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BRIEF COMMUNICATION

# *SPTAN1* variants as a potential cause for autosomal recessive hereditary spastic paraplegia

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## Abstract

More than 80 known or suspected genes/loci have been reported to be involved in hereditary spastic paraplegia (HSP). Genetic and clinical overlap have been reported between HSP and other neurological condition, yet about 50% of HSP patients remain genetically undiagnosed. To identify novel genes involved in HSP, we performed a genetic analysis of 383 HSP patients from 289 families with HSP. Two patients with biallelic *SPTAN1* variants were identified; one carried the c.2572G>T p.(Ala858Ser) and c.4283C>G p.(Ala1428Gly) variants, and the second also carried the c.2572G>T p.(Ala858Ser) variant, and an additional variant, c.6990G>C p.(Met2330Ile). In silico predictive and structural analyses suggested that these variants are likely to be deleterious. *SPTAN1* was highly intolerant for functional variants (in the top 0.31% of intolerant genes) with much lower observed vs. expected number of loss-of-function variants (8 vs. 142.7, $p < 5 \times 10^{-15}$). Using public databases of animal models and previously published data, we have found previously described zebrafish, mouse, and rat animal models of *SPTAN1* deficiency, all consistently showing axonal degeneration, fitting the pathological features of HSP in humans. This study expands the phenotype of *SPTAN1* mutations, which at the heterozygous state, when occurred de novo, may cause early infantile epileptic encephalopathy-5 (EIEE5). Our results further suggest that *SPTAN1* may cause autosomal recessive HSP, and that it should be included in genetic screening panels for genetically undiagnosed HSP patients.

## Introduction

Hereditary spastic paraplegia (HSP) is a group of rare hereditary neurodegenerative motor neuron disorders, characterized by symmetrical spasticity and weakness of the lower extremities. Based on the absence or presence of additional neurological symptoms, HSP can be classified as pure or complex. Pure HSP may also be characterized by lower/upper limb hyperreflexia and extensor plantar responses, with or without urinary dysfunction; any

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additional neurological signs or symptoms will define complex HSP. The main pathological hallmark of HSP is thought to be degeneration of axons within the descending corticospinal tract and ascending sensory fibers [1].

To date, there are more than 80 genes or loci suggested to be involved in HSP, which include all patterns of Mendelian and non-Mendelian inheritance [2–4]. However, between 50 and 60% of HSP patients remain genetically undiagnosed [5], suggesting that numerous genes involved in HSP are yet to be discovered. While HSP is defined as an independent clinical entity, both clinical and genetic overlap exist between HSP and other disorders such as ataxia, seizure disorders, and others [4, 6]. This is further exemplified by the identification of clinically diagnosed HSP patients, who have variants in genes typically causing other disorders, such as *POLR3A* [7] (OMIM 607694), *SLC2A1* [8] (OMIM 612126), *AAAS* [9] (OMIM 231550), and *ATP13A2* [10] (OMIM 617225).

In the current study, we performed a thorough genetic analysis in one of the world's largest cohorts of HSP, CanHSP [11], to identify novel genes involved in HSP. Based on our findings, including in silico analysis and previously published zebrafish, mouse and rat models, we report that biallelic *SPTAN1* (OMIM 613477) variants may cause autosomal recessive pure HSP.

## Materials and methods

### Population

A total of 696 HSP patients from 431 families were recruited from eight major medical centers across Canada (Montreal, Quebec, Toronto, Ottawa, Calgary, Edmonton, Hamilton, and Vancouver) from February 1, 2012 to December 31, 2018, and data on diagnosis, recruitment and the cohort were previously published [11]. All participants signed informed consent forms, and the study protocol was approved by the institutional review board. Of these, 383 HSP patients from 289 families went through whole exome sequencing (WES) and were included in the analysis. In addition, 251 unrelated healthy individuals that went through WES in our lab served as controls.

### Genetics analysis

Whole exome capture, sequencing, alignment, annotation, and variant calling was done as previously described [11]. For detection of autosomal recessive genes, filtering was applied to select variants with a frequency < 0.005 in the exome aggregation consortium (ExAC) database. Nonsynonymous, frameshift and stop -gain variants that segregated with the disease were filtered in. Evaluation of the pathogenic potential of the variants was based on their frequency of in ExAC and genome aggregation database (gnomAD), and by prediction and conservation tools: combined annotation dependent depletion (CADD), MutationTaster, and genomic evolutionary rate profiling (GERP ++). Segregation analysis was performed and lists of potential disease-causing variants were generated for each family. Subsequently, we generated a list of all genes known or suspected to be involved in HSP, as well as genes that are associated with diseases that can mimic HSP or may have spasticity as one of their symptoms (a total of 660 genes, Supplementary Table 1), and cross-examined the filtered -in segregating variants with this list. Validation and further segregation of the suspected pathogenic variants were performed using Sanger sequencing, primer sequences are available upon request. WES data from 251 unrelated healthy individuals of European descent, without any family history of neurological diseases, were screened for presence of missense or LoF variants in *SPTAN1*.

### In silico analysis of *SPTAN1* and the identified variants

Genic intolerance of *SPTAN1* was assessed using the residual variation intolerance score (RVIS) tool [12], and observed vs. expected variant frequencies in gnomAD. To examine the potential effect of these variants on *SPTAN1* function and structure, SWISS-MODEL was used to generate homology models of human spectrin repeats [13]. Human α-spectrin repeats 7–8 were modelled using the chicken α-spectrin repeats 15–16 (pdb 1u5p). Human α-spectrin repeat 20 and EF hands 1–2 were modelled using the structure of human muscle α-actinin-2 (pdb 4d1e). Coordinates of human α-spectrin repeats 12–13 were derived from the original crystal structure (pdb 3fb2, a.a. 1337–1544). Structural analysis of the variants and images were generated using PyMOL v.2.2.0. Pathways and protein–protein interaction network were analyzed using WebGestalt [14] and STRING [15].

### Literature and database search for animal and cellular SPTAN1 models

Since *SPTAN1* was already implicated in other disorders, we examined the literature and publicly available databases to examine whether animal and cellular models already exist that can explain HSP in the studied patients. PubMed was searched using the search words "SPTAN1", "spectrin alpha", "α-II Spectrin", "Nonerythrocytic 1", with the word "model", and all relevant abstracts were screened to identify relevant animal or cellular models. The public databases Mouse Phenome Database, the International Mouse Phenotyping Consortium, Rat Genome Database, Mouse

Genome Informatics, the Zebrafish Information Network, and Alliance of Genome Resources were accessed.

## Results

### Biallelic *SPTAN1* variants may explain HSP in two families

Following quality control and filtration, biallelic variants in *SPTAN1* remained the only explanation for HSP in two individuals. In proband A, two *SPTAN1* variants were identified, c.2572G>T p.(Ala858Ser) and c.4283C>G p.(Ala1428Gly) (NM_003127), and segregation was further confirmed by Sanger sequencing of the parents. Proband B also carried one of these variants, c.2572G>T p.(Ala858-Ser), and an additional variant, c.6990G>C p.(Met2330Ile) (NM_003127). DNA from other family members of patient B was not available for segregation analysis. All three variants were predicted to be deleterious by CADD and MutationTaster, and were located in highly conserved amino acids with all GERP++ scores > 4.7 (Fig. 1a–c). According to the American College of Medical Genetics criteria and using Varsome tool, these variants were classified as "variants of uncertain significance". One of these variants, p.(Met2330Ile), was not reported in gnomAD and the other two variants are rare and no homozygous carriers of either were reported. Furthermore, in 251 unrelated healthy controls, no biallelic carriers of missense, splice site, or nonsense mutations were identified.

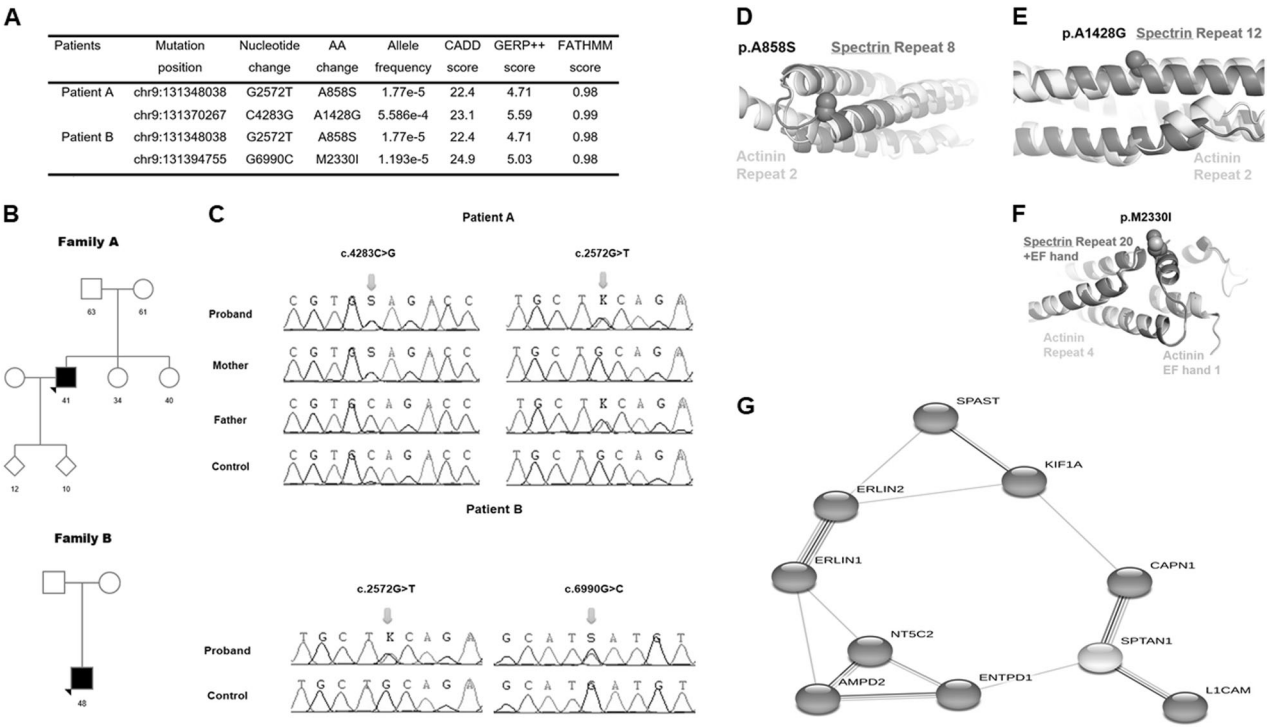


**Fig. 1** *SPTAN1* variants, in silico analysis. **a** Four *SPTAN1* variants were identified in patients A and B. One of these variants is the same in both patients. All variants are rare enough in gnomAD to be disease causing in a recessive manner, are highly conserved and predicted to be deleterious. CADD combined annotation dependent depletion, GERP++ genomic evolutionary rate profiling, FATHMM functional analysis through hidden Markov models. **b** Pedigrees of the two HSP probands harbouring the *SPTAN1* variants. Open symbol: unaffected; filled symbol: affected; arrow: proband. **c** Sanger sequencing traces confirming the two variants (c.4283C>G and c.2572G>T) in patient A. c.4283C>G p.(Ala1428Gly) and c.2572G>T p.(Ala858Ser) variants were observed in the mother and father of patient A, respectively. NM_003127:c.[2572G>T]; [6990G>C] variants were confirmed in patient B, but segregation analysis could not be performed as DNA was not available. The healthy controls did not present any of the variants. Genomic positions are based on the GRCh37/hg19 genome assembly. **d** Model of human α-spectrin repeat 8 (a.a. 785–887) derived from the structure of repeat 15 from chicken α-spectrin (pdb 1u5p). The side chain of Ala858 is shown as spheres. The model is superposed on the structure of α-actinin repeat 2 (pdb 4d1e) to highlight the proximity of the variant site to the preceding repeat. **e** Structure of human α-spectrin repeat 12 (pdb 3fb2, a.a. 1337–1544). The side chain of Ala1428 is shown as spheres. The model is superposed on the structure of α-actinin repeat 2 to highlight the kink that might be introduced in the helix harboring the variant site. **f** Model of human α-spectrin repeat 20 and EF hands 1–2 (a.a. 2206–2400) derived from the structure of α-actinin repeat 4 and EF hands 1-2 (pdb 4d1e). The position of Met2330 is shown as sphere and makes contact with repeat 20. **g** Protein–protein interaction network of SPTAN1 using STRING. The interaction partners of SPTAN1 are known to cause spastic paraplegia in this figure. SPTAN1 protein closely interacts with *CAPN1* (SPG76), *L1CAM* (X-linked SPG), and *ENTPD1* (SPG64)

The α-spectrin protein, encoded by *SPTAN1*, is 2472 a.a. long and consists of eight spectrin repeats, followed by an SH3 domain, 12 additional repeats, and 3 calcium-binding EF hands [16]. While there are structural coordinates for fragments of α-spectrin [17], they do not contain all the variants. We thus performed homology modelling of missing fragments, using crystal structures with the highest sequence identity to the target, in order to predict the effect of missense variants on the structure and function of the protein. The c.2572G>T p.(Ala858Ser) variant is located in the eighth spectrin repeat, which we modelled on the chicken α-spectrin-repeats 15–16 [18]. This variant would not create any steric clash but might affect the conformation of the loop that precedes Ala858 (Fig. 1d). Comparison with the structure of full-length α-actinin [19], which is homologous to spectrin, shows that this loop is in proximity with the preceding repeat. Therefore, the variant c.2572G>T p.(Ala858Ser) might affect the rigidity of the interaction between α-spectrin-repeats 7 and 8. The variant c.4283C>G p.(Ala1428Gly) is located in the 12th spectrin repeat. The structure of human α-spectrin-repeats 12–13 has been determined by X-ray crystallography at 2.3 Å resolution (NSGC target HR5563a; https://doi.org/10.2210/pdb3FB2/pdb). The variant site is located in the middle of a long helix, and variant to a glycine might lower the rigidity of the helix in this position (Fig. 1e). Superposition with the structure of α-actinin reveals a kink in the helix at this position, suggesting this is a pivotal point in the structure. The variant c.6990G>C p.(Met2330Ile) is found in the first EF hand, a calcium-binding domain that regulates contacts with F-actin in response to calcium [20, 21]. The variant is very close to the spectrin-repeat 20, and thus we modelled both repeat 20 and EF hands 1–2 using the structure of α-actinin [19]. The side chain of Met2330 interacts with repeat 20, and variant to an isoleucine might destabilize this interaction and "uncouple" these two domains (Fig. 1f).

*SPTAN1* is highly intolerable for functional genetic variations with an RVIS score of −3.53, putting it on the top 0.31% of human genes in terms of genic intolerance. Comparing the expected number of loss-of-function (LoF) variants ($n = 142.7$) vs. the observed number of LoF variants ($n = 8$) in gnomAD, yielded a likelihood of 1.00 for intolerability with $p < 5 \times 10^{-15}$. Comparing observed vs. expected rare missense variants (allele frequencies < 0.001), highly significant z-scores were reported in ExAC ($z = 6.8$, $p < 0.00001$) and gnomAD ($z = 5.8$, $p < 0.00001$), further demonstrating lack of tolerability of *SPTAN1* for rare missense variants. Protein interaction analysis using STRING, including all the known HSP genes and *SPTAN1* suggested that *SPTAN1* interacts directly or indirectly with multiple HSP genes (Fig. 1g). Pathway-based analysis revealed SPTAN1 role in "intracellular transport", "axon development", and "axon" pathways, closely interacting with other HSP-related genes (Supplementary Table 2).

### Clinical characteristics of HSP patients with *SPTAN1* variants

Both patients presented with pure HSP, and their clinical characteristics together with other findings are detailed in Table 1. Onset ages were 33 and 15 in patients A and B, respectively, with a slowly progressive course, involving the lower limbs, with minor involvement of the urinary bladder in patient A, and hyperreflexia of the upper limbs in both patients. SPATAX-EUROSPA disability stage was 0 (no functional handicap) and 3 (moderate, unable to run, and limited walking without aid) in patients A and B, respectively. In both, brain and spine MRI were normal, with no seizures or intellectual disability. Phenotypically, both patients cannot be distinguished from other patients with pure HSP.

### Previously published *SPTAN1* models are highly relevant for HSP

A zebrafish model with homozygous nonsense *SPTAN1* variants was reported to disrupt clustering of sodium channels around the nodes of Ranvier in CNS and PNS myelinated axons. In this model, α-II Spectrin, encoded by *SPTAN1*, was shown to be detrimental for the assembly of these nodes [22]. Similar results were observed in a mouse model [23] where loss of α-II Spectrin also disrupted the assembly of nodes of Ranvier and thus the ability of axons to rapidly propagate action potentials using salutatory conduction. Importantly, loss of α-II Spectrin led to degeneration of large myelinated axons in this model, which is similar to the pathology observed in HSP. Furthermore, these mice demonstrating hindlimb clasping reflex [23], which is a measure of neurodegeneration relevant to neurological disorders such as spasticity/ataxia [24]. In a rat model of loss of α-II Spectrin, axon development was impaired, demonstrating disruption of the formation of axon initial segment, as well as decreased and disorganized arborization [25].

## Discussion

This is the first report suggesting that biallelic *SPTAN1* variants may lead to pure autosomal recessive HSP, further expanding the phenotypic spectrum associated with *SPTAN1* variants. However, additional patients with biallelic *SPTAN1* variants need to be identified to conclusively determine that *SPTAN1* variants cause recessive HSP. However, the fact that in the two affected individuals the

**Table 1** Demographic and clinical characteristics of the two HSP patients

| Characteristics | Patient A | Patient B |
|---|---|---|
| General information | | |
| Gender | Male | Male |
| Age at evaluation | 41 | 48 |
| Age of onset | 33 | 15 |
| Consanguinity | No | No |
| Mode of inheritance | Recessive | Recessive |
| Ancestral background | French Canadian | French Canadian |
| Core symptoms | | |
| Low extremity weakness | − | − |
| Low extremity spasticity | + | + |
| Low extremity hyperreflexia | + | + |
| Extensor plantar responses | − | + |
| Abnormal bladder function | + | − |
| Ankle clonus | − | + |
| Other symptoms | | |
| Cognitive deficits | − | − |
| Retinopathy or optic atrophy | − | − |
| Extraocular movement | + | − |
| Deafness | − | − |
| Swallowing difficulties | − | − |
| Dysarthria | − | − |
| Upper extremity weakness | − | − |
| Upper extremity hyperreflexia | + | + |
| Amyotrophy | − | − |
| Sensory abnormalities | − | + |
| Peripheral neuropathy | − | − |
| Pes cavus | − | − |
| Ataxic gait | − | − |
| Upper extremity ataxia | − | − |
| Upper extremity intent tremor | − | − |
| Lower extremity ataxia | − | − |
| Lower extremity intent tremor | − | − |
| Seizures | − | − |
| Skeletal abnormalities | − | − |
| Myoclonus | − | − |
| Imaging | | |
| Brain MRI | Normal | Normal |
| Total spine MRI | Normal | Normal |

same variant was identified, c.2572G>T p.(Ala858Ser), support the pathogenicity of this variant and this gene in HSP. This was further supported by the structural analysis of these *SPTAN1* variants, as well as by the genic intolerance analysis and the previously reported animal models that have features that are similar to those seen in HSP. While we acknowledge as a limitation of the current study that only two patients are reported here, our data support the pathogenicity of the identified *SPTAN1* variants. Another limitation is that segregation analysis could not be performed for patient B, as DNA from the parents or other relatives was not available.

Dominant de novo *SPTAN1* mutations may cause early infantile epileptic encephalopathy-5 (EIEE5), with a suggested dominant-negative effect of the mutations [25]. In contrast to the patients described here, patients with EIEE5 have a much more severe disease, with MRI findings, which include diffuse hypomyelination and widespread brain atrophy which affects their cortex, corpus callosum, brainstem, and cerebellum [26, 27]. These phenotypic differences may suggest that the de novo mutations are severe, while the variants described in the current study are probably tolerable in heterozygous carriers, as evident by their rare presence in ExAC and gnomAD, and with an additional mutation may lead to a milder phenotype of pure HSP. Similar instances exist in other forms of HSP. For example, mutations in *PLP1* may lead to a pure form of HSP, but also to severe forms of Pelizaeus–Merzbacher disease [28]. Of note, only a few EIEE5 patients with spasticity were reported, and it was also more severe than in the patients described here, accompanied by many other symptoms [27]. This may suggest that heterozygous *SPTAN1* mutations may also lead to HSP, considering that other HSP-related genes were also reported to cause HSP in both autosomal recessive and autosomal dominant manners (e.g., *ATL1*, *ALDH18A1,* and *SPG7*) [29–32].

The animal models that were previously published [22, 23] provide an additional potential link to HSP, as some of the phenotypic consequences of loss of α-II Spectrin in these models, mainly the axonal neurodegeneration [23], are very similar to those observed in HSP [33]. Mutations in other HSP-related genes, such as *PLP1* [28], and *FA2H* [34], also affect myelination, as was seen in the aforementioned models. Therefore, the current findings further imply that disturbances in myelination may also be important in the pathogenesis of HSP.

Based on our findings, *SPTAN1* should be considered in HSP and included in sequencing panels for HSP. *SPTAN1* variants are likely to be rare in HSP, as in our

cohort only 2/696 patients (0.3%) carry these variants. Nevertheless, additional studies in other populations are required to confirm the role of *SPTAN1* in HSP, and functional studies are needed to determine the exact mechanism by which *SPTAN1* variants cause HSP.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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