

The First Genetically Confirmed Case of Ataxia with Oculomotor Apraxia Type 1 (AOA1) Due to an APTX Nonsense Variant in a Rwandan Patient: A Case Report

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ABSTRACT

INTRODUCTION: Ataxia with oculomotor apraxia type 1 (AOA1) is a rare autosomal recessive neurodegenerative disorder caused by mutations in the APTX gene, which encodes the DNA repair protein aprataxin. The condition is characterized by early-onset progressive cerebellar ataxia, oculomotor apraxia, peripheral neuropathy, and metabolic abnormalities. Despite increasing recognition in Europe and Asia, AOA1 remains underreported in Sub-Saharan Africa due to limited access to advanced genetic diagnostics.

CASE PRESENTATION: We report the clinical and molecular findings of a 10-year-old Rwandan boy who presented with progressive gait instability, dysarthria, developmental delay, and oculomotor apraxia. Neurological examination revealed cerebellar ataxia, dysarthria, muscle weakness, and peripheral neuropathy. Brain magnetic resonance imaging demonstrated cerebellar atrophy with vermis hypoplasia. Genetic analysis, utilizing whole-exome sequencing and an ataxia/spastic paraplegia gene panel, identified a rare homozygous nonsense variant in APTX (NM_001195248.1:c.958C>T; p.Arg320), predicted to result in premature protein truncation and loss of function.

CONCLUSION: This report describes the first genetically confirmed case of AOA1 in Rwanda and, to our knowledge, in Sub-Saharan Africa. The findings expand the geographic and genetic spectrum of AOA1 and highlight the critical importance of integrating genomic diagnostics into clinical practice in under-resourced settings. Improved access to genetic testing is essential for accurate diagnosis, management, and genetic counseling of rare neurogenetic disorders in these regions.

Keywords: Ataxia with Oculomotor Apraxia Type 1, AOA1, APTX gene, Whole Exome Sequencing, Case Report

INTRODUCTION

Ataxia with Oculomotor Apraxia Type 1 (AOA1,

OMIM 208920) is an autosomal recessive neurodegenerative disorder [1]. Affected individuals typically present with slow, early-onset

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progressive cerebellar ataxia, oculomotor apraxia, sensorimotor peripheral neuropathy, movement disturbances, and metabolic disturbances such as hypoalbuminemia and hypercholesterolemia [2]. The Aprataxin (APTX) gene (OMIM 606350), located on chromosome 9p13, encodes the protein aprataxin, which plays a critical role in single-strand DNA repair [3,4]. Aprataxin contains three main functional regions: an amino-terminal FHA domain that binds phosphorylated proteins involved in DNA break repair, a central histidine-triad (HIT) domain common to nucleotide-processing enzymes, and a carboxy-terminal C2H2 zinc-finger domain that attaches to DNA [5,6]. Most known disease-associated variants occur in the HIT domain, while nonsense mutations tend to affect the zinc-finger region [7,8].

The disease presents a wide range of clinical features due to different variants and can be difficult to differentiate from other forms of recessive ataxias, such as ataxia-telangiectasia, ataxia with oculomotor apraxia type 2, or type 4 [1,9,10]. Genotype-phenotype correlations have been explored, with the mean age of onset being higher and the phenotype milder in patients with missense mutations compared to those with frameshift mutations [11,12].

While the global prevalence of AOA1 remains unknown, regional data provide some context. In Portugal, AOA1 accounts for 3.6% of autosomal recessive ataxias, and in Japan, it is the most frequent form [13]. In a French cohort of patients with progressive cerebellar ataxia, the relative frequency was 5% [2,13]. The condition is diagnosed more frequently in regions with advanced genetic testing capabilities.

To our knowledge, there are no prior reports of genetically confirmed AOA1 in Sub-Saharan Africa. Limited access to genetic testing in this region hinders the identification of hereditary ataxias. In Rwanda, advanced testing capabilities, such as next-generation sequencing, are not yet available locally and must be outsourced, creating significant barriers to diagnosis.

This case report describes a rare homozygous variant in the APTX gene in a 10-year-old boy of Rwandan descent, representing the first genetically confirmed AOA1 case from Rwanda and, to our knowledge, the first documented case in Sub-Saharan Africa.

CASE PRESENTATION

Patient's history

The patient is a Rwandan 10-year-old boy who was brought to the Clinical Genetics Department of the Rwanda Military Teaching Hospital by his parents due to progressive difficulty walking and imbalance that had worsened over the preceding three years. His parents are non-consanguineous and report no family history of similar neurological symptoms.

The patient had early developmental delays noted in childhood. He achieved independent walking at age 2.5 years. His gait had been unsteady since early childhood but progressively worsened, leading to frequent falls. He also developed slurred speech and difficulty with handwriting. There was no history of perinatal complications, trauma, or recurrent infections. No previous interventions had been sought before presentation.

Physical examination

Relevant physical examination findings included significant weakness of the upper and lower limbs, with muscle wasting observed in the hands and feet. Neurological examination revealed dysarthria. Motor system evaluation using the Modified Ashworth Scale showed increased muscle tone in the lower limbs (score 2), indicating spasticity through most of the range of movement, while the limbs could still be moved easily. Deep tendon reflexes were diminished, and Babinski signs were absent. The patient exhibited postural instability and was unable to walk without light support for balance. The Romberg test was positive.

Medical imaging

Brain Magnetic Resonance Imaging (MRI) revealed cerebral atrophy with cerebellar vermis hypoplasia. No structural abnormalities of the spine were noted.

Molecular analysis

The molecular analysis in this case involved a comprehensive approach to identify the genetic cause of the patient's progressive ataxia. Key steps included:

Whole exome sequencing (WES): After Peripheral blood was collected from the patient, WES was performed and genomic DNA was enriched for coding regions (around 41 Mb, >98% of RefSeq coding exome) and sequenced on an Illumina

platform at an accredited laboratory (Centogene, Germany), and the analysis included the mitochondrial genome.

Ataxia/Spastic Paraplegia Panel: A targeted gene panel was used to sequence coding regions and flanking intronic sequences (± 10 bp) of genes associated with hereditary ataxia and spastic paraplegia, including APTX, SETX, ATM, FXN, and others.

Repeat expansion analysis: PCR and capillary electrophoresis, along with repeat primed assays, were performed to exclude pathogenic repeat expansions in ATXN1, ATXN2, FXN, and other relevant loci.

Variant calling and annotation: The Centocloud bioinformatics pipeline mapped reads to GRCh37/hg19. Variants were annotated and classified according to ACMG/AMP/ClinGen SVI guidelines. Identified variant: A homozygous nonsense variant in APTX: NM_001195248.1:c.958C>T (p.Arg320). This variant creates a premature stop codon, predicted to result in a truncated, non functional aprataxin protein.

Pathogenicity classification: The variant was classified as likely pathogenic (Class 4) based on: PVS1 (null variant in a gene where loss of function is a known disease mechanism); PM2 (extremely low allele frequency in population databases [gnomAD: 0.000032]); PP4 (patient's phenotype is highly specific for AOA1); and PP5 (reputable source [CentoMD®] reports variant as pathogenic).

Copy number variant (CNV) detection: A proprietary algorithm was used to detect CNVs (sensitivity >95% for events spanning ≥ 3 exons). No clinically relevant CNVs were reported.

Mitochondrial variant analysis: Reported for heteroplasmy levels $\geq 15\%$; none were identified as disease causing.

Splice effect prediction: In silico tools (Ada, RF) gave inconclusive results, but the nonsense mutation itself is sufficient to predict loss of function.

All quality control metrics met clinical diagnostic standards, and no other clinically relevant variants were found.

Diagnosis

The patient's presentation with slow, early-onset progressive ataxia, dysarthria, developmental delay, and oculomotor apraxia fulfilled the clinical criteria for a recessive cerebellar ataxia, initially suggesting AOA1. Differential diagnoses considered included cerebral palsy, leukodystrophies, spinal cord lesions, and ataxia-telangiectasia (Table 1). These were ruled out based on the progressive nature of symptoms, lack of perinatal complications, distinguishing clinical features of cerebellar ataxia, absence of telangiectasias or systemic symptoms, and presence of oculomotor apraxia.

Given the progressive nature of AOA1, the patient's prognosis is for gradual worsening of ataxia, peripheral neuropathy, and functional decline. Early diagnosis facilitates supportive care

Table 1. Differential Diagnoses Considered

Condition	Key Features	Reason for Exclusion in This Case
Ataxia with Oculomotor Apraxia Type 1 (AOA1)	Early-onset progressive ataxia, oculomotor apraxia, peripheral neuropathy, hypoalbuminemia	Confirmed by genetic testing
Ataxia-Telangiectasia	Progressive ataxia, oculomotor apraxia, telangiectasias, immune deficiency, elevated AFP	Absence of telangiectasias, normal immune function, confirmed by genetic testing
Cerebral Palsy	Non-progressive motor impairment, often with history of perinatal insult	Progressive symptom course; no history of perinatal complications
Friedreich Ataxia	Progressive ataxia, areflexia, pyramidal signs, cardiomyopathy	Absence of cardiomyopathy; genetic testing negative for FXN repeat expansion
Leukodystrophies	Progressive motor/cognitive decline, white matter changes on MRI	No white matter abnormalities on brain MRI

and genetic counseling.

Management

After diagnostic confirmation through molecular genetic testing, a multidisciplinary supportive care plan was initiated. The patient was enrolled in physiotherapy to maintain mobility and prevent contractures. Occupational therapy was recommended to assist with activities of daily living and fine motor tasks. Speech therapy was initiated to manage dysarthria and communication difficulties.

Genetic counseling was provided to the family, explaining the autosomal recessive inheritance pattern, recurrence risk, and implications for family members.

Follow-up and outcomes

During follow-up, the patient is under ongoing multidisciplinary care. His condition is consistent with progressive cerebellar ataxia. He continues to use light support for ambulation and remains engaged in physiotherapy. No adverse events related to interventions were reported. The patient remains on the supportive interventions well, and adherence to physiotherapy and speech therapy is good, facilitated by family support.

Prior to publication of this case report, informed consent for participation in the study and for publication of this case report was obtained from the patient's parents.

DISCUSSION

This case proves the importance of using whole-exome sequencing and a comprehensive ataxia gene panel to achieve a definitive molecular diagnosis, which is particularly challenging in a resource-limited setting. This approach allowed for the precise identification of the causative APTX variant and ruled out other overlapping conditions. However, there is a lack of functional studies, such as aprataxin enzyme activity, to further confirm the variant's pathogenicity. Additionally, while hypoalbuminemia and hypercholesterolemia are common in AOA1 [14,15], these biomarkers were not assessed in this patient, representing an incomplete metabolic evaluation.

This case might inform practice or clinical practice guidelines in Rwanda as it demonstrates the feasibility and critical importance of advanced

genetic testing for diagnosing rare neurogenetic disorders in Sub-Saharan Africa. It highlights the need to integrate genomic diagnostics into clinical practice in under-resourced settings and suggests that clinicians should consider AOA1 in the differential diagnosis of progressive childhood ataxia, even in populations where it has not previously been reported. The findings underscore the value of partnerships with international diagnostic laboratories to overcome local testing limitations.

The identification of the APTX c.958C>T variant in a Sub-Saharan African patient suggests that this specific variant, or other AOA1-causing mutations, may be more prevalent in this region than currently recognized. This could be tested through targeted screening of individuals with undiagnosed progressive ataxia in Rwanda and neighboring countries. Furthermore, the patient's derived cells could be used to generate induced pluripotent stem cell (iPSC) models to study the cellular consequences of this specific nonsense mutation and test potential therapeutic compounds, as has been done with other APTX mutations [16]. The role of aprataxin in innate immune signaling also warrants the need for further investigating whether immune modulation could be a therapeutic strategy [17].

CONCLUSION

This case report documents a rare homozygous APTX nonsense variant causing AOA1 in a 10-year-old boy from Rwanda, representing the first genetically confirmed case in Sub-Saharan Africa. It expands the known population distribution of AOA1, emphasizes the phenotypic and genetic heterogeneity of hereditary ataxias, and underscores the importance of developing genomic medicine capacity in the region. Strengthening infrastructure for genetic testing, bioinformatics analysis, and variant interpretation, along with training local clinicians and scientists, is essential to enable early and accurate diagnosis, provide informed genetic counseling, support research on rare hereditary disorders, and ultimately improve patient care in under-resourced and underrepresented regions such as Sub-Saharan Africa. Larger regional studies are needed to determine the prevalence of AOA1 and related disorders, improve variant interpretation, and support the equitable integration of genomic

medicine into global healthcare systems.

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