A novel case of congenital spinocerebellar ataxia 5: further support for a specific phenotype associated with the p.(Arg480Trp) variant in SPTBN2

BMJ Case Reports

TITLE OF CASE

A novel case of congenital SpinoCerebellar Ataxia 5: further support for a specific phenotype associated with the p.Arg480Trp variant in *SPTBN2*

SUMMARY

A 4-year-old girl was referred to the geneticist with an history of ataxia associated with intention tremor of the hands, strabismus and hypermetropy. Her symptoms presented about 2 years earlier with inability to walk unaided and lower limbs hypotonia. Cognitive functions were normal. Brain MRI showed a cerebellar and vermian atrophy with enlargement of both the cerebrospinal fluid spaces and the IV ventricle. Family history was unremarkable. A genetic screening using a 42-gene panel for hereditary ataxia/spastic paraparesis identified a *de novo* c.1438C>T – p.(Arg480Trp) missense change in the *SPTBN2* gene (NM_006946.2). This variant is reported associated with congenital ataxia later evolving into ataxia and intellectual disability.
This case further supports the existence of a specific *SPTBN2* p.(Arg480Trp)-associated phenotype, with a *de novo* recurrence of this variant in the heterozygous state.

BACKGROUND

Spinocerebellar ataxia type 5 (SCA5, OMIM 600224) is an autosomal dominant form of pure cerebellar ataxia initially described in a large kindred descended from the paternal grandparents of United States President Abraham Lincoln (1), and later confirmed in a family from France and Germany (2, 3). Heterozygous missense variants or in-frame deletion in the beta Spectrin, noneritrocitic 2 (*SPTBN2*) gene on chromosome 11q13.2 have been reported as causative of SCA5 (4-6).
The initial symptoms are disturbance of gait, incoordination of limbs, abnormal eye movements and slurred speech. Age of onset is variable within families, starting between the second and seventh decade. Typically the onset is between 10 and 68 years (mean 33 years) and cerebellar symptoms are rarely complicated by extra-cerebellar anomalies such as myokymia, rest and intention tremor, brisk reflexes, and impaired vibration sense (7). Brain MRI shows atrophy of the cerebellum and cerebellar vermis (4).
An allelic autosomal recessive condition associated with *SPTBN2*, recently reported in two families with cerebellar ataxia from childhood and cognitive impairment, and named SCAR14 (8, 9). In these cases, pathogenic variants are nonsense. A complete loss of β-III spectrin function is thus implicated in motor and cognitive deficits from birth.
The prevalence of *SPTBN2* pathogenic variants may be higher than expected among congenital or early-onset cerebellar ataxia. In a recent report an overall prevalence of 5% *SPTBN2* was described among non-progressive congenital ataxia and psychomotor delay cases (10).
Finally, a heterozygous missense change (p.Arg480Trp) has been reported in three patients exhibiting infantile onset and global developmental delay (11-13). Although an undetected mutation in *trans* or an environmental modifier in a more severe phenotype than SCA5 have

been suspected in these patients, evidence that p.Arg480Trp is more deleterious than other heterozygous *SPTBN2* mutations is accumulating.

CASE PRESENTATION

The girl was born at term (40 weeks+5 days) from healthy non-consanguineous Italian parents after an uncomplicated pregnancy. Birth weight was 3,120 gr, length was 49.5 cm, cranial circumference (CC) was 35 cm and Apgar score at ten minutes was 10. No history of neurological diseases was reported in both the maternal and paternal families.
At 17 months, she was referred to the neuropsychiatric unit for motor delay. She was able to sit, she could stand with two aids, and showed lower limbs hypotonia. Her relational abilities and communication skills were normal for the age.
A brain MRI showed cerebellar and vermian atrophy with enlargement of both the cerebrospinal fluid spaces and the IV ventricle.
At 4 yrs, she was able to stand with little aid and to take few steps with an ataxic wide-based gait. To move in a room, she crawled near walls. A subtle intentional tremor when grasping and manipulating objects was noted. No cognitive or relational problem was reported at this age. Sphincter continence was reached. Autonomous in feeding and sleeping. Strabismus and hypermetropy were also present. Weight was 15 kg and CC was 35 cm. Abdomen ultrasound and Doppler echocardiography were normal.
The study was approved by the Internal Ethics Committee of the Department of Medical Sciences (University of Torino, Italy).

INVESTIGATIONS *If relevant*

We identified the c.1438C>T-p.(Arg480Trp) variant (Figure 1) using a custom screening next generation sequencing panel of 42 ataxia/spastic paraparesis related genes on a MiSeq platform (Illumina, San Diego, CA, USA). The panel was designed to cover 98% of target regions, including ± 50bp of intronic/exonic regions of *AFG3L2, CACNA1A, CACNB4, CCDC88C, DNMT1, EEF2, ELOVL4, ELOVL5, FGF14, IFRD1, ITPR1, KCNA1, KCNC3, KCND3, PDYN, PRKCG, SLC1A3, SPTBN2, TGM6, TMEM240, TTBK2, ADCK3, ANO10, APTX, C10orf2, FXN, KIAA0226, PCNA, POL3RA, POLR3B, PIK3R5, POLG, PNKP, SACS, SETX, SYNE1, SYT14, TPP1, TTPA, SPG7, SPG11* and *SPAST/SPG4*. After data extraction and alignment to the reference genome sequence, bioinformatics analysis was performed using standard bioinformatics tools. Validation was performed by Sanger sequencing, and classification of variants followed ACMG rules.
In the patient analysis, coverage was 99.6% and 96.5% of sequences had at least 50 reads. The c.1438C>T variant was not present in the GnomAD public database (14), and was absent in the proband's parents.
Using array-CGH (180K, Agilent Technologies, Santa Clara, CA, USA), we also found a 75-137 kb deletion on chromosome 4q23 involving the *STPG2* gene [arr[GRCh37]4q23(98893553x2,98922189_98996684x1,99030399x2)]. This copy number variant has never been reported in the literature or public databases, and no known disease is associated with *STPG2*. The deletion was therefore labeled as of uncertain significance.

OUTCOME AND FOLLOW-UP

A follw-up of the patient is not yet available.

DISCUSSION *Include a very brief review of similar published cases*

Here, we report the fourth patient worldwide carrying the c.1438C>T-p.(Arg480Trp) de novo variant in the *SPTBN2* gene. A first case with c.1438C>T-p.(Arg480Trp) was described in 2013 in a 12-year-old girl with dysarthria, horizontal jerk nystagmus on lateral gaze that did not extinguish, rotatory nystagmus on upgaze, facial myokimia, moderate dysrmethria evident on finger-to-nose, severe dysdiadochokinesia, severe difficulty with finger tapping and heel-to-shin maneuver, diffuse hyperreflexia including cross adductors, wide-based gait and down going plantars with ankle clonus bilaterally. Neuroimaging at 1 year of age revealed diffuse cerebellar hypoplasia with otherwise normal cerebrum and brainstem. Follow up images at 2 and 9 yrs. Revealed mild progression of the cerebellar atrophy (15). Although, in this case it was not possible to verify parents, the variant was highly suspected to be de novo. A few years later a child of non-consanguineous parents of Mediterranean origin with the same de novo variant was described. The girl was noted to have unsteady hand and arm movements within a few weeks from birth. A brain MRI showed cerebellar hypoplasia. The ataxic features were present at 4 years and 10 months; social interaction with other children was good, and had better receptive than expressive language development. Clinical features lead to a diagnosis of cerebral palsy (13).
Finally, a 2-year-old girl with c.1438C>T-p.(Arg480Trp) was recently described. She presented with generalized hypotonia, global developmental delay, and alternating esotropia. At 12 months, she said her first words and got head control, but could not sit without support. She progressively developed a cerebellar syndrome with gait ataxia and dysarthria. Brain MRI performed at age 1 year 10 months showed global cerebellar hypoplasia with enlarged interfolial spaces, in the absence of any brainstem or supratentorial abnormalities (12).
All reported cases heterozygous for *SPTBN2* p.Arg480Trp and ours share a common overlapping phenotype of congenital ataxia with onset in the neonatal age with abnormal ocular movements and developmental delay, later evolving into ataxia and intellectual disability. Additional neurological signs have been occasionally detected.

Since the clinical picture closely resembles the recessive *SPTBN2*-related SCAR14, it has been hypothesized that a second, unidentified mutation in the same gene or in a modifier one could explain this unusual phenotype (9). However, it has been previously demonstrated in cultured hippocampal neurons that the p.Arg480Trp variant has a deleterious effect (13) and both the presence of a second single nucleotide variant in *SPTBN2* or in another ataxia-related gene have been ruled out by us and by (12).
Taken together, our data confirm the presence of a peculiar phenotype in SPTBN2-related diseases, resembling the autosomal-recessive SCAR14 and associated with the occurrence of a de novo p.Arg480Trp variant.
Further variants in this gene may be associated with autosomal dominant early onset severe ataxia.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

The *SPTBN2* gene is associated with autosomal dominant (adult-onset) and recessive (childhood-onset) ataxia.
The *SPTBN2* p.Arg480Trp variant is associated with congenital ataxia, later evolving into ataxia and intellectual disability.
The analysis of *SPTBN2* may reveal unexpected variants associated with congenital ataxia.

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FIGURE/VIDEO CAPTIONS

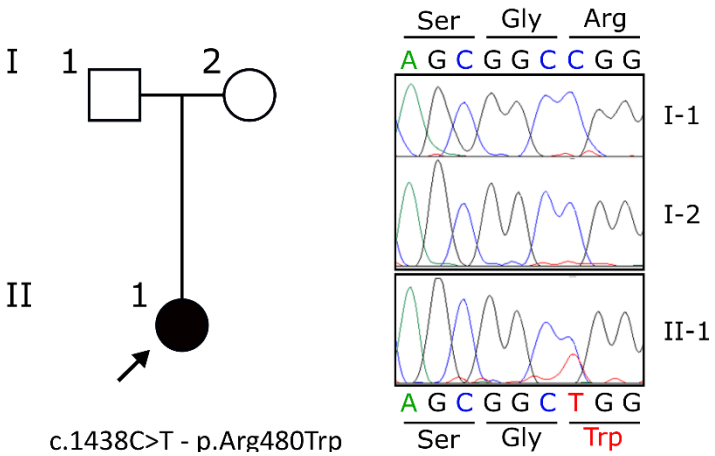

Figure 1. Pedigree and Sanger sequencing. The pedigree of the family is represented. On the right the electropherograms show the c.1438C>T (p.Arg480Trp) in the *SPTBN2* gene was present in the proband and absent in her parents.

PATIENT'S PERSPECTIVE

Not available

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