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2020-12

Ylikallio , E , Ritari , N , Sainio , M , Toppila , J , Kivirikko , S , Tynismaa , H , Auranen , M & Isohanni , P 2020 , ' De novo SPTAN1 mutation in axonal sensorimotor neuropathy and developmental disorder ' , Brain : a journal of neurology , vol. 143 , 104 . <https://doi.org/10.1093/brain/awaa344>

<http://hdl.handle.net/10138/336473>

<https://doi.org/10.1093/brain/awaa344>

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De novo *SPTAN1* mutation in axonal sensorimotor neuropathy and developmental disorder

Running title: SPTAN1 in neuropathy

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Key words: Hereditary neuropathy, Charcot-Marie-Tooth disease, SPTAN1, developmental disorder

Abbreviations: SD = standard deviation, ESP = exome sequencing project

Sir,

We have read with great interest the recent article by Beijer et al. (Beijer *et al.*, 2019), detailing heterozygous nonsense mutations in non-erythrocytic alpha-II spectrin *SPTAN1* as the cause of autosomal dominant hereditary motor neuropathy in twelve individuals from three families. Alpha-II spectrin is a mechanical support protein that is important for axonal maintenance and synaptogenesis in both central and peripheral nervous systems (Huang *et al.*, 2017; Wang *et al.*, 2018). Beijer et al. showed that neuropathy-associated variants were subject to nonsense mediated mRNA decay, thus implicating a haploinsufficiency mechanism of disease (Beijer *et al.*, 2019).

Before this, alterations of *SPTAN1* have been linked to early-infantile epileptic encephalopathy or neurodevelopmental phenotypes often with epilepsy (Syrbe *et al.*, 2017; Gartner *et al.*, 2018). De novo in-frame deletions/duplications, missense, truncating and splice mutations have been described behind these phenotypes. The in-frame insertions/deletions are likely to cause dominant negative effects (Saito *et al.*, 2010; Huang *et al.*, 2017), whereas splice and truncating mutations decrease mRNA levels of *SPTAN1* (Gartner *et al.*, 2018; Beijer *et al.*, 2019). Furthermore, a recent report described bi-allelic missense mutations of *SPTAN1* in two individuals with hereditary spastic paraplegia (Leveille *et al.*, 2019), which further implicates the gene as important for axonal maintenance.

We report a male patient who gave written informed consent to the study, and the study was approved by the HUS Helsinki University ethics committee. The patient was born following a full-term

pregnancy by emergency caesarean section because of reduced heart sounds. The patients' older sister had been examined for clumsiness and diagnosed with attention deficit hyperactivity disorder but had not undergone genetic testing. Both parents were neurologically healthy. The patient was referred to paediatric neurology at age 11 months because of slow motor development. He had muscle hypotonia, delayed motor development, and hypermobile joints. He did not have clear dysmorphic features. His initial investigations included creatine kinase level, nerve conduction study with EMG, brain MRI, spine X-ray, kidney ultrasound, karyotype and ophthalmologic investigations, which were all normal. He learned to walk at age 2 years. He remained clumsy but his motor skills developed with the aid of weekly physiotherapy. During preschool years difficulties in visual and language development were also noted. He received regular speech therapy and was followed by neuropsychologist. He attended normal school but required special education for learning difficulties.

His height growth started to accelerate around age 2 years. At age 6 years he was growing at +2.5 standard deviations (SD). Endocrinologic tests revealed no abnormalities of growth hormone, thyroid, insulin-like growth factor, gonadotropins or androgens. Re-examination at age 13 showed the patient growing at +3.0 SD. His weight to height was -31%, he had long fingers, narrow and high palate, flat feet and asymmetric, carinatum-shaped thorax. Suspicion of Marfan syndrome was raised, but *FBNI* sequencing was normal. Heart ultrasound was normal. Weak ankle dorsiflexion was noted, leading to repeated nerve conduction study. This showed decreased motor and sensory amplitudes, and needle EMG showed slight spontaneous activity and polyphasic units in distal muscles. The findings were consistent with chronic, lower-limb predominant, axonal sensorimotor polyneuropathy. Repeat brain MRI at the age of 14 years was normal.

At his latest clinical exam, age 20, his height was 194 cm and weight 60 kg with Marfanoid features as previously noted (Fig 1A-C). He was alert and communicated adequately. He was able to walk

independently with supportive insoles; he had some difficulty running but he was fully able to climb stairs. His gross motor functions were clumsy and muscle tone was decreased. He walked with slightly broad base, was able to walk on his toes but not on his heels. Dorsiflexion of ankle and big toe were weakened symmetrically. He also had mild Achilles tendon shortening. Deep tendon reflexes were symmetric with intermediate briskness, Babinski signs were negative. Distal vibration sensation was intact. Cranial nerves were normal. The patient has had no seizures.

The latest neuropsychological evaluation age 16 revealed severe dyslexia and difficulties of executive functions. Verbal reasoning skills were within normal range and perceptual reasoning was in borderline range. Furthermore, his processing speed was extremely slow. He was able to finish school and applied to study at a university that provides support for students with special needs.

A molecular karyotype (Agilent 180K) was normal. After this, trio exome sequencing was performed, revealing c.6367del (p.Val2123Cysfs*45) change in exon 49/57 of *SPTANI* (RefSeq NM_001130438.3) at chromosome 9 position 131388757 (GRCh37/hg19). This variant was absent in the parents' samples suggesting *de novo* occurrence. It is not found in the public databases gnomAD (v2.1.1), NHLBI Exome Sequencing Project (ESP) or 1000 genomes. The variant was confirmed by Sanger sequencing.

This is to our knowledge the first report of a *de novo SPTANI* mutation as the cause of a peripheral neuropathy. Our patient's frameshift variant leads to a premature stop codon. It is therefore likely to cause nonsense mediated mRNA decay and lead to haploinsufficiency of *SPTANI* similar to the mutations described by Beijer et al. However, as cells from our patient were not available, we were not able to confirm this hypothesis. Our case is important as it gives additional confirmation to the

association of variants in *SPTANI* with neuropathy and gives new insights into the phenotypic spectrum related to this gene.

Our patient had early onset motor symptoms, which developed into manifest neuropathy by age 13. It is not possible to distinguish *SPTANI* neuropathy purely on clinical grounds, but motor-predominant symptoms with emphasis on weak ankle and toe dorsiflexion and progression that is slow to none appear to be characteristic. The patients described by Beijer et al. had a phenotype fitting this description. Our case further shows that presence of decreased sensory amplitudes and diagnosis of sensorimotor neuropathy is also possible for a *SPTANI* mutation. There appears to be variability in the age at onset. Onset in childhood was found in 7 of Beijer's patients, but two had onset after age 20 and there were two individuals who were possible unaffected mutation carriers.

Our patient's neuropathy and neuropsychological profile provide an interesting link between axonal neuropathy phenotypes described by Beijer et al, and previously described non-epileptic neurodevelopmental phenotypes. Gartner et al. reported two patients, aged 12 and 7, with *de novo* nonsense or splice mutations that decreased the level of alpha-II spectrin (Gartner *et al.*, 2018) consistent with a haploinsufficiency mechanism. These patients resembled our patient by having developmental disorder and impairment of motor performance from early age. However, the severity of developmental disorder was different, they had severe intellectual disability with marked difficulties in expressive language whereas our patient had mixed disorder of scholastic skills with normal intelligence. One of Gartner's patients also had microcephaly and the other had pontine and cerebellar hypoplasia while our patient had repeatedly normal brain MRI. One of them also had dysmorphic features, and both had thyroid dysfunction, which were not found in our patient. Neuropathy was not found in Gartner's patients, but it cannot be excluded that they may develop neuropathy later, as our patient's neuropathy became evident only at age 13. The Marfanoid

appearance of our patient has not been observed in other patients. Despite absence of other genetic explanations for these features in *FBNI* sequencing, karyotype or exome sequencing, the possibility remains that they are unrelated to the *SPTANI* variant.

Hence, our case raises the possibility of a phenotypical spectrum for haploinsufficient *SPTANI* mutations, which ranges from peripheral to central: Mild peripheral neuropathy without central involvement (Beijer *et al.*, 2019), via a combination of mild neuropathy, delayed motor development, developmental disorder and normal brain structure (our case), to severe intellectual disability with motor impairment and hypoplastic brain structures but no neuropathy (Gartner *et al.*, 2018). Furthermore, several *de novo* missense or in-frame insertion/deletion mutations with dominant-negative on alpha-II spectrin aggregation (Saitsu *et al.*, 2010), have been described in *SPTANI*. These mutations are linked to even more severe phenotypes, with infantile onset epileptic encephalopathy at the most severe end (Syrbe *et al.*, 2017). However, the dominant-negative mutations may also result in less severe neurodevelopmental syndromes, which have only mild epilepsy or even no epilepsy (Syrbe *et al.*, 2017). Although peripheral involvement has not been reported in these patients, these variants could be seen as continuing the same phenotypic spectrum towards more severe central phenotypes.

Further studies are needed to address the mechanisms by which different *SPTANI* mutations cause damage to either central or peripheral nervous systems or both, and to analyse whether additional genetic variants or environmental factors can account for the wide range of phenotypic expression.

ACKNOWLEDGEMENTS

The authors thank the patient for participating in the study.

DATA AVAILABILITY STATEMENT

This work includes no new software and/or algorithms. Data are available upon reasonable request.

FUNDING

Work was supported by grants from Academy of Finland Clinical Researcher Funding, University of Helsinki 3 year grant, Emil Aaltonen foundation and HUS Helsinki University hospital to EY; Foundation for Pediatric Research and Pediatric Research Center to PI.

COMPETING INTERESTS

The authors report no competing interests.

SUPPLEMENTARY MATERIALS

This work includes no supplementary materials.

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Figure 1. Clinical images and sequencing. When photographed age 20, the patient was tall and had flat feet, long narrow limbs (A and B) and long fingers (C). Exome sequencing showed c.6367 del (p.Val2123Cysfs*45) in *SPTAN1*, which was confirmed with Sanger sequencing (D).

