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REVIEW

SPTAN1 encephalopathy: distinct phenotypes and genotypes

Jun Tohyama[1,2], Mitsuko Nakashima[3], Shin Nabatame[4], Ch'ng Gaik-Siew[5], Rie Miyata[6], Zvonka Rener-Primec[7], Mitsuhiro Kato[8], Naomichi Matsumoto[3] and Hirotomo Saitsu[3]

Recent progress in genetic analysis reveals that a significant proportion of cryptogenic epileptic encephalopathies are single-gene disorders. Mutations in numerous genes for early-onset epileptic encephalopathies have been rapidly identified, including in *SPTAN1*, which encodes α-II spectrin. The aim of this review is to delineate *SPTAN1* encephalopathy as a distinct clinical syndrome. To date, a total of seven epileptic patients with four different in-frame *SPTAN1* mutations have been identified. The major clinical features of *SPTAN1* mutations include epileptic encephalopathy with hypsarrhythmia, no visual attention, acquired microcephaly, spastic quadriplegia and severe intellectual disability. Brainstem and cerebellar atrophy and cerebral hypomyelination, as observed by magnetic resonance imaging, are specific hallmarks of this condition. A milder variant is characterized by generalized epilepsy with pontocerebellar atrophy. Only in-frame *SPTAN1* mutations in the last two spectrin repeats in the C-terminal region lead to dominant negative effects and these specific phenotypes. The last two spectrin repeats are required for α/β spectrin heterodimer associations and the mutations can alter heterodimer formation between the two spectrins. From these data we suggest that *SPTAN1* encephalopathy is a distinct clinical syndrome owing to specific *SPTAN1* mutations. It is important that this syndrome is recognized by pediatric neurologists to enable proper diagnostic work-up for patients.
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INTRODUCTION

Early-onset epileptic encephalopathies (EOEEs) are neurological disorders in children characterized by frequent severe seizures and persistent abnormality of cortical function, which can be documented on electroencephalograms (EEGs). These features lead to impaired neurodevelopmental outcomes during neonatal or early infantile periods and beyond.[1,2] The clinical and EEG characteristics depend on the age at onset and may change over time according to the successive age range.[3] These serious conditions during the first 6 months after birth include early myoclonic encephalopathy, Ohtahara syndrome, West syndrome, migrating partial seizure in infancy and unclassified infantile epileptic encephalopathy. In patients with West syndrome and Ohtahara syndrome, structural brain malformations, inborn errors of metabolism and acquired brain insults are the major underlying causes. After the initial identification of mutations for cryptogenic West syndrome and Ohtahara syndrome, in the genes *ARX*, *CDKL5* and *STXBP1*,[4–8] numerous other mutated genes for West syndrome and Ohtahara syndrome have been found,[9–14] revealing that a significant proportion of cryptogenic EOEEs are single-gene disorders. Recent progress in DNA sequencing technologies has undoubtedly contributed to this progress. This enables the rapid detection of point mutations, and *de novo* mutations can be systematically identified by family based exome sequencing.[15] In the future, comprehensive genetic analysis will come into widespread use in clinics, which will contribute greatly for the further elucidation of EOEE genetics. However, at present, the genetic diagnosis of EOEEs remains challenging; therefore, more detailed studies of EOEEs are needed to establish efficient gene testing based on detailed clinical information of EOEEs.[2,16,17]

In 2010, we found *de novo* in-frame mutations in *SPTAN1* in two patients showing early-onset West syndrome with severe hypomyelination and developmental delay.[18] *SPTAN1* at 9q34.11 consists of 53 exons and encodes α-II spectrin, which is essential for proper myelination in zebrafish.[19] The phenotypes of patients with *SPTAN1* mutations are not well recognized because the number of identified patients is small despite extensive genetic testing of epileptic encephalopathy cases. This review aims to: (1) describe the electroclinical and neuroradiological features of patients with *SPTAN1* mutations; (2) delineate *SPTAN1* encephalopathy as a distinct clinical syndrome with specific genotypes and (3) lead clinicians towards the efficient and appropriate choice of genetic testing.

[1]Department of Child Neurology, Nishi-Niigata Chuo National Hospital, Niigata, Japan; [2]Niigata University Medical and Dental Hospital, Niigata, Japan; [3]Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [4]Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan; [5]Department of Genetics, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia; [6]Department of Pediatrics, Tokyo Kita-Social Insurance Hospital, Tokyo, Japan; [7]Department of Pediatric Neurology, University Children's Hospital, Ljubljana, Slovenia and [8]Department of Pediatrics, Yamagata University Faculty of Medicine, Yamagata, Japan
Correspondence: Dr J Tohyama, Department of Child Neurology, Nishi-Niigata Chuo National Hospital, 1-14-1 Masago, Nishi-ku, Niigata 950-2085, Japan.
E-mail: jtohyama@masa.go.jp
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IDENTIFICATION OF *DE NOVO SPTAN1* MUTATIONS

In 2008, we reported four patients showing early-onset West syndrome with cerebral hypomyelination and reduction of cerebral white matter, as observed by magnetic resonance imaging (MRI).[20] Among these patients, we identified a *de novo* microdeletion at 9q33.3–q34.11 involving *STXBP1* and *SPTAN1* in one patient and *de novo* in-frame mutations in *SPTAN1* in two patients,[18] including an in-frame 3 bp deletion (c.6619_6621 del) leading to p.E2207 del in the continuous helix region between the last two spectrin repeats and an in-frame 6 bp duplication (c.6923_6928 dup, p.R2308_M2309 dup) within the last spectrin repeat. An additional four patients with *de novo* in-frame *SPTAN1* mutations within the last spectrin repeat were subsequently identified in Slovenian,[21] Japanese[22] and Malaysian patients with West syndrome (c.6619_6621 del; p.E2207 del in the Slovenian patient, and c.6908_6916 dup; p.D2303_L2305 dup in two Japanese patients and one Malaysian patient). The Malaysian patient (subject 5) and one Japanese patient (subject 6) are presented here for the first time. Three patients (subjects 3, 4 and 6) were suspected as having *SPTAN1* mutations based on the clinical features consistent with the initial report. Whole-exome sequencing (WES) unexpectedly revealed a *SPTAN1* mutation in subject 5, in whom a *SPTAN1* mutation was never suspected. In addition to West syndrome, Hamdan *et al.*[23] identified an in-frame *de novo SPTAN1* mutation (c.6605_6607 del; p.Q2202 del) within the continuous helix region between the last two spectrin repeats in a patient with generalized epilepsy, intellectual disability (ID) and pontocerebellar atrophy. A total of seven epileptic patients with four different in-frame *SPTAN1* mutations have been identified to date. Interestingly, Hamdan *et al.*[23] also reported a *de novo* p.R566P mutation in a patient with mild nonsyndromic ID without epilepsy. The pathological significance of this missense mutation is unclear because the patient's sister, who has similar clinical features, does not carry the *SPTAN1* mutation.[23] Therefore, in this review, we are focusing on patients with in-frame *SPTAN1* mutations, who showed epileptic encephalopathy or epilepsy.

It is notable that no *SPTAN1* mutations were detected through genetic screening by WES or whole-genome sequencing in epileptic encephalopathy cases[24–27] or in patients with ID.[28] This suggests that patients with *SPTAN1* mutations are quite rare. Alternatively, it is possible that in-frame mutations were not considered as pathogenic in the routine WES workflow. The recognition of clinical and neuroradiological features characteristic of in-frame *SPTAN1* mutations means that such in-frame mutations should not be overlooked when carrying out WES analysis for epileptic encephalopathy.

CLINICAL FEATURES

Among the seven individuals with *SPTAN1* mutations, six patients showed West syndrome symptoms since early infancy and one patient showed generalized epilepsy during childhood. With respect to the six patients with West syndrome, all patients were born at term without asphyxia. Their body weight, height and head circumference at birth were normal, but postnatal microcephaly was noted in all six patients. The range of microcephaly was under the 3rd centile at their respective follow-up ages (Table 1). Three patients showed spastic tetraplegia and the other three showed hypotonia during the neonatal period, which evolved to spastic tetraplegia with generalized hypotonia. All patients were blind, and one patient had coloboma-like optic discs. No apparent abnormality of visceral organs was observed except for atrial septal defect in one patient. At an age of 2 years, they were bedridden and needed tube feeding, except for the youngest patient. All had profound ID and spoke no meaningful words. Two patients passed away at 2 and 3 years of age.

Seizures were characterized by epileptic spasms, which appeared from 3 weeks to 3 months of age. Two patients suffered myoclonic seizures, three patients tonic seizures and one patient asymmetric tonic seizures. In addition, one patient showed neonatal seizures. These seizures were refractory to various antiepileptic and hormonal therapies. In two patients, adrenocorticotrophic hormonal therapy was partially effective, and another patient partially responded to a ketogenic diet.

In contrast, one male patient with generalized epilepsy showed a much milder phenotype. Although he had severe ID and spoke no meaningful words, he could sit alone without support. He did not show postnatal microcephaly. His seizure that developed at 2 years of age consisted of generalized tonic–clonic seizures and absence seizures, which were well controlled by valproic acid.

Detailed clinical information of individuals is summarized in Table 1.

ELECTROENCEPHALOGRAM AND LABORATORY FINDINGS

In all six patients with West syndrome, EEGs showed hypsarrhythmia or modified hypsarrhythmia. EEGs in two patients initially showed multifocal spikes that evolved to hypsarrhythmia. No patient showed a suppression-burst pattern, even though the seizure onset was at early infancy. In contrast, interictal EEG was normal in the one milder variant.

No specific laboratory findings were determined in relation to this disease. Routine hematological and chemical examinations were normal in all patients. Cerebral spinal fluid analysis showed no abnormality, including amino-acid and lactate analysis. Metabolic screening tests were negative, including analysis of plasma amino acids, urine organic acids, and blood lactate and pyruvate. Chromosome analysis of peripheral blood lymphocytes showed normal karyotypes.

NEURORADIOLOGICAL FINDINGS

Initially, we noted that hypomyelination and reduced volume of white matter are characteristic features of this syndrome. By taking account of the neuroradiological findings of additional patients, it turned out that atrophy/hypoplasia of the brainstem and cerebellum is also the hallmark of patients with *SPTAN1* mutations.

All six patients with West syndrome showed severe hypomyelination, hypoplasia of the corpus callosum, cortical atrophy, and atrophy of the brainstem and cerebellum. In addition, five patients showed marked attenuation of white matter volume in combination with hypomyelination, especially in the frontal lobes. These findings were sometimes misdiagnosed as influences of severe hypoxia. Follow-up study in four patients was able to demonstrate that atrophy of the brain was progressive and myelination of the hemispheric white matter had never commenced. No migrational abnormality was observed. The patient with generalized epilepsy showed only atrophy of the brainstem and cerebellum without involvement of the cerebrum. Calcification was not observed by computed tomography.

Characteristic MRI pictures of individuals are presented in Figure 1.

ROLE OF SPECTRINS

Spectrins are considered to be membrane skeletons involved in the stabilization of membrane proteins and activation of membrane channels, receptors and transporters.[29–31] The spectrin repertoire in humans includes two α subunits and five β subunits. Spectrins are long flexible molecules consisting of α and β subunits, which are assembled in an antiparallel side-by-side manner into heterodimers.[29,30] Heterodimers form by end-to-end tetramers

Table 1 Summary of clinical features in seven individuals

Subject	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Sex	F	M	F	M	F	M	M
Nationality	Japanese	Japanese	Slovenian	Japanese	Malaysian	Japanese	Canadian
Mutation	c.6619_6621 del p.E2207 del *De novo*	c.6923_6928 dup p.R2308_M2309 dup *De novo*	c.6619_6621 del p.E2207 del *De novo*	c.6908_6916 dup p.D2303_L2305 dup *De novo*	c.6908_6916 dup p.D2303_L2305 dup *De novo*	c.6908_6916 dup p.D2303_L2305 dup *De novo*	c.6605_6607 del p.Q2202 del *De novo*
Dx	West syndrome	West syndrome	West syndrome	West syndrome	West syndrome	West syndrome	Generalized epilepsy
Age at onset	2 months	3 months	1 month	1 month	3 weeks	1 day	2 years
Initial symptoms	No visual contact	No visual contact	No visual contact	Failure to thrive	Seizure	Seizure, apnea	Seizure
Seizure type	Spasms, tonic sz	Spasms, tonic sz	Myoclonic sz, spasms, tonic sz	Spasms	Spasms	Spasms, myoclonic sz, asymmetric tonic seizure	Generalized tonic–clonic sz, absence
Age at onset of seizure/spasms	3 months	3 months	2 months	3 months	3 weeks	4 months (spasms)	2 years
Initial EEG	Hypsarrhythmia	Hypsarrhythmia	Focal spikes	Hypsarrhythmia	Multifocal spike	NA	Normal
Age at onset hypsarrhythmia	3 months	4 months	4 months	3 months	2 years[a]	4 months	—
Response to therapy	Intractable, daily	Intractable, daily	Intractable, daily	Intractable, daily	Intractable, daily	Intractable, daily	Good
Effective treatment	—	Clobazam partially effective	Topiramate and ketogenic diet partially effective	ACTH partially effective	—	ACTH partially effective	Valproic acid
Development	No head control, no social contact	No head control, no social contact	No head control, no social contact	No head control, no social contact	No head control, no social contact	No head control, no social contact	Sitting, no word
Neurologic examination	Profound ID, spastic quadriplegia	Profound ID, spastic quadriplegia	Profound ID, spastic quadriplegia with hypotonia	Profound ID, spastic quadriplegia, dystonia	Profound ID, spastic quadriplegia with hypotonia, dystonia	Profound ID, spastic quadriplegia with hypotonia	Profound ID, hypotonia
OFC at birth (cm)	31.5 (10th centile)	33 .0 (25–50th centile)	34.0 (25th centile)	31.5 (10th centile)	34.0 (75th centile)	32.4 (10–25th centile)	NA
Postnatal OFC (cm)	46.5 (3rd centile>) at 143 months	42.4 (3rd centile >) at 36months	44.5 (2nd centile>) at 40 months	41.5 (3rd centile>) at 12 months	42.0 (3rd centile>) at 24 months	44.8 (3rd centile>) at 70 months	56.0 (90–97th centile) at 11 years
Others	—	Myocarditis	Coloboma	Atrial septal defect	—	—	—
Magnetic resonance imaging	Cortical atrophy, thin CC, hypomyelination, atrophy of cbll and brainstem (at 8 years old)	Cortical atrophy, thin CC, hypomyelination, atrophy of cbll and brainstem (at 3 years old)	Cortical atrophy, thin CC, hypomyelination, atrophy of cbll and brainstem (at 3 months old)	Cortical atrophy, thin CC, hypomyelination, atrophy of cbll and brainstem (at 2 years old)	Cortical atrophy, thin CC, hypomyelination, atrophy of cbll and brainstem (at 5 months old)	Brain atrophy, thin CC, hypomyelination, atrophy of cbll and brainstem (at 5 years old)	Atrophy of cbll and brainstem (at 11 years old)
Last follow-up age	11 years old	Died at 3 years	3 years old	Died at 2 years	2 years old	6 years old	11 years old
Reference	Saitsu *et al.*[18]	Saitsu *et al.*[18]	Writzl *et al.*[21]	Nonoda *et al.*[22]	This paper	This paper	Hamdan *et al.*[23]

Abbreviations: ACTH, adrenocorticotrphic hormone; cbll, cerebellum; CC, corpus callosum; Dx, diagnosis; EEG, electroencephalogram; F, female; ID, intellectual disability; M, male; NA, not applicable; OFC, occipitofrontal circumference.
[a]Subject 5 recored EEG only twice at 5 months and 2 years of age.

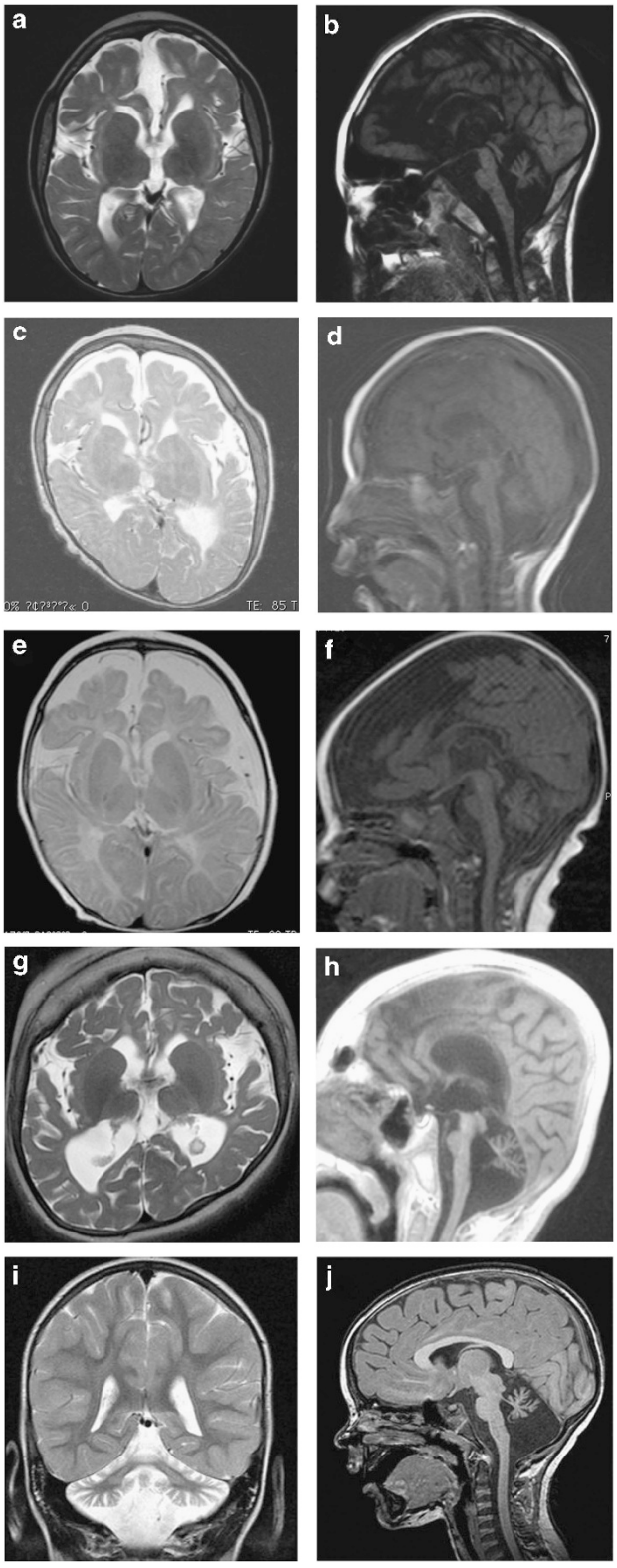

Figure 1 Brain MRI of subjects with *SPTAN1* mutations. T2-weighted axial and T1-weighted mid-sagittal images of subject 1 (**a**, **b**), subject 2 (**c**, **d**), subject 5 (**e**, **f**), subject 6 (**g**, **h**) and T2-weighted coronal and T1-weighted mid-sagittal images of subject 7 (**i**, **j**). Severe hypomyelination, hypoplasia of corpus callosum, cortical atrophy, and atrophy of brainstem and cerebellum are evident in subject 1, 2, 5 and 6. Only atrophy of brainstem and cerebellum are observed in subject 7.[23] Images of **i** and **j** are adapted from ref. 23.

integrating into the membrane cytoskeleton.[29,30] Defects of erythroid α-I and β-I spectrins and neuronal β-III spectrin are associated with hereditary spherocytosis (SPH3 and SPH2 [MIM#270970 and +182870]) and spinocerebellar ataxia type 5 (SCA5 [MIM #600224]), respectively.[29,32,33] α-II spectrin is considered as the major α spectrin expressed in nonerythroid cells, and α-II/β-II spectrin heterodimers are the predominant species in these cells.[29,34] Abnormal node of Ranvier development and destabilization of nascent voltage-gated sodium channel clusters were observed in zebrafish α-II spectrin mutants harboring a nonsense mutation. These mutants also showed impaired myelination in motor nerves and in the dorsal spinal cord, suggesting that α-II spectrin has important roles in the maintenance of the integrity of myelinated axons.[19]

DOMINANT NEGATIVE EFFECT OF *SPTAN1* MUTATIONS

The effect of *SPTAN1* mutations on the function of spectrin is important in elucidating pathogenesis of *SPTAN1* encephalopathy. What is interesting is that all the in-frame mutations found are located at the last two spectrin repeats in the C-terminal region (Figure 2). The last two spectrin repeats are required for α/β spectrin heterodimer associations;[29] therefore, these mutations could alter heterodimer formation between the spectrins. In fact, we previously showed that two mutant α-II spectrins (p.E2207 del and p.R2308_M2309 dup) caused aggregation, predominantly in the cell bodies and axons.[18] Double immunostaining revealed that these aggregations were colocalized with β-II and β-III spectrins, indicating that unstable α-II/β-II and α-II/β-III spectrin heterodimers were involved in the aggregation.[18] In contrast, the p.Q2202 del mutation showed a similar pattern of expression to that of the wild-type α-II spectrin in N2A cells. Furthermore, in primary neuronal cultures, the p.Q2202 del mutation showed a similar aggregation profile, but in a lower proportion of cells.[23] These expression data suggest that the degree of aggregation involving α-II/β-II and α-II/β-III spectrin heterodimers could correlate with the severity of clinical symptoms. It is also notable that two patients (subjects 2 and 4) with a duplication mutation in the last spectrin repeat passed away early in childhood. In contrast to these patients, one patient (subject 1) with a p.E2207 del mutation within the continuous helix region between the last two spectrin repeats has survived longer despite severe motor impairment. In addition, among the four in-frame mutations, the p.Q2202 del mutation, in the patient with generalized epilepsy (milder than West syndrome), is located in the N-terminal region. Therefore, it is possible that the location of in-frame mutations within the last two spectrin repeats may correlate with phenotype severity; C-terminally located mutations cause more severe phenotypes, including West syndrome, and are associated with the characteristic MRI findings. However, analysis of additional patients with *SPTAN1* mutations will be needed to validate this hypothesis.

Whether other types of *SPTAN1* mutation cause epileptic encephalopathy is an interesting issue. Apart from the patients with exonic deletion of *STXBP1*, 13 patients having 9q34.11 microdeletion (where *STXBP1* and *SPTAN1* are located) have been reported in the literature.[8,35–40] Three patients had *STXBP1* deletion but intact *SPTAN1*.[35,36] Among these patients, one patient revealed infantile spasms without infratentorial involvement on MRI, another exhibited nonsyndromic infantile epilepsy with severe ID and the other suffered from moderate ID, which are within the clinical spectrum of *STXBP1* mutations.[35,41,42] Six patients showed deletion of both *SPTAN1* and *STXBP1*,[8,36–39] and clinical features closely resemble those of *STXBP1*-mutated patients with Ohtahara syndrome or West syndrome.[8,37,43] In contrast, three patients had *SPTAN1* deletion but intact *STXBP1*.[36,40]

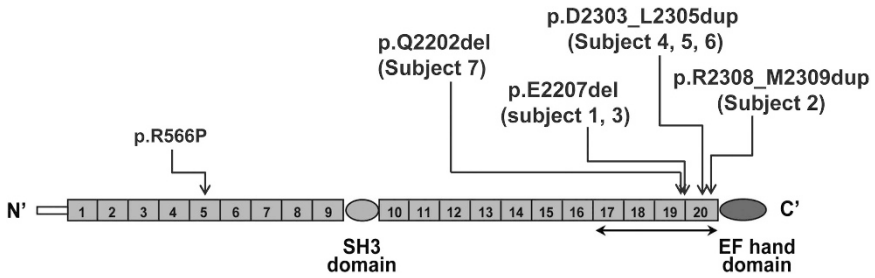

Figure 2 *De novo* mutations identified in *SPTAN1*. Schematic representation of the SPTAN1 protein[23] consisting of 22 domains, including 20 spectrin repeats, an SH3 domain and an EF hand domain. All identified mutations including p.Q2202 del, p.E2207 del, p.D2303_L2305 dup and p.R2308_M2309 dup are shown. The last four spectrin repeats, which are required for α/β heterodimer association, are indicated by a bidirectional arrow. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

Clinical phenotypes of these three patients varied and their phenotypic inconsistency might depend on the content of other deleted genes. It is notable that the patient with deletion of only *SPTAN1* had no epileptic encephalopathy.[36,40] In addition, one patient had complete *SPTAN1* deletion with partial deletion of *STXBP1* (exons 16–20), and this patient also showed only profound ID with normal brain MRI.[36]

Collectively, these results suggest that *SPTAN1* haploinsufficiency alone does not cause epileptic encephalopathy or brainstem and cerebellar lesions, and that only in-frame *SPTAN1* mutations at specific positions can cause specific phenotypes (*SPTAN1* encephalopathy) in a dominant negative manner. The p.Q2202 del mutation may cause a milder form of *SPTAN1* encephalopathy.

DIFFERENTIAL DIAGNOSIS

SPTAN1 encephalopathy may be differentiated from other diseases associated with West syndrome and brainstem and cerebellar hypoplasia/atrophy or cerebral hypomyelination by MRI.

Clinical features in *SPTAN1* encephalopathy are mostly shared with progressive encephalopathy with edema, hypsarrhythmia and optic atrophy (PEHO) syndrome.[44] Patients with PEHO syndrome exhibit progressive encephalopathy, microcephaly, edema of the extremities, infantile spasms, severe hypotonia and optic atrophy. Psychomotor development ceases in early infancy and patients show profound mental retardation. Poor or absent visual fixation from the first months of life is also observed. Brain CT or MRI in PEHO syndrome shows progressive generalized atrophy, more in cerebellar and brainstem areas than in supratentorial regions. Underlying causes of PEHO syndrome remain elusive. Patients suspected of PEHO syndrome are good candidates for *SPTAN1* testing.

Pontocerebellar hypoplasia (PCH) is sometimes accompanied by intractable epilepsy. PCH type 6 is caused by recessive mutations in the gene encoding mitochondrial arginyl-tRNA synthetase (*RARS2*). Some PEHO-like features were reported in a nonconsanguineous British female patient with PCH type 6.[45] The patient suffered myoclonic seizures from the neonatal period onwards and her MRI showed generalized hypoplasia, but hypsarrhythmia was absent. Lactate levels in the plasma and cerebrospinal fluid were elevated, implying mitochondrial dysfunction.

Recently, *CASK* aberrations were reported in two patients with Ohtahara syndrome and cerebellar hypoplasia.[46] Both patients showed epileptic encephalopathies with severe cerebellar hypoplasia along with other congenital anomalies. Originally, *CASK* mutations were found in four female patients with X-linked ID, microcephaly and PCH,[47] and their phenotypes expanded to epileptic encephalopathy. In patients with *CASK* mutations, the supratentorial region is not usually involved according to MRI.

Haploinsufficiency of *STXBP1* is an important cause of Ohtahara syndrome and West syndrome. In patients with *STXBP1* mutations, delayed myelination in the cerebrum is observed.[8,43,48] MRI shows that patients with *STXBP1* mutations do not usually involve brainstem and cerebellum, whereas those with *SPTAN1* encephalopathy show brainstem and cerebellum atrophy.

The clinical manifestations of 3-phosphoglycerate dehydrogenase deficiency, which results from a defect of serine biosynthesis, mimic those of *SPTAN1* mutations.[49] This disorder is characterized by congenital microcephaly, profound mental retardation, hypertonia and intractable seizures, and occasional West syndrome. 3-Phosphoglycerate dehydrogenase is diagnosed by amino-acid analysis of plasma and cerebrospinal fluid.

Molybdenum cofactor deficiency, which is due to the combined enzymatic deficiency of xanthine oxidase and sulfite oxidase, presents with epileptic encephalopathy and PCH with retrocerebellar cyst.[50] In this condition, epileptic encephalopathy usually occurs during the neonatal period as neonatal seizures emerge. Brain MRI demonstrates distinct features, such as cerebral infarction, symmetric involvement of basal ganglia and cerebral atrophy, in addition to PCH. Molybdenum cofactor deficiency can be screened for by the presence of urine sulfite and low plasma urate.

Acquired white matter disorders during infancy, hypoxic-ischemic disorders and congenital infectious disorders, such as cytomegalovirus, can also be considered as differential diagnoses.

DISCUSSION

SPTAN1 encephalopathy patients all had in-frame mutations in the last two spectrin repeats of the C-terminal region. However, it remains unclear which types of mutation are pathogenic. Three answers to this question can be considered. First, mutations cluster at the C-terminal region only by chance, and other types of mutation may result in the same clinical phenotype. Second, other types of mutation, such as missense mutations, may cause different phenotypes or no phenotype. A *de novo* missense mutation was found in a nonsyndromic ID patient,[23] and no *SPTAN1* mutations have been found despite extensive genetic screening of epilepsy or ID patients. As mentioned above, patients with *SPTAN1* haploinsufficiency showed no epileptic encephalopathy. Therefore, it is most likely that missense mutations or haploinsufficiency of *SPTAN1* results in different phenotypes. Third, mutation in the N-terminal region could severely affect spectrin function and result in lethality. It would be difficult to prove this possibility through patient screening. Animal models harboring various types of *Sptan1* mutation may provide further evidence for impaired spectrin functions.

Regardless of severe neurological features caused by in-frame *SPTAN1* mutations, no apparent visceral organ involvement is known. Only atrial septal defect in one patient and acquired myocarditis in another are seen. Exceptionally, one patient developed coloboma-like optic discs. It is not conclusive whether these complications were coincidence or can be explained by incomplete penetrance and variable expressivity of *STPAN1* mutational effects. Identification and characterization of more patients with *STPAN1* mutations would be required to investigate the phenotype spectrum and involvement of other organs.

The onset of epilepsy ranged from 3 weeks to 3 months of age in patients with West syndrome. In addition, one patient showed neonatal seizure that disappeared without specific treatment. Epileptic seizures were refractory to various antiepileptic drugs in all cases and to adrenocorticotrophic hormone or hydrocortisone in one case. Among the various antiepileptic drugs, clobazam, valproic acid and topiramate were partially effective in some patients. In addition to epileptic seizures, two patients showed dystonia or dystonic movement. Recently, choreoballistic movement and generalized tremor were reported in patients with *STXBP1* mutations,[35,48,51] and *ARX* and *FOXG1* mutations are also associated with movement disorders.[52,53] In-frame *SPTAN1* mutations may also be considered for epileptic encephalopathy and involuntary movements.

CONCLUSION

SPTAN1 encephalopathy has distinct clinical and neuroradiological phenotypes. Brainstem and cerebellar atrophy and cerebral hypomyelination, identified by MRI, are specific hallmarks of this disorder. These phenotypes are caused by in-frame *SPTAN1* mutations in the C-terminal region that act in a dominant negative manner. Knowledge of clinical profiles and MRI features in *SPTAN1* encephalopathy will help clinicians to perform efficient genetic testing and to identify *SPTAN1* mutations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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