

# Hereditary Ataxia with a Novel Mutation in the *Senataxin* Gene: A Case Report

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## What's Known

- At least 115 different mutations in the *senataxin* (*SETX*) gene have been identified to cause ataxia.
- There are no reports of any *SETX* gene mutation among the Iranian population.

## What's New

- A novel mutation, c.5268delT (p.Phe1756LeufsX30), in the *SETX* gene has been identified.
- For the first time, we report on two Iranian cases with *SETX* gene mutation in homozygous and heterozygous states.

## Abstract

Hereditary ataxias (HA) are a group of inherited neurological disorders caused by changes in genes. At least 115 different mutations in the *senataxin* (*SETX*) gene causing ataxia have been identified. There are no reports of any *SETX* gene mutation among the Iranian population. Here we report on two cases with homozygous and heterozygous mutations in which one patient was affected by HA with oculomotor apraxia type 2, and the other was a carrier of the disorder. In 2016, the affected patient was referred to the Biogene Medical and Genetic Laboratory (Tehran, Iran) suffering from imbalance and tremor of both head and body. The coding regions of 18 genes, including the *SETX* gene, were screened. The target regions were captured using the NimbleGen chip followed by next-generation sequencing (NGS) technology on the Illumina HiSeq2500 platform. NGS, a DNA sequencing technology, has greatly increased the ability to identify new causes of ataxia; a useful tool for the prevention of primary manifestations and treatment of affected patients. In the present study, a novel mutation in the *SETX* gene has been identified.

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**Keywords** • Spinocerebellar degenerations • Mutation • *SETX* gene • Nervous system diseases • Ataxia

## Introduction

The HA are a group of genetically and clinically heterogeneous disorders characterized by gradually progressive uncoordinated gait accompanied by poor hand coordination and speech impairment. Often, atrophy of the cerebellum occurs. Most affected individuals additionally have oculomotor apraxia, which impairs purposeful eye movement. Based on the Mendelian modes of inheritance, the HA are classified as autosomal recessive, autosomal dominant, and X-linked.<sup>1</sup> They are caused by changes in the genes and can be inherited. HA are most often diagnosed through genetic testing by identifying the defective gene. Ataxia with oculomotor apraxia has been classified into several types, among which types 1, 2, and 4 are the most common.<sup>2</sup> Although the types are very similar, they are caused by mutations of different genes. Here we report HA with oculomotor apraxia type 2 caused by a pathogenic mutation in the *SETX* gene.

## Case Presentation

The first case was a 24-year-old male patient suffering from imbalance and tremor of both head and body. The patient was referred to our clinic in the Biogene Medical and Genetic

Laboratory, Tehran, Iran. A magnetic resonance imaging (MRI) scan was performed and probable ataxia with oculomotor apraxia was diagnosed. Subsequently, DNA analysis was performed to determine the genetic status of the patient. After obtaining a written informed consent, his DNA was extracted from peripheral blood cells using the standard method. Genetic analysis was performed on 18 genes, including *KCNA1*, *CACNA1A*, *CACNB4*, *SLC1A3*, *VAMP1*, *APTX*, *SETX*, and *PNKP*. The target regions were captured using the NimbleGen chip on the genes of interest followed by NGS on the Illumina Hiseq2500 platform. The second case, a carrier of HA, was a 36-year-old asymptomatic man who was a blood relative of the affected patient. He voluntarily participated in laboratory analysis and his DNA was extracted from peripheral blood cells using the standard method. The DNA was subjected to genetic analysis for the *SETX* gene using the polymerase chain reaction (PCR) DNA sequencing method.

Neurological examination of the affected patient revealed dysarthria, bilaterally restricted upward and lateral eye movements, limb and gait ataxia. The onset of his symptoms was at the age of 20. The MRI of his head revealed cerebellar atrophy (figure 1). DNA analysis showed a pathogenic mutation, c.5268delT (p.Phe1756LeufsX30), in the *SETX* gene in a homozygous state (figure 2). Additionally, the result of the BLAST analysis revealed that the deleted nucleotide was a type T on the site of 5468 in *SETX* mRNA. *SETX*-related ataxia with oculomotor apraxia type 2 was inherited in an autosomal recessive manner. Mutation detection in parent cells showed the heterozygote status of this mutation. The same *SETX* gene mutation, c.5268delT (p.Phe1756LeufsX30), in heterozygous status was detected in the second case (figure 2). Therefore, he was a carrier of the familial mutation. The family pedigree of the patient is depicted in figure 3.

### Discussion

The HA are a genetically heterogeneous group of disorders which are difficult to separate clinically as they are all diagnosed with poor motor coordination arising from a malfunction of the cerebellum and its connections.<sup>3</sup> Based on the Mendelian modes of inheritance, the HA are classified as autosomal recessive, autosomal dominant, and X-linked.<sup>1</sup> The prevalence of the autosomal dominant cerebellar ataxias is reported to be 1-5:100,000 population. The prevalence of the autosomal recessive type of HA is roughly estimated to be 3:100,000 with ataxia-telangiectasia, Friedreich ataxia, and

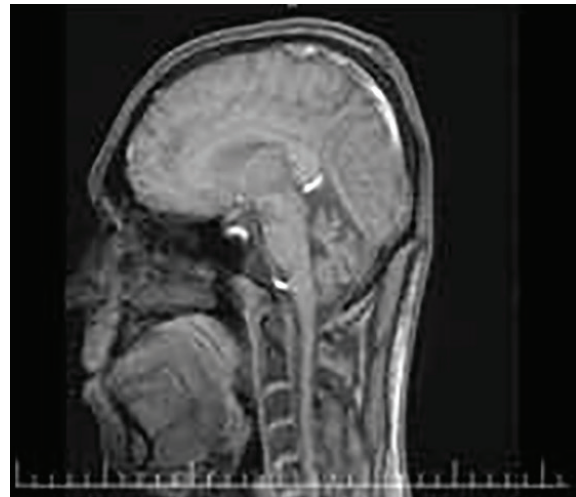


Figure 1: Brain MRI of the proband with cerebellar atrophy.

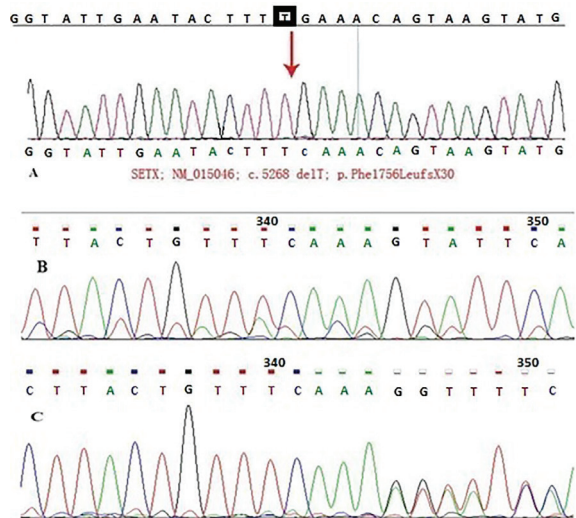


Figure 2: The DNA sequence of the *SETX* gene in the affected patient with the frameshift mutation, c.5268delT (p.Phe1756LeufsX30), in homozygous state (A). Mutation confirmation by reverse primer (B). The DNA sequence of the *SETX* gene in the second case showing the same mutation in heterozygous status (C).

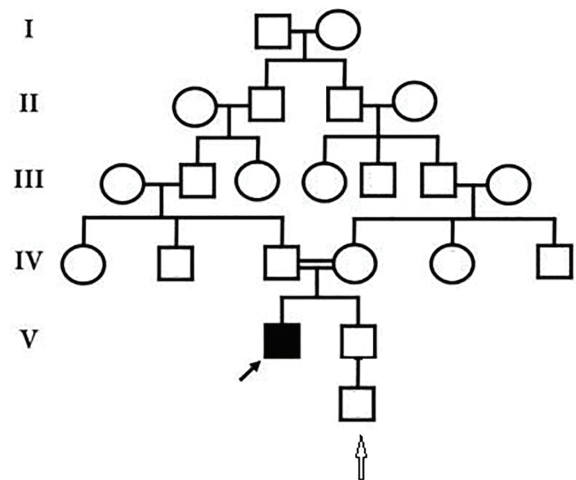


Figure 3: Family pedigree of the cases (affected patient and the carrier of HA).

ataxia with oculomotor apraxia being the most frequent.<sup>4</sup> HA are caused by changes in the genes and can be inherited.<sup>1</sup>

Mutations in the *APTX*, *SETX*, and *PNKP* genes result in ataxia with oculomotor apraxia types 1, 2, and 4, respectively. These genes provide instructions for the production of proteins that are involved in repairing damaged DNA. Mutations in any of these genes reduce the amount of produced functional proteins. The lack of functional proteins disrupts DNA repair and can lead to the accumulation of DNA damage in cells, particularly affecting brain cells in the part of the brain involved in coordinating movements (the cerebellum).<sup>5-8</sup>

At least 115 different *SETX* gene mutations causing ataxia have been identified.<sup>9</sup> Most mutations replace single amino acids in the *SETX* gene. There are no reports of any *SETX* gene mutation among the Iranian population. For the first time, we have reported two Iranian cases with homozygous and heterozygous mutations in which one was affected and the other was a carrier of HA with oculomotor apraxia type 2.

In the present study, we identified a novel mutation [c.5268delT (p.Phe1756LeufsX30)]. Bioinformatics tools such as SIFT, PolyPhen-2, and Project Hope predicted this mutation to be a deleterious mutation. This frameshift mutation causes an early termination of the amino acid coding, which affects the protein's function. Genetic diagnosis is routinely performed by sequence analysis of candidate genes to confirm previously identified mutations. NGS of the DNA using gene panels enabled us to simultaneously examine coding regions and splice-junctions of several candidate genes. It shortened the duration of the analysis which was not only beneficial in the treatment, but also in the prenatal diagnosis and carrier detection of the disease.

## Conclusion

Due to the diversity of symptoms and various genetic causes of ataxia, clinicians and geneticists are faced with a diagnostic challenge. Advancement in DNA sequencing technology (e.g., NGS) has greatly increased our ability to identify new causes of ataxia, which can be effective in the prevention of primary manifestations and treatment of the affected patients.

## Acknowledgment

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**Conflict of Interest:** None declared.

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