A novel *SETX* gene mutation producing ataxia with oculomotor apraxia type 2

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Abstract

Aim of the Study: This paper documents a patient with ataxia with oculomotor apraxia type 2 (AOA2) caused by an *SETX* mutation (c.502C>T) combined with a large *SETX* deletion (including exons 11-15).

The first symptoms appeared in a female Caucasian patient at the age of 25, in the form of deteriorating dexterity, gait instability and dizziness. The diagnostic work-up demonstrated dysarthria, an extraocular muscle dysfunction, smooth ataxia in all four limbs and in the trunk, mild pyramidal symptoms with an elevated alpha-fetoprotein level in the serum and cerebellar atrophy revealed on MRI. The family history was unremarkable. The diagnosis of AOA2 was confirmed by genetic testing.

Conclusions: We have found a novel *SETX* gene missense mutation, combination of which with an extensive *SETX* deletion results in AOA2. The results of clinical, laboratory, radiographic and genetic tests are described and compared with those of the cases in the literature.

KEYWORDS: ataxia with oculomotor apraxia type 2, early-onset ataxia, novel senataxin mutation

Introduction

After Friedreich's ataxia, ataxia with oculomotor apraxia type 2 (AOA2) is the second most common autosomal recessive inherited ataxia in the European population. This disease, which has an early onset and progresses slowly, is characterized by cerebellar symptoms, oculomotor apraxia, axonal sensorimotor neuropathy, a cognitive impairment and other neurological features, including pyramidal symptoms, involuntary movements such as head tremor, dystonia and chorea [1, 2]. A typical laboratory finding is an elevated serum alpha-fetoprotein (AFP) level. In most of the cases, the brain MRI scans demonstrate marked cerebellar atrophy, mainly in the vermis. The genetic cause of AOA2 is a mutation in the *SETX* gene on chromosome 9q34, which encodes senataxin, a nuclear protein that has DNA/RNA helicase activity and possibly plays a role in DNA repair and RNA processing.

This report describes a female Caucasian patient with an AOA2 phenotype with one novel *SETX* gene mutation.

Case presentation:

A 28-year-old female patient was referred to our clinic with signs of impaired coordination. The first symptoms appeared at the age of 25, with dizziness, imbalance and clumsiness of the hands. Some months later, her speech became slower and mildly slurred. She also had gaze fixation difficulty, with intermittent diplopia and blurred vision.

Her neurological examination revealed mild overshooting saccadic pursuits, horizontal gaze fixation instability, oculomotor apraxia, slurred speech, smooth ataxia

in all four limbs and in the trunk, brisk tendon reflexes in the lower extremities and normal sensory functions. She had no other diseases. Her family history was unremarkable. Her parents and her brother did not report any neurological problems (Figure 1/a).

The routine laboratory findings, including a complete blood count, creatine kinase and cholesterol were normal. The serum AFP level was elevated, at 21.9 ng/ml (normal < 7.0 ng/ml). The brain MRI revealed moderate cerebellar atrophy with normal supratentorial structures (Figure 2).

Cardiological, diabetological and fundoscopic examinations did not demonstrate any pathological markers. Genetic testing for Friedreich's ataxia resulted in normal GAA repeat numbers (7 and 13 repeats). The cerebellar atrophy seen in the MRI scan, the elevated AFP serum level and the lack of oculocutaneous telangiectasias led to a presumed diagnosis of AOA2. *SETX* gene sequencing analysis was therefore performed (Centogene AG, Rostock, Germany).

Gene sequencing identified a novel heterozygous point mutation in the gene: c.502C>T p.Arg168Trp in exon 6 (Figure 1/b). Multiplex ligation-dependent probe amplification testing revealed a large heterozygous deletion, including exons 11-15. The presence of the c.502C>T variant in the ExAC database at a very low frequency (1/73,152 alleles in the European population) and the absence of homozygous healthy individuals, is suggestive its pathogenic effect (http://exac.broadinstitute.org/variant/9-135211899-G-A).

The identified arginine 嘅 tryptophan change caused by the missense mutation is located within a highly conserved region of the protein senataxin (Fig. 1/c). We presume that this compound heterozygous state is responsible for the *SETX* insufficiency.

We were unable to perform the segregation analysis because the patient's father has already died and her closest relatives (mother and brother) did not give their consent to genetic testing.

Discussion

The majority of the AOA2 mutations reported earlier involved frameshift, missense, nonsense and splice-site mutations and deletions to various extents in the *SETX* gene. We report here a novel missense mutation and a large deletion in this gene, observed in a young woman with cerebellar ataxia, oculomotor apraxia, an elevated serum AFP level and cerebellar atrophy. This missense mutation, located outside the helicase domain of the protein senataxin, affected the N-terminal domain, while the extensive deletion gave rise to a truncating protein structure, including loss of the nuclear localization signal and in part the C-terminal helicase domain [2].

Table 1 presents the major clinical signs of 13 other AOA2 patients with exon 6 mutations [3-6] in comparison with the profile of our patient. Our patient manifested a later age at onset and brisk tendon reflexes relative to the other AOA2 cases. In our patient, the milder phenotype and the later onset of disease, compared to classic AOA2 cases, may be suggestive of a residual activity of *SETX* due to the hypomorph missense mutation.

The previous genotype to phenotype correlations coincide moderately with the clinical presentation of our patient. Despite the observation of brisk tendon reflexes in the lower limbs, pyramidal signs were more prevalent with missense mutations in the helicase domain. Dystonia was frequent, primarily with missense mutations in the helicase domain [2], and the lack of dystonia in our patient is therefore not surprising.

Oculomotor apraxia was present in about half of the literature AOA2 patients, and also in our patient. The elevated AFP levels and the cerebellar atrophy were significant diagnostic findings in almost all AOA2 cases, including our patient. The earlier studies reported that the phenotype was most severe when the mutation was missense and located outside the helicase domain, in contrast with the truncating mutations and the missense mutations affecting the helicase domain [2]. Our patient's symptoms are so far mild, possibly because of the compound heterozygous state and respectively the short time that has elapsed since the onset of the disease.

Declaration of Interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgement

This work was supported by KTIA Grant No. 13 NAP-A-II/17.

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Table 1. Comparison of our patient with 13 other AOA2 patients with exon 6 mutations of the *SETX* gene [3-6]

	Data on 13 previously reported patients with exon 6 mutations	Our patient
Age at onset (years)	Mean: 12.7	25
Initial signs	Ataxia:11/13 cases	Ataxia
	Dysarthria: 3/13 cases	
	Chorea: 2/13 cases	
	Head tremor: 1/13 cases	
Oculomotor apraxia	6/13 cases	Present
Other ocular signs	Strabism: 6/13 cases	Absent
	Nystagmus: 3/13 cases	
Tendon reflexes	Absent: 9/13 cases	Brisk
	Decreased: 4/13 cases	
Head tremor	4/13 cases	Absent
Deep sensory loss	9/13 cases	Absent
Cerebellar atrophy	Mild: 2/13 cases	Moderate
	Moderate: 6/13 cases	
	Severe: 3/13 cases	
	Not available: 2/13 cases	
AFP level (ng/ml)	32.9	21.9

Figure 1. a) Family tree of the patient. b) Upper: DNA sequence of the patient, showing the heterozygous form of the exon 6 missense mutation c.502C>T p.Arg168Trp. Lower: DNA sequence of the healthy individuals c) The identified aminoacid change is located within a highly conserved region of the protein

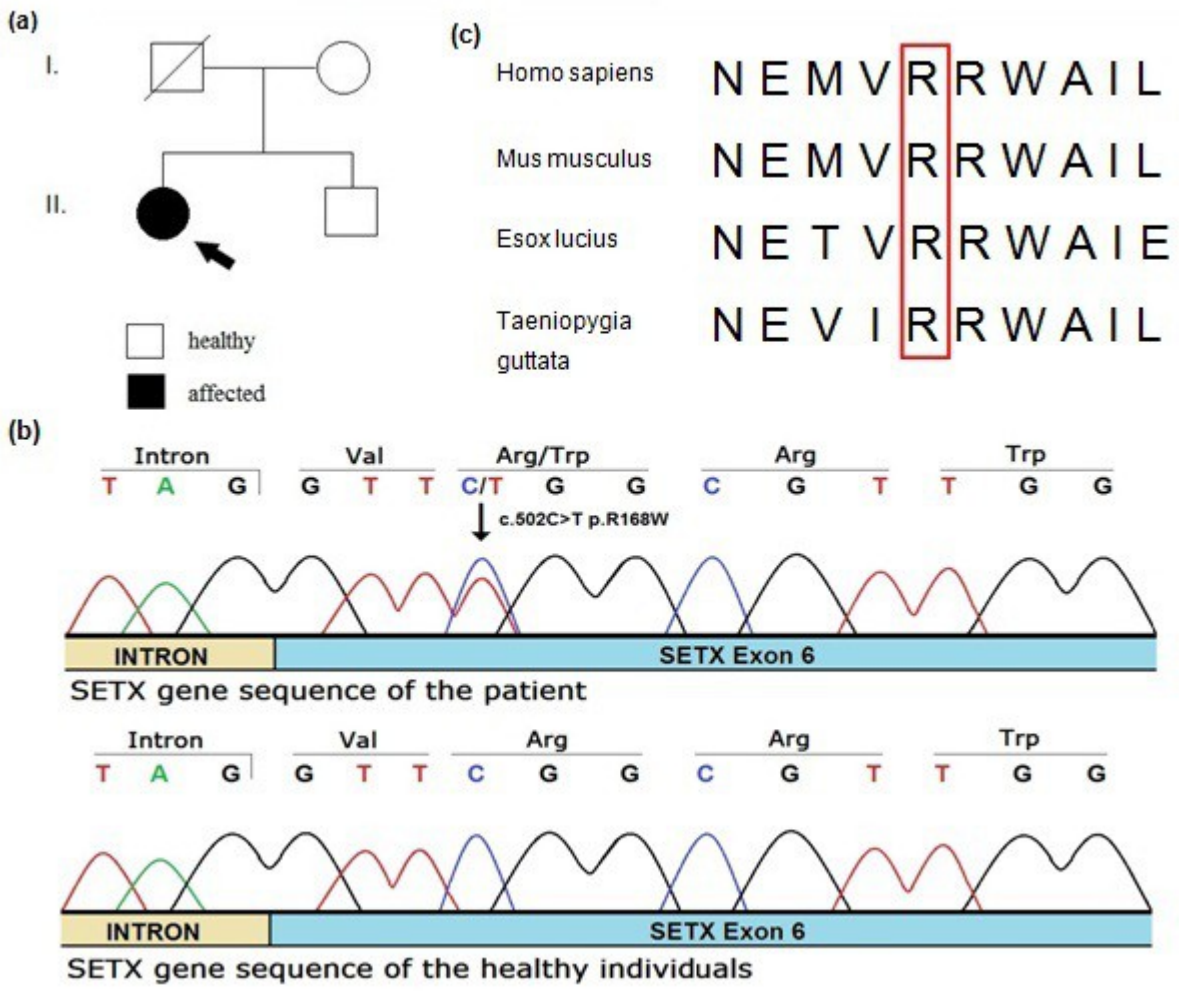

Figure 2. Brain MRI of the patient, sagittal T1-weighted, indicating moderate cerebellar atrophy