

Ataxia with ocular apraxia type 2 not responding to 4-aminopyridine: A rare mutation in the *SETX* gene in a Saudi patient

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Summary

Ataxia with ocular apraxia type 2 is an autosomal recessive disorder caused by a mutation in the senataxin (*SETX*) gene. The disease is characterized by early onset cerebellar ataxia, cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia, and increased levels of α -fetoprotein. Reported here is a rare homozygous frameshift deletion c.5308_5311del, p.(Glu1770Ilefs*15) in the *SETX* gene in a Saudi family. Ataxia with ocular apraxia type 2 was diagnosed based on the patient's history, an examination, and genetic testing. Genetic testing remains the only definitive method with which to identify the gene responsible. This is the third case report of this rare mutation in the literature. Ataxia with ocular apraxia type 2 continues to be a challenging disease to manage with no therapeutic options available to date. In the current case, the medication 4-aminopyridine was inefficacious in improving walking or balance. Further research is needed to identify potential treatments for this challenging condition.

Keywords: *SETX*, senataxin, ataxia with ocular apraxia type 2, rare mutation, Saudi Arabia

1. Introduction

The inherited ataxias are a clinically and genetically heterogeneous group of diseases that occur due to dysfunction of the cerebellum and its connections (1). In most of these disorders, the disease develops between 30-50 years of age. Several mutations in a variety of genes have been identified as causing these ataxias (2). Ataxia with ocular apraxia type 2 is an autosomal recessive disorder caused by a mutation in the senataxin (*SETX*) gene. The disease typically develops between 10-25 years of age. The disease is characterized by early onset cerebellar ataxia, cerebellar atrophy, axonal sensorimotor neuropathy, and oculomotor apraxia. Other clinical features include abnormal movements

such as chorea and dystonic posturing of the hands and head or postural tremors. Serum α -fetoprotein is elevated in more than 90% of affected individuals. Other possible biochemical changes include high levels of serum cholesterol and creatine kinase (3). A defective response to DNA damage has been noted in several autosomal recessive ataxias. Senataxin is a nuclear 2,667-amino acid protein involved in the response to DNA damage and RNA metabolism (4). The patient in the current case presented clinically with ataxia with ocular apraxia and elevated serum α -fetoprotein, and a molecular analysis was performed. Reported here is a rare homozygous frameshift deletion c.5308_5311del, p.(Glu1770Ilefs*15) in the *SETX* gene causing ataxia with ocular apraxia type 2 in a Saudi patient with no response to 4-aminopyridine therapy. To the extent known, this is the only reported case of this mutation in an Arab county.

2. Case Report

A 33-year-old Saudi woman presented with a history

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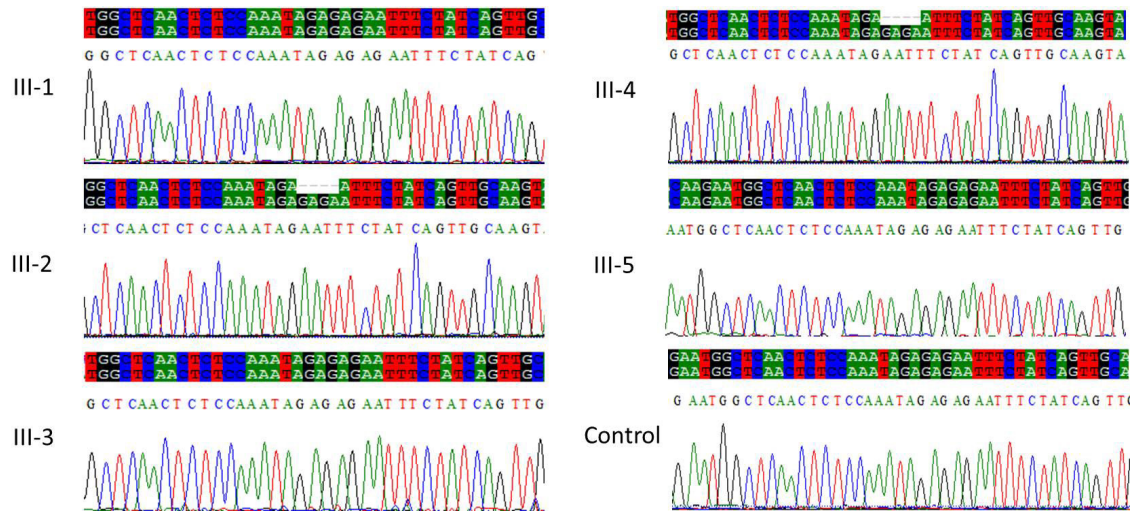


Figure 1. Sanger sequence analysis for validation of exome sequencing. Probands III-2 and III-4 are affected family members who clearly exhibit a deletion of 4 bases from the *SETX* gene compared to the normal and wild-type control groups.

of gradually progressive ataxia, a lack of balance, frequent falls, and tremors in the trunk for many years. There was no history of weakness or sensory changes, a previous infection, a fever, a skin rash, mouth or genital ulcers, or photosensitivity. The patient denied having memory loss or psychiatric symptoms. Her past medical history was unremarkable and did not include endocrine disorders, infections, sleep disorders, or trauma. Her family history indicated a similar condition in her older sister. Her parents are first-degree relatives. She was not on any medications. On examination, the patient was conscious and oriented with normal cognitive functions. The patient had limited language skills and scanning speech. She was able to comprehend language, *i.e.* naming and repetition were intact, but she was unable to read or write. Her short-term memory was affected, but her long-term memory was normal. There was no telangiectasia in her mucous membranes or sclera, and a cranial nerve examination was normal. She had nystagmus in all directions, and a motor examination revealed decreased tone all over with 5/5 power. Hyporeflexia was noted. A cerebellar examination revealed dysmetria and dysdiadokinesia. She had difficulty walking without assistance. There were no associated skeletal deformities, and a fundus examination was normal. A gait examination revealed a wide-based gait with a tendency to fall to either side.

Extensive blood work, including both routine and specific tests to rule out the cause of ataxia in the patient's age group, was negative. These included vitamin E levels, vitamin B-12 levels, a blood smear for acanthocytes, viral serology, a thyroid function test, serology for celiac disease, and lipoprotein electrophoresis. Alpha-fetoprotein was elevated at 64.8 ng/mL (normal < 10 ng/mL). Genetic testing was performed and sequencing identified a homozygous frameshift deletion c.5308_5311del, p.(Glu1770Ilefs*15) in the *SETX* gene. Probands III-2

and III-4 are affected family members clearly exhibiting a deletion of 4 bases (Figure 1). This mutation was verified in 100 unrelated healthy persons, but none had this sequence variation. This variant has been identified in three heterozygotes in the Exome Aggregation Consortium (ExAC) dataset, which includes a total of over 60,000 unrelated individuals. The variant has four nucleotides deleted from exon 11/26 of the *SETX* gene. This causes a change from Glutamic acid to Isoleucine at amino acid residue 1,770/2,677 of the full-length protein and a shift in the reading frame that introduces a premature termination at codon 15 of the new reading frame. This is predicted to cause a lack of or abnormal protein function either through protein truncation or nonsense-mediated mRNA decay.

The patient was a heterozygous carrier of three missense novel mutations in *GBA2* gene c.2201G>A, p.(Arg734His), *SETX* c.5360A>T, p.(Tyr1787Phe), and *WDR81* c.2051A>C, p.(Gln684Pro). In addition, she was a heterozygous carrier of a novel mutation in *VAMP1* gene c.2+12C>T. The diseases caused by mutations in *GBA2* and *WDR81* are inherited in an autosomal recessive manner, while both autosomal recessive and dominant patterns have been identified with *SETX*, and the disease caused by mutations in *VAMP1* is inherited in an autosomal dominant manner.

This variant is classified as pathogenic in light of the current evidence (established association between the gene and the patient's phenotype, rarity in control populations, identification of the variant in a homozygous state in four related individuals with the same phenotype, proof of segregation, and mutation type (frameshift)). Ataxia caused by a mutation in *SETX* is inherited in an autosomal recessive manner. The patient is homozygous for the variant, which is in line with autosomal recessive inheritance.

A nerve conduction study and electromyography revealed a mixed axonal and demyelinating motor and

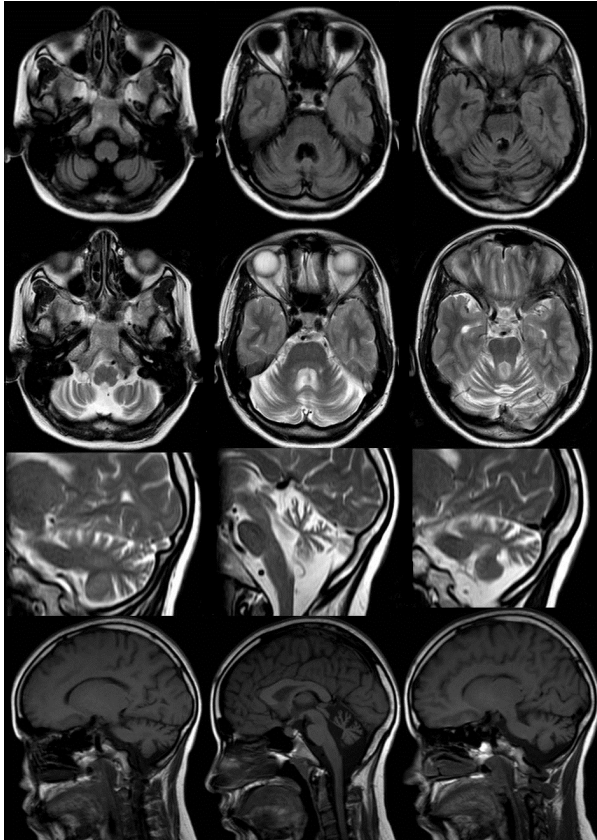


Figure 2. MRI of the brain showing cerebellar atrophic changes with prominent cerebrospinal fluid spaces.

sensory neuropathy. Magnetic resonance imaging (MRI) of the brain revealed cerebellar atrophic changes with prominent cerebrospinal fluid spaces (Figure 2).

A detailed family pedigree was drawn after obtaining detailed information from the parents, as shown in Figure 3. Family and genetic counseling were offered through a genetic consultant. The patient was tentatively given 4-aminopyridine for four months with no improvement. Pre-, periodic, and post-treatment assessment of gait consistently indicated a lack of response to this medication. The patient was last seen two months prior to publication of this report and is being followed up by the outpatient department at regular intervals every 4 months. The course of this disease is slow and progressive, and the patient is currently wheelchair-bound.

3. Discussion

SETX encodes senataxin, which is a 2,667-amino acid protein that contains a DNA/RNA helicase domain at its C-terminal end. The function of senataxin is poorly understood. It is believed to be involved in DNA repair, replication, recombination, and transcription, RNA processing, transcript stability, and translation initiation (4). In addition, *SETX* has been found to play a role in the defense against oxidative DNA damage (5).

Mutations in this gene have been associated

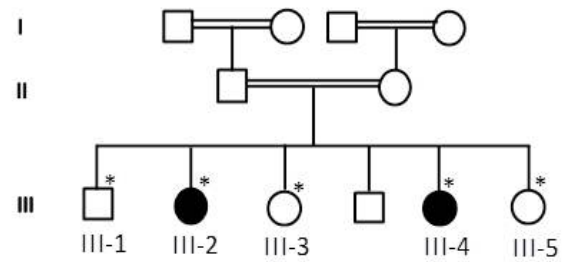


Figure 3. A family pedigree was drawn after receiving detailed information from family members. Individuals marked with asterisks were available for genetic testing.

with autosomal recessive ataxia with ocular apraxia type 2 and an autosomal dominant form of juvenile amyotrophic lateral sclerosis. Ataxia with ocular apraxia type 2 is considered to be the second most common autosomal recessive cerebellar ataxia after Friedreich ataxia (6). Of > 120 unique *SETX* mutations reported to date, different types including missense, nonsense, splice site, frameshift, and deletion/insertion mutations have been noted in patients with ataxia with ocular apraxia type 2. These mutations are presumed to silence the functioning of *SETX*, resulting in a recessively inherited disorder (7).

A review of the literature revealed two reports of an *SETX* c.5308_5311del, p.(Glu1770Ilefs*15) variant (8,9). One report described a Cypriot family with four affected members with autosomal recessive cerebellar ataxia. The c.5308_5311del variant was found to co-segregate with the disease in the family, and it was homozygous in all four affected members. The affected family members had an age of onset of 8-14 years, and they presented with clinical manifestations such as slow progressive ataxia of the limbs and trunk, eye movements with multidirectional nystagmus, peripheral neuropathy, spasticity, the Babinski sign, and areflexia (8). This variant was heterozygous in a singular patient with ataxia in combination with the *SETX* variant c.6547-1G>C variant (9). The previously reported cases are similar to the current case in terms of the age of onset, sex, clinical manifestations, disease severity, family history, and the method of genetic diagnosis. Minor differences in the current case were the race of the patient (Arab descent) and tentative treatment with 4-aminopyridine.

Ataxia with ocular apraxia type 2 is clinically characterized by a group of symptoms involving the cerebellum, oculomotor apparatus, and peripheral nervous system and other findings involving other parts of the neuraxis (10). Cerebellar symptoms include ataxia, gait difficulties, head or postural tremors, dysmetria, dysdiadochokinesia, and nystagmus. Oculomotor symptoms (present in approximately 50% of patients) include oculomotor apraxia, saccadic pursuit, gaze-evoked nystagmus, poor horizontal optokinetic nystagmus, and square-wave jerks.

Oculomotor apraxia is characterized by a dissociation between the movement of the eyes and head when the head is free, *i.e.* the head reaches the lateral target before the eyes. Peripheral nervous system involvement includes areflexia and subsequent peripheral axonal sensorimotor neuropathy. The disease progresses slowly with no cardiac involvement, cancer predisposition, or immunodeficiency. Other clinical manifestations include pyramidal signs, a dystonic posture of the hands, choreic movements, and mild cognitive impairment (11).

Ataxia with ocular apraxia type 2 is diagnosed based on the patient's history, an examination, and genetic testing. A history and a physical examination are of paramount importance to diagnosing cerebellar ataxia, and this is especially true if other family members are affected. MRI of the brain is crucial to evaluating structural abnormalities such as cerebellar atrophy. Genetic testing remains the only method with which to definitively identify the gene responsible (12). The only biochemical marker that is typically found is elevated serum α -fetoprotein, but that finding is not specific to ataxia with ocular apraxia type 2. Electromyography typically reveals signs of axonal neuropathy. A nerve biopsy typically reveals chronic axonal neuropathy with preferential loss of large (and to a lesser degree small) myelinated fibers, but it is rarely performed (13).

Management of ataxia with ocular apraxia type 2 mainly includes occupational and physical therapy for gait dysfunction and speech therapy. There is currently no treatment that can cure the disease or alter its progression (14). 4-aminopyridine (prolonged-release fampridine) is a lipid-soluble selective potassium channel blocker that readily crosses the blood-brain barrier and that can improve walking in adult patients with multiple sclerosis. It acts on the surface of nerve fibers to reduce the leakage of ionic current from potassium channels in demyelinated axons, thereby inhibiting repolarization and prolonging the duration of action potentials, presumably allowing for more action potential propagation along the cell membrane. This medication is used off-label to improve walking in patients with hereditary ataxia, and it has had success in some patients. However, the current case suggests that this medication is not effective in the management of ataxia with ocular apraxia type 2. Patients with that condition have a varied prognosis, but improvement in their condition is unlikely (15).

Saudi Arabia has a high rate of consanguinity, which according to some studies ranges from 25% to 65% (16). This favors the occurrence of autosomal recessive diseases. Proper education emphasizing this fact should be offered to the Saudi community. Premarital or preimplantation genetic screening allows a genetic diagnosis early on and can help couples who carry the same disease-causing variants to make an informed decision regarding their marriage and the consequences

of their decision. The current authors have previously reported a wide variety of novel and rare genetic mutations causing a broad spectrum of diseases and clinical manifestations in the Saudi community (17-24). Molecular testing of potential carriers of those mutations may be urgently needed.

In conclusion, reported here is a rare homozygous frameshift deletion c.5308_5311del, p.(Glu1770Ilefs*15) in the *SETX* gene in a Saudi family. This is the third case report of this rare mutation in the literature. Ataxia with ocular apraxia type 2 continues to be a challenging disease to manage, with no therapeutic options available to date. In the current case, the medication 4-aminopyridine was inefficacious in improving walking or balance. Further research is needed to identify potential treatments for this challenging condition.

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