including dyspraxia, dysphagia, dyskinesia and ataxia.

3.2. Genetic findings

A pathogenic or likely pathogenic variant in *STX1B* (NM_052874.3) was identified in all reported individuals. This included one missense variant (c.293G>A, p.(Ser98Asn)), one canonical splice-site variant (c.537+1G>A, p.(?)) and two frameshift variants (c.165dup, p.(Gln56Thrfs*3); c.642_643dup, p.(Phe215Cysfs*9)). In three of the four variants a *de novo* origin could be confirmed, while no parental blood samples were available in one case (Patient 3). All four reported variants were absent from gnomAD and our in-house database.

The main clinical characteristics of the four reported individuals are summarized in Table 1. All variants and core phenotypes of previously reported and novel patients are summarized in Fig. 1.

3.3. Individual patient characteristics

Patient 1: This currently 7-year-old girl was born in Iraq as the first of three children of distantly related parents. Two siblings are reportedly healthy. As the family moved to Germany when the patient was 5 years old, no detailed documents reporting the previous medical history are available. Global developmental delay was noted early on, but initially attributed to perinatal hypoxia. An examination at 7 years showed growth retardation and microcephaly. Additionally, the patient had facial hypotonia, hearing difficulties and severe speech impairment. No epileptic seizures were reported, but EEG revealed spikes and spike-and-wave discharges with a parietal maximum. A neurological examination showed brisk tendon reflexes, dysarthria, dysphagia with hypersalivation and a dyskinetic movement disorder with an ataxic component, for which a treatment with levodopa was initiated. The patient currently attends a special needs school and at last follow-up, she was not taking any medication but received physiotherapy, occupational and speech therapy.

Trio ES identified a heterozygous *de novo* missense variant c.293G>A, p.(Ser98Asn) in *STX1B*, leading to the exchange of a conserved amino acid, which was classified as likely pathogenic. In addition, a pathogenic homozygous splice-site variant c.258+2T>C was found in *SBDS*, the gene associated with Shwachman-Diamond syndrome. Epileptiform discharges on EEG and developmental delay can be explained by the *STX1B* variant, while short stature and microcephaly are more likely associated with *SBDS*.

Patient 2: This 7-year-old girl was born as the second child of unrelated parents. After an unremarkable pregnancy and birth, she learned to sit unaided at the age of 9 months and to walk at the age of 16 months. At 2 years of age, she spoke one-word sentences. Just before her third birthday, she experienced a febrile seizure (FS) directly following tick-borne encephalitis vaccination. Subsequently, she developed additional FS as well as afebrile myoclonic, astatic, absence and bilateral tonic-clonic seizures (BTCS). They could only be poorly controlled by various ASM, including levetiracetam, lacosamide, lamotrigine, clobazam, zonisamide and ethosuximide. Under valproic acid she developed a hepatopathy. Aside from ASM, a modified Atkins diet and steroid treatment did not lead to significant improvements. EEG recordings showed generalized epileptic discharges (spike-waves with a frontal maximum), high-voltage slowing and intermittent paroxysmal activity. At 3 years of age, she experienced status epilepticus which was successfully treated with benzodiazepines and phenobarbital. At the age of about 4 years, the family decided to withdraw the recommended treatment. At last follow-up, the girl has suffered ongoing seizures several times per week. After seizure onset, a regression of neurodevelopment (including speech) was noted. Given the combination of treatment-refractory seizures and developmental regression, she was eventually diagnosed with DEE.

Trio ES led to the identification of the pathogenic heterozygous *de novo* frameshift variant c.165dup, p.(Gln56Thrfs*3) in *STX1B*. The variant is predicted to result in a truncated protein.

Patient 3: In this 45-year-old male patient, pregnancy, birth and

Table 1
Summary of clinical and genetic characteristics of the 4 reported patients with *STX1B*-related epileptic disorders.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Female	Male	Female
Current age	7 years	7 years	45 years	15 years
Febrile (infection- or vaccination-related) seizures	None	Yes, first FS following vaccination	Yes, first seizure during flu-like illness	None
Age of seizure onset	No reported seizures	3 years	9 years	3 years
Neurodevelopment	Global developmental delay, severe language delay	Developmental delay and regression (pronounced language delay)	Normal	Global developmental delay
Epilepsy syndrome	Unclassified neurodevelopmental disorder	DEE (LGS/MAE)	Focal epilepsy (TLE)	DEE (LGS)
Seizure types	No reported seizures	BTCS, absences, myoclonic and atonic seizures	BTCS, auras (dizziness), dyscognitive seizures	BTCS, myoclonic and atonic seizures, dyscognitive seizures
EEG findings	Parietal spikes and spike-and-wave discharges	Generalized spike-waves (with bifrontal maximum), high-voltage slowing and intermittent paroxysmal activity	Focal temporal spikes (right > left), ictal: right seizure origin, after temporal lobe resection left hemispheric onset	Multifocal spike-wave and poly-spike-wave activity
MRI brain	N/A	Normal	Right temporal lobe/temporal pole hypoplasia	Normal
Additional findings	Dysphagia, dysarthria, dyskinesia, ataxia, microcephaly	None	Brain histology: mMCD	Gait ataxia
Epilepsy treatment and outcome	No ASM – no apparent seizures	LTG, ESM, CLB, DZP, LCM, LEV, MDZ, VPA, PB, RUF, PHT, ZNS, CZP, modified Atkins diet, steroid infusions – treatment-refractory	CBZ, LTG, LEV, LCM, VPA, CLB, OXC, PRM, PER, ESL, BRV, epilepsy surgery, DBS – treatment-refractory	VPA, CLB, LTG, RUF, ZNS, LEV, PER – treatment-refractory
Detected variant in *STX1B* (NM_052874.3)	c.293G>A, p.(Ser98Asn) *de novo*	c.165dup, p.(Gln56Thrfs*3) *de novo*	c.537+1G>A, p.(?) inheritance not determined	c.642_643dup, p.(Phe215Cysfs*9) *de novo*
Variant classification according to ACMG	Likely pathogenic	Pathogenic	Likely pathogenic	Pathogenic

ACMG = American College of Medical Genetics and Genomics, ASM = anti-seizure medication, BRV = brivaracetam, BTCS = bilateral tonic-clonic seizures, CBZ = carbamazepine, CLB = clobazam, CZP = clonazepam, DBS = deep brain stimulation, DEE = developmental and epileptic encephalopathy, DZP = diazepam, EEG = electroencephalography, ESL = eslicarbazepine, ESM = ethosuximide, FS = febrile seizure, LCM = lacosamide, LEV = levetiracetam, LGS = Lennox-Gastaut syndrome, LTG = lamotrigine, MAE = myoclonic-astatic epilepsy, MDZ = midazolam, mMCD = mild malformation of cortical development, MRI = magnetic resonance imaging, N/A = not applicable, OXC = oxcarbazepine, PB = phenobarbital, PER = perampanel, PHT = phenytoin, PRM = primidone, RUF = rufinamide, TLE = Temporal lobe epilepsy. VPA = valproic acid, ZNS = zonisamide.

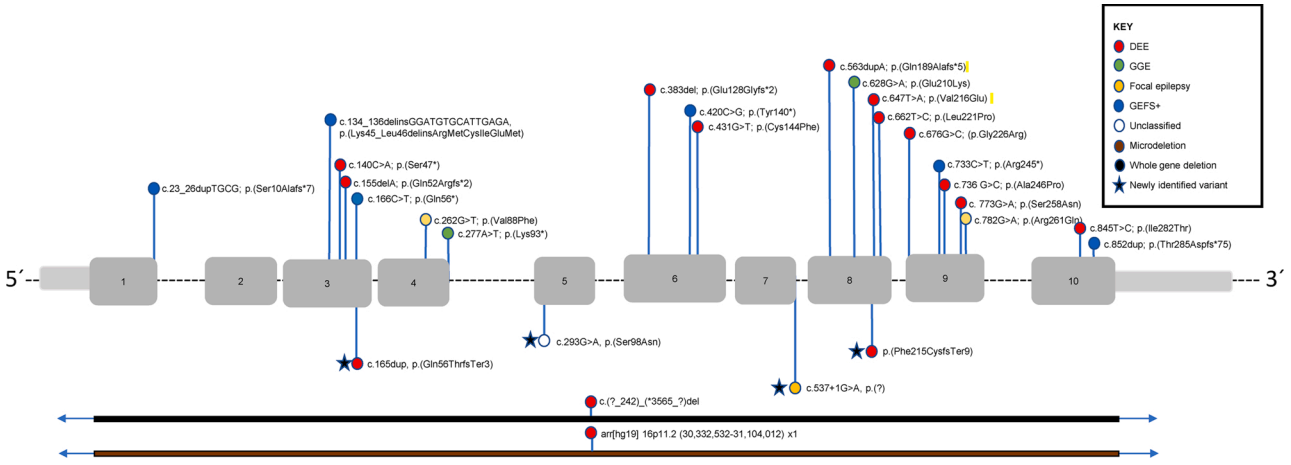

Fig. 1. Overview of pathogenic and likely pathogenic variants in *STX1B*.
Schematic overview and distribution of previously reported and novel (likely) pathogenic variants in *STX1B* (exons 1–10). The colors either indicate the associated epilepsy phenotypes, developmental and epileptic encephalopathy (DEE), genetic generalized epilepsy (GGE), focal epilepsy, genetic epilepsy with febrile seizures plus (GEFS+), or the type of deletion. Variants reported in this study are marked with a blue asterisk. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

psychomotor development were reported as normal. He went to school, passed his A-levels and started to work for a security company. Apart from meningitis at the age of 6 years, no general medical problems were reported. He has three healthy siblings, and the family history is unremarkable for epilepsy. At age 9, he experienced the first BTCS during a flu-like illness. He subsequently developed auras with dizziness either evolving into focal seizures with impaired awareness or directly into BTCS. In addition, the patient had BTCS during sleep and focal seizures with impaired awareness at night. On average, he experienced several seizures per month. Multiple ASM trials (carbamazepine, lamotrigine, levetiracetam, lacosamide, valproic acid, clobazam, oxcarbazepine, primidone) were ineffective. Video-EEG monitoring at the age of 31

years led to the diagnosis of non-lesional bilateral TLE (bitemporal spike distribution, predominantly right temporal seizure onset with propagation to the left hemisphere). Three years later, a reevaluation with video-EEG monitoring showed a right temporal seizure onset and right temporal spikes. A high-resolution MRI scan of the brain showed right temporal lobe/temporal pole hypoplasia. In view of these results, the patient underwent right anterior temporal lobectomy at age 35. The neuropathological analysis (Fig. 2) of resected brain tissue revealed microscopic neuronal clusters or small glioneuronal lesions in white matter (1 mm) that were not grossly visible. In addition, excessive neurons within the molecular layer of the temporal cortex without alterations of radial or tangential cortical lamination and without dysplastic features (i.e., mild malformation of cortical development, mMCD) were identified [10]. Moreover, chronic epilepsy-associated changes with band-like subpial gliosis (Chaslin gliosis) were observed. Epilepsy surgery did not result in a reduction of seizures. Aged 38, the patient underwent a second presurgical reevaluation, which revealed a left hemispheric seizure onset. Therefore, he was included in a clinical trial using DBS as a palliative therapeutic option which again did not lead to an ongoing improvement in seizure frequency. At last follow-up (age 45), he reported five to 15 seizures per month under a treatment with brivaracetam, lacosamide, valproic acid, eslicarbazepine and clobazam.

Singleton ES revealed the heterozygous canonical splice-site variant c.537+1G>A in *STX1B*, which was classified as likely pathogenic. As the parents were not available for genetic testing, inheritance could not be determined.

Patient 4: In this currently 15-year-old girl, pregnancy and birth were reported as normal. The family history was unremarkable, and she has three healthy half-brothers. Developmental delay was noted early on, as she was only able to walk a few steps at the age of 2 and started speaking at the age of 3 years. Global developmental delay was confirmed by neuropsychological testing. An MRI scan of the brain was normal. Focal seizures with impaired awareness first occurred at the age of 3 years, sometimes evolving into BTCS. Further, atonic and myoclonic seizures were observed, and she additionally developed gait ataxia. EEG showed multifocal spike-wave and poly-spike-wave activity. Seizures were refractory to treatment with numerous ASM such as valproic acid, clobazam, lamotrigine and levetiracetam, used as monotherapy or in combination. Aged 15 years now, she attends a special needs school and receives an ASM regimen including rufinamide, perampanel and zonisamide. Nonetheless, she experiences one to three seizures per month. Based on clinical and EEG findings, she was eventually diagnosed with DEE (LGS).

Trio ES identified a heterozygous *de novo* frameshift variant c.642_643dup, p.(Phe215Cysfs*9) in *STX1B*, which was classified as pathogenic.

4. Discussion

In this study, we report four unrelated patients with different epileptic and neurodevelopmental phenotypes associated with diagnostic variants in *STX1B*, thus further delineating the clinical and molecular spectrum of this rare monogenic condition.

From a phenotypic standpoint, the clinical presentations of our patients overlap with the so far largest cohort of *STX1B*-related epilepsies that included GEFS+, DEE, GGE and focal epilepsy in its spectrum [5]. However, in our report, one individual (Patient 1) did not suffer from apparent epileptic seizures. Therefore, we hypothesize that pathogenic variants in *STX1B* do not invariably lead to clinically manifest epilepsy. Yet, we acknowledge that phenotypic information is scanty for this patient, so that especially subtle seizures before the age of 5 years cannot be excluded based on history taking alone. Further, the presence of a second genetic diagnosis bedevils the ascription of specific clinical features to either *STX1B* or *SBDS*. However, epileptiform discharges detected by EEG in the same individual indicate that epileptic activity – ranging from isolated EEG abnormalities to severe treatment-refractory seizures – represents the core phenotype shared between the so far reported patients with *STX1B* variants [3–5].

Moreover, it has already been noted that the age of seizure onset is

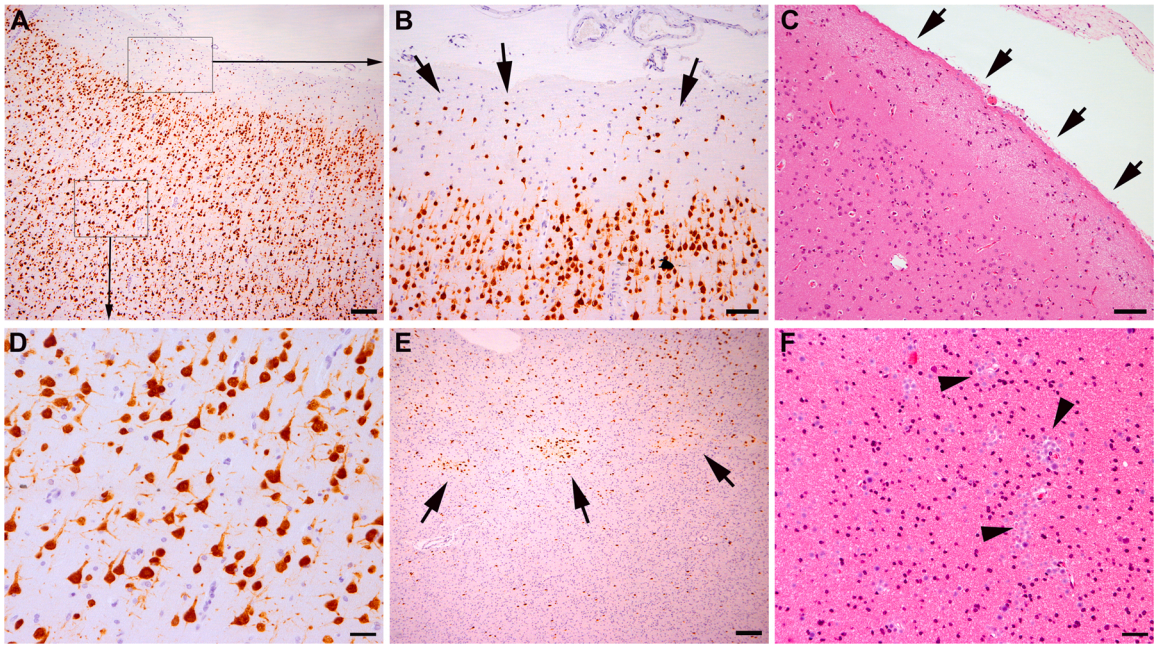

Fig. 2. Neuropathological workup of resected temporal lobe tissue in *STX1B*-related focal epilepsy (Patient 3) showing a mild malformation of cortical development. A: Overview of cortical lamination (immunohistochemistry for NeuN). A regular 6-layered cortex is observed. However, there is an increase of neurons in molecular layer (upper box and B, arrows). There is also a band of subpial gliosis (C, arrow), as frequently observed in chronic epilepsy. No dysmorphic/dysplastic neurons are identified at higher magnification (D). In the white matter, there is also an increase of non-migrated neurons as well as small nests of smaller neurons (E, arrows). There is also an increase of corpora amylacea (F), which is frequently observed in chronic epilepsy.
Scale bars: 100 μm in A and E; 50 μm in B and C; 20 μm in D and F.

later in *STX1B* when compared to most other infantile monogenic epilepsies, including *STXBP1*, which is a direct interaction partner of *STX1B* [5,11]. This is also in concordance with our findings, as two DEE patients experienced the first seizure at the age of 3 years and the TLE patient not before the age of 9 years. Albeit rare, it can be concluded that causative mutations in *STX1B* should also be considered in the genetic-diagnostic workup of adult patients with epilepsy [12].

Most notably, we provide the first report of a patient with *STX1B*-related epilepsy that underwent epilepsy surgery. There is already anecdotal evidence suggesting that patients with genetic defects of ion channel function (e.g., *SCN1A*) and synaptic transmission (e.g., *STXBP1*) show a poor postoperative outcome [13]. Interestingly, this is in line with our observations in Patient 3, who showed a treatment-refractory disease course even after anterior temporal lobectomy and palliative DBS. In all three of our reported patients with apparent epileptic seizures, multiple therapeutic trials were used without lasting success, thus highlighting difficult-to-treat epilepsy as a major challenge in *STX1B*-related disorders.

A large proportion of such treatment-resistant genetic epilepsies show additional structural malformations in some patients [14]. However, in *STX1B*, brain imaging did not reveal any structural epileptogenic lesions in the patients reported to date [5]. To our knowledge, no neuropathological analyses of brain tissue have been reported so far. *STXBP1*, the only established epilepsy gene inextricably related to *STX1B*, has been associated with MRI-negative focal cortical dysplasia (FCD) type 1a in one case [15]. Our work for the first time shows neuropathological alterations in a patient with *STX1B*-related epilepsy, revealing signs of mMCD with microscopic neuronal clusters in the deep white matter or small hamartia and excessive heterotopic neurons in layer I of the temporal cortex, without alterations of the radial or tangential lamination and without dysplastic neurons. However, the clinical relevance of these morphological changes is still unclear, and further replication studies are required to clarify a definite association between *STX1B* and structural brain abnormalities.

We also have to affirm that there generally remains a degree of uncertainty with regard to genetic variant interpretation. As in our study, variants classified as pathogenic or likely pathogenic (according to ACMG criteria) are usually considered causative and therefore used for clinical decision making. However, it has been shown that more than 99 % of likely pathogenic variants that eventually reach a definitive ACMG classification status, change to pathogenic [16].

Furthermore, it is still widely unclear to what extent genotypic information may be useful to predict the clinical course of *STX1B*-related conditions. The analysis of previous cases led to the hypothesis that missense variants may rather lead to more severe, encephalopathic phenotypes (presumably through a dominant-negative effect), whereas truncating mutations (resulting in haploinsufficiency) may more often be associated with benign epilepsies [5]. However, our observations argue against this proposition as a general rule. The so far only reported patient with no clear evidence of epileptic seizures carried a *de novo* missense variant, while all three cases with intractable seizures were caused by loss-of-function mutations. The three truncating variants were found in clinically very differently affected patients, suggesting that a clear genotype-phenotype correlation cannot be established. However, it still remains open to speculation what exactly causes this clinical heterogeneity. Recently, a thorough functional analysis of different disease-causing *STX1B* mutations pointed towards remarkably different molecular phenotypes of neuronal dysfunction depending on specific variants [17].

Taken together, our report substantiates the clinical heterogeneity of *STX1B*-related disorders, with epileptic activity being the core clinical feature. The first detailed neuropathological analysis of brain tissue suggests that subtle subcortical heterotopia may be part of the phenotypic spectrum of *STX1B*-related disease. In synopsis with previous data, it can also be assumed that epilepsy surgery does not represent a promising therapeutic approach for refractory focal epilepsy associated with *STX1B*.

Declaration of Competing Interest

The authors declare that they have no conflict of interest related to the content of this article.

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