CASE STUDY

Strand Clinical Exome Test Provides Answers for Ataxia in a Young Child

Introduction

Ataxia with oculomotor apraxia type 1 is a severely disabling neuromuscular disorder. Uncoordinated movement of limbs (Ataxia) is usually the first manifestation of this inherited disorder. The inability to move eyes sideways (Apraxia) also limits peripheral vision of the affected person. Ataxial disorders can be classified into ataxia with oculomotor apraxia type 1 (AOA1), ataxia with oculomotor apraxia type 2 (AOA2), ataxia telangecstasia, Friedrich's ataxia and ataxia with vitamin E deficiency (Pearson 2016). Type 1 AOA has an early age of onset and is usually detected around age 4.

Type 2 AOA is a slow and progressively debilitating neuromuscular disease which can manifest as symptoms around the age of 15 years. Degeneration of nerves is also a feature of both kinds of ataxia disorders, leading to additional disability.

Ataxial disorders can be differentiated based on the presence of specific genetic mutations. The Strand Clinical Exome Test has been designed to assess genetic variants as well as deletions in genes that cause these multiple ataxial disorders. An exact diagnosis can be arrived at, based on the mutations identified using this test.

Patient Profile

Ardarferoze Vakil*, aged 7 years, had been a physically active child born to Rustom* and Gulnaz Vakil*. Around his 4th birthday, he began experiencing uncoordinated movements and had several instances of physical imbalance and resulting injuries.

Rustom and Gulnaz had been relieved that their fourth child appeared to be normal, especially since the middle ones, Farah* and Aftab*, suffered from ataxia-like developmental problems. The first daughter, Behnoush was unaffected by ataxia. Ardarferoze did not show similar degeneration like his two older siblings in early childhood and they were hopeful that this child would not require the constant assistance and care that they did.

Gender: Male

Age: 7 years

Location: Mumbai, Maharashtra

Diagnosis: Ataxia with oculomotor apraxia, type 1.

Strand Test: Clinical Exome

Conclusion:

- A pathogenic recessive mutation in the *APTX* gene identified.
- Differential diagnosis between various ataxial disorders achieved.
- MST helped to understand parents' status as heterozygous carriers of the same mutation.
- Prenatal counseling provided to parents.

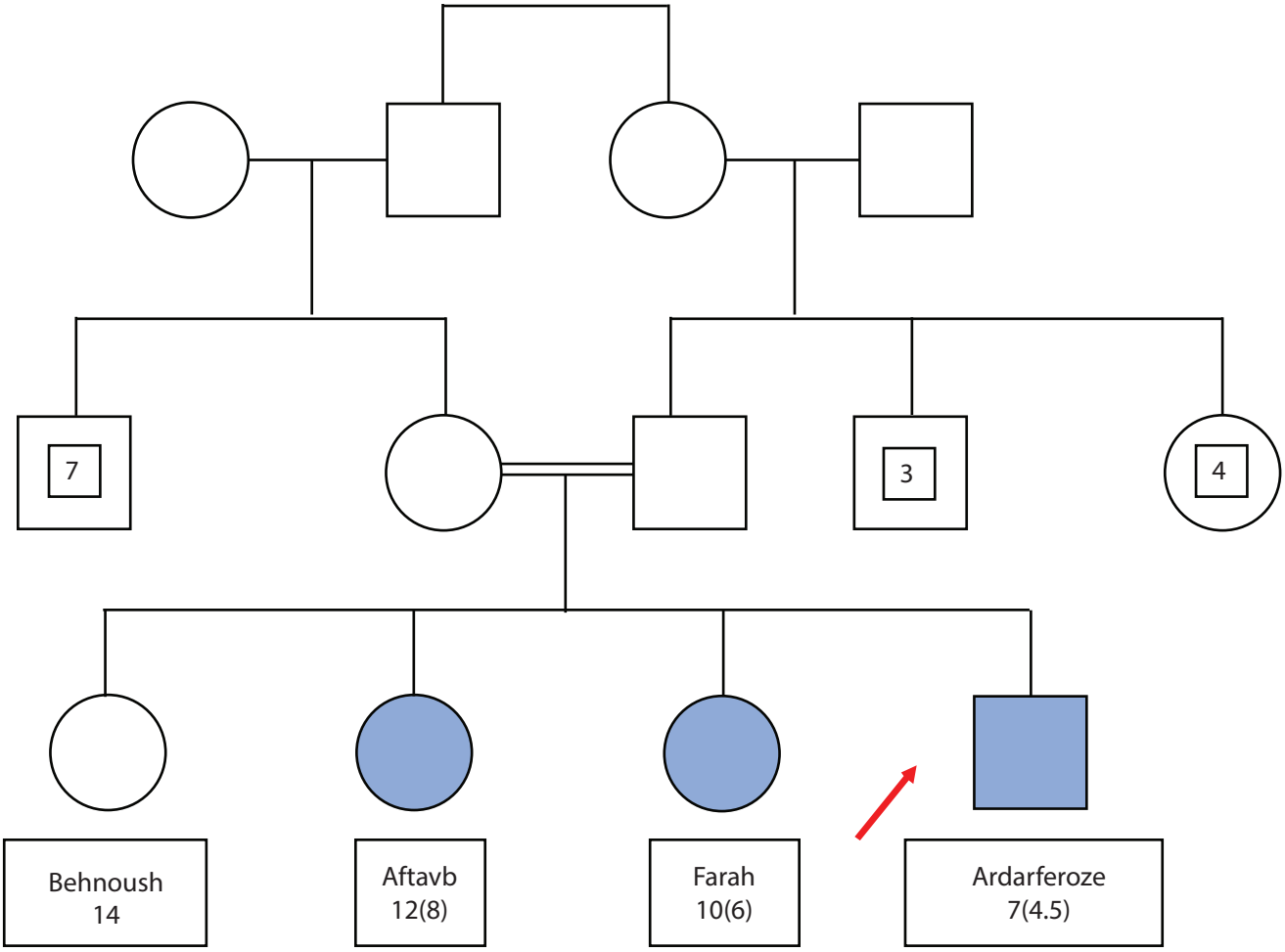
The appearance of uncoordinated movements together with the observation that Ardarferoze had to actually turn his whole body to respond to visual signals that were to his extreme left and right prompted the couple to consult Dr. Rini Kothari and Dr. Arpita Adhikari, two renowned geneticists in Mumbai. Rustom and Gulnaz also intended to have another child and they were anxious to understand their chances of having another kid suffering from ataxia.

Family History

Rustom and Gulnaz are a consanguineous couple. Rustom's mother and Gulnaz's father are siblings. Considering the fact that two daughters and a son were affected by ataxia, and the consanguinity, presence of a hereditary mutation leading to the development of ataxia was suspected. In order to confirm or refute this possibility, the Strand Clinical Exome Test was prescribed for Ardarferoze.

* *Name changed to protect patient privacy*

Family Tree - Pre-Test Genetic Counselling



Results of Genetic Testing

RESULT Positive for a **homozygous**, recessive, pathogenic mutation in the *APTX* gene

A pathogenic recessive mutation was identified in the *APTX* gene in this case. Ardarferoze was homozygous for this mutation and therefore, although the mutation is recessive, symptoms of AOA1 were evident.

Gene	Variation	Zygosity	Inheritance	Clinical significance
APTX	chr9:32973652T>C c.875-2A>G	Homozygous	Recessive	Pathogenic

Key Findings

- The identified homozygous variant (c.875-2A>G) lies in the essential splice acceptor site, in intron 8 of the *APTX* gene. In silico splice prediction tools (SplicePort and NNSPLICE) suggest that this variant might affect splicing due to the loss of constitutive splice site and introduction of a new splice site, which in turn might lead to a frameshift and consequent premature termination of the protein; which will likely result in loss of function. Loss of function resulting from mutations in the *APTX* genes has been considered as a main causative factor for the development of ataxial and apraxial symptoms, as against variations in gene expression levels (Hirano et al. 2004).
- The identified variant is a rare variant and has been reported in very few studies. It is found in the vicinity of other known pathogenic variants like c. 875-1G>A and is therefore considered to be 'Pathogenic' (American College of Medical Genetics and Genomics 2013).
- Identification of this mutation in the *APTX* gene has led to a confirmed diagnosis of AOA1 in this child. The identified novel pathogenic mutation is in the vicinity of another well-characterized pathogenic mutation that is known to be inherited in an autosomal recessive manner.
- Ardarferoze has received one copy each of the mutant *APTX* gene from both his parents.
- Since the couple was considering having another child, Dr. Adhikari advised Rustom and Gulnaz to undergo mutation-specific testing* to ascertain their status as carriers of this gene variant.

Mutation-Specific Test (MST) is a customized and rapid, follow-through test that is designed to test the family members of probands, once a specific gene variant has been identified. An MST can help to trace the inheritance pattern of genes that cause inherited disorders.

Mutation-Specific Test: Gulnaz Vakil

An MST designed to identify the c.875-2A>G mutation was performed on DNA obtained from Gulnaz (saliva sample).

Gulnaz was found to be heterozygous for the same mutation in the *APTX* gene as her son.

Results

- **Heterozygous** for the tested variant, c.875-2A>G, in the *APTX* gene.

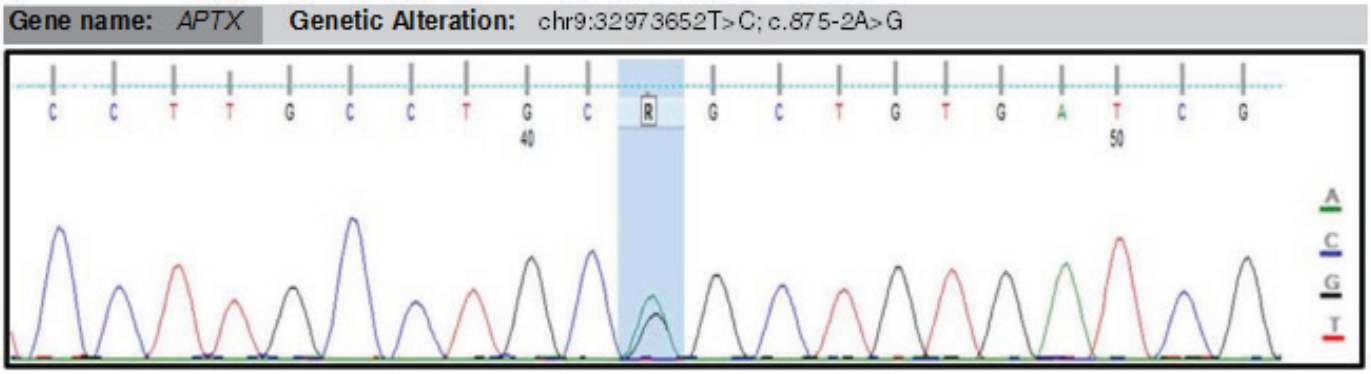


Figure 1. Sanger sequencing data (electropherogram) from the individual showing a heterozygous nucleotide change 'A>G' at position c.875-2 in the APTX gene (RefSeq id: NM_175073). This variation was confirmed by sequencing with reverse primer in two independent experiments.

The parameter marked with an * are not accredited by NABL and CAP.

Mutation-Specific Test: Rustom Vakil

Similarly, a DNA sample obtained from Rustom was analyzed for the presence of this mutation. Rustom was also found to be heterozygous for the same mutation.

Mutation specific testing thus confirmed that both parents are heterozygous carriers of this recessive pathogenic mutation.

Results

- **Heterozygous** for the tested variant, c.875-2A>G, in the *APTX* gene.

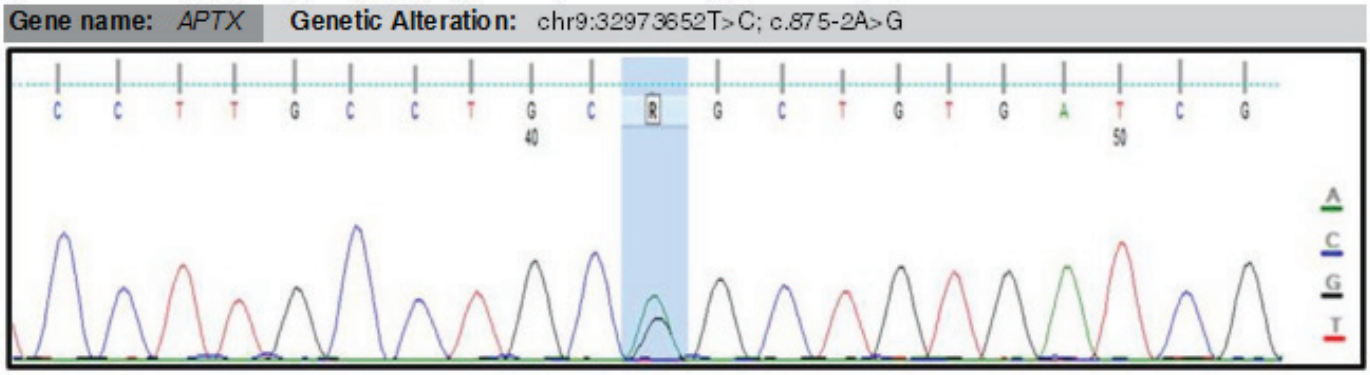


Figure 2. Sanger sequencing data (electropherogram) from the individual showing a heterozygous nucleotide change 'A>G' at position c.875-2 in the APTX gene (RefSeq id: NM_175073). This variation was confirmed by sequencing with reverse primer in two independent experiments.

Key Findings

- Ataxia with oculomotor apraxia type 1 was diagnosed in a 7-year-old child, based on clinical findings as well as genetic analysis provided by the Strand Clinical Exome Test.
- A pathogenic, autosomal recessive mutation in the *APTX* gene was identified in the proband. Proband was found to be homozygous for this mutation.
- Mutation-specific testing was advised to both parents. The MST confirmed the parents' status as heterozygous carriers of the same mutation.
- Since the couple was planning another pregnancy, they were advised that their chances of having another child that would be homozygous for the same *APTX* mutation were 25%.
- Rustom and Gulnaz were advised about these probabilities. They can plan another child and perhaps have the fetus tested by amniocentesis and chorionic villus sampling.

Strand Clinical Exome Test

The Strand Clinical Exome Test is a laboratory-developed test designed for the identification of genetic variants that can cause several developmental disorders. The test covers more than 4500 genes and has been effective in diagnosing neuromuscular, skeletal, nephrological, neurological and mitochondrial disorders as well as inborn errors of metabolism.

References

American College of Medical Genetics and Genomics, 2013. Incidental findings in clinical genomics: a clarification. Genetics in medicine : official journal of the American College of Medical Genetics, 15(8), pp.664–6. Available at: http://www.nature.com/articles/gim201382 [Accessed January 1, 2018].

Hirano, M. et al., 2004. Loss of function mechanism in aprataxin-related early-onset ataxia. Biochemical and Biophysical Research Communications, 322(2), pp.380–386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15325241 [Accessed January 1, 2018].

Pearson, T.S., 2016. More Than Ataxia: Hyperkinetic Movement Disorders in Childhood Autosomal Recessive Ataxia Syndromes. Tremor and other hyperkinetic movements (New York, N.Y.), 6, p.368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27536460 [Accessed January 1, 2018].

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