World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

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Intrafamilial Variability in Ataxia-Telangiectasia: A Case Report of Three Siblings with Identical ATM Mutations

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World Journal of Advanced Research and Reviews, 2025, 27(02), 1807-1811

Publication history: Received on 16 July 2025; revised on 24 August 2025; accepted on 26 August 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.27.2.3077

Abstract

Ataxia-telangiectasia (A-T) is a rare, autosomal recessive neurodegenerative disorder caused by pathogenic variants in the ATM (ataxia-telangiectasia mutated) gene, located on chromosome 11q22–23. The ATM protein is a serine/threonine kinase essential for the detection of DNA double-strand breaks and activation of cell-cycle checkpoints. Classic A-T typically manifests in early childhood with progressive cerebellar ataxia, oculocutaneous telangiectasias, immunodeficiency, radiosensitivity, and a high predisposition to malignancy.[1]

We describe a non-consanguineous family with three siblings affected by ataxia-telangiectasia (A-T) due to identical compound heterozygous pathogenic variants in the ATM gene: c.72+2T>C (splice donor mutation) and c.6100C>T (p. Arg2034Ter, nonsense mutation). Despite sharing the same genotype, the siblings exhibited marked variability in age of onset and clinical progression, ranging from early-childhood gait instability to late-onset regression of previously normal motor skills. All affected siblings had elevated serum alpha-fetoprotein (AFP) and cerebellar signs, but differed in the timing of telangiectasia appearance and severity of motor impairment. This report highlights the role of genetic background and possible modifier factors in the phenotypic expression of A-T.

Keywords: Ataxia-Telangiectasia; ATM Gene; Alpha-Fetoprotein; Intrafamilial Variability; Cerebellar Atrophy; Telangiectasia

1. Introduction

Ataxia-telangiectasia (A-T; OMIM #208900) is an autosomal recessive neurodegenerative disorder caused by biallelic pathogenic variants in the ATM (ataxia-telangiectasia mutated) gene located on chromosome 11q22.3. The ATM protein is a serine/threonine kinase critical for the detection and repair of DNA double-strand breaks, maintenance of genomic stability, and regulation of cell cycle checkpoints [1].

The classic phenotype usually presents between ages 1 and 4 years with progressive cerebellar ataxia, followed by oculocutaneous telangiectasias, immunodeficiency, increased susceptibility to malignancy, and radiation sensitivity [1,2]. Laboratory features include elevated AFP levels after age two and chromosomal instability. According to Gene Reviews, genotype–phenotype correlation is imperfect, and considerable variability exists—even among individuals with identical mutations—due to environmental, epigenetic, or modifier gene effects [1].

We report a family with three compound heterozygous siblings harboring the ATM variants c.72+2T>C and c.6100C>T, exhibiting substantial variability in symptom onset and progression.

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2. Case report

The family under investigation originates from a rural region in Morocco where both parents were born and raised; however, there is no known consanguinity. The couple is healthy, with no neurological or immunological symptoms, but both were found to be heterozygous carriers of distinct pathogenic variants in the ATM gene. The father carries the c.72+2T>C splice site variant, while the mother carries the c.6100C>T nonsense variant (p.Arg2034Ter). They have five children, three of whom are affected by ataxia-telangiectasia, each inheriting both variants in trans, resulting in compound heterozygosity.

The first affected child, a boy, was born after an uncomplicated pregnancy and normal delivery. His early psychomotor development was age-appropriate, and he reached all motor and speech milestones without delay. From early childhood, he experienced recurrent episodes of abdominal pain, which were initially considered functional. At the age of five, his parents noticed progressive speech difficulties, a waddling gait, and frequent imbalance. These symptoms gradually worsened, leading to significant gait instability. Neurological examination revealed a cerebellar syndrome with dysarthria, truncal ataxia, dysmetria, and gait disturbance. Laboratory analysis demonstrated elevated AFP levels, a finding characteristic of A-T. Brain computed tomography (CT) showed marked vermian cerebellar atrophy along with mild cortical–subcortical atrophy, consistent with the neurological presentation.

The second affected child, a girl, is currently five years old. She presented with gait instability from early childhood, which progressed gradually. By the age of five, ocular telangiectasias were evident on ophthalmological examination. Like her brother, she had elevated AFP levels. Neurological evaluation confirmed cerebellar involvement, and oculomotor abnormalities, including abnormal saccadic movements, were observed. Her disease course was more rapid in the appearance of telangiectasias compared with her older brother.

The youngest affected child, a boy, is three years old. He began showing signs of gait imbalance during toddlerhood, but his motor impairment remains milder than that of his older siblings at comparable ages. Telangiectasias have not yet been detected on clinical examination. Nevertheless, AFP levels are elevated, indicating a biochemical marker of disease even in this early stage. His neurological symptoms are currently limited to mild cerebellar signs, with preserved speech and no significant dysarthria.

2.1. Genetic Testing

Molecular analysis was initiated with whole-exome sequencing in the first affected child, which identified two pathogenic variants in the ATM gene: c.72+2T>C, a splice donor site variant predicted to result in aberrant mRNA processing, and c.6100C>T (p. Arg2034Ter), a nonsense variant leading to premature protein truncation. Both variant were reported in clever database as pathogenic in numerous cases. These findings established a diagnosis of ataxia-telangiectasia (Figure 1).

Subsequent Sanger sequencing was performed for targeted variant analysis in the rest of the family, confirming that all three affected siblings were compound heterozygotes for the same two ATM variants, inherited in trans from their carrier parents.

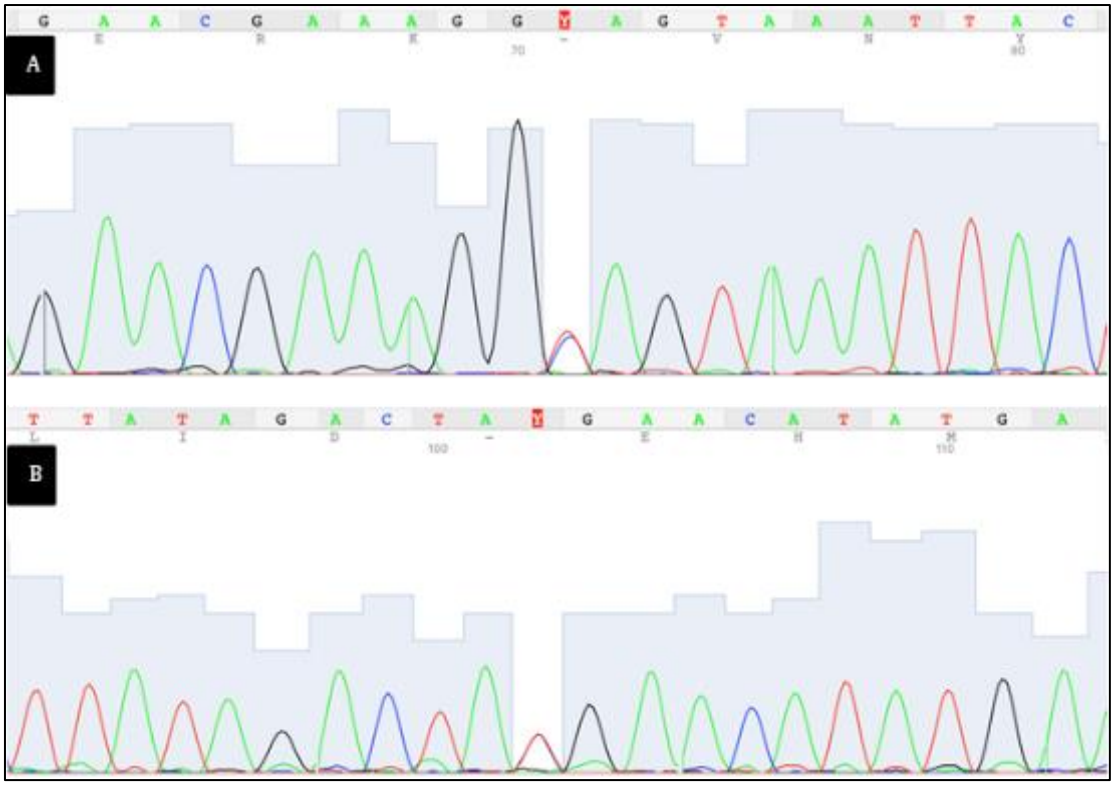

Figure 1 Electropherograms depicting the genetic profiles of individuals in the family

A: Heterozygous Variant C.72+2T>C (Splice Donor Mutation), B: Heterozygous Variant C.6100C>T (P. Arg2034Ter)

3. Discussion

This family illustrates several important aspects of ATM-related disease: compound heterozygosity for two clearly pathogenic variants, the classical neurological and laboratory features of A-T, and striking intrafamilial phenotypic variability.

The c.72+2T>C mutation affects the invariant +2 position of the donor splice site in intron 4, predicted to result in exon skipping or cryptic splice site usage, producing a frameshift and premature termination. The c.6100C>T variant introduces a premature stop codon at position Arg2034, predicted to trigger nonsense-mediated decay. Both alleles are loss-of-function mutations typically associated with complete loss of ATM kinase activity, correlating with classic early-onset A-T.[3]

Several published reports describe patients carrying either c.72+2T>C or c.6100C>T in compound heterozygosity with another truncating ATM variant. Sandoval et al., Poturalski et al., and Taylor et al. consistently report onset of gait instability between ages 1–3 years, early telangiectasia appearance, rapid neurological decline, and frequent immunodeficiency [2,3,4]. Cases with the exact combination of c.72+2T>C and p. Arg2034Ter have been linked to severe phenotypes, often with wheelchair dependence before adolescence and marked cerebellar atrophy [5].

In contrast, our family showed delayed onset in two siblings (5 years), milder early course in the youngest (onset at 3 years with preserved speech and no telangiectasia), and variable progression rates. Telangiectasia appeared only in the middle child by age 5, whereas the eldest had marked vermian cerebellar atrophy without ocular involvement at the same age, and the youngest remains without telangiectasia. AFP elevation was universal and present even in the youngest child, as reported in >95% of A-T cases.[1]

Phenotypic variability in A-T despite identical genotypes is well recognized [23†source]. Possible explanations include differences in environmental exposures, modifying genes, stochastic developmental factors, and epigenetic influences. Sandoval et al. (1999) [4] and Poturalski et al. (2014) [5] both reported intrafamilial differences in age at onset and severity, even among patients with the same truncating ATM variants. This variability complicates prognosis and highlights the need for individualized clinical surveillance (Table 1).

All three siblings had markedly elevated AFP, consistent with >95% prevalence in A-T [6], and neuroimaging revealed cerebellar atrophy, predominantly vermian, in the eldest proband. The middle child displayed ophthalmologic signs of telangiectasia, a hallmark feature, while the youngest presented primarily with gait instability. None had yet developed immunodeficiency-related infections severe enough to require hospital admission, but mild recurrent respiratory infections were noted, warranting immunological follow-up.[7]

From a management perspective, early recognition of A-T enables anticipatory guidance, including immunologic monitoring, pulmonary care, avoidance of ionizing radiation exposure, and malignancy surveillance [23†source]. Given the increased lifetime cancer risk even for heterozygous ATM mutation carriers [24†source], genetic counseling for extended family members is essential. [8,9]

This report adds to the body of evidence on intrafamilial clinical heterogeneity in A-T and reinforces the importance of comprehensive family-based genetic evaluation. Understanding the mechanisms behind variable expressivity in identical ATM genotypes remains an important research goal, with implications for prognosis, counseling, and targeted therapy development.

Table 1 Comparison of Clinical Features Between Reported Patients with ATM c.72+2T>C and/or p. Arg2034Ter Mutations and the Present Family

Feature	**Literature [5,6,9] (same or similar variant)**	**Your Family**
Genotype	c.72+2T>C + truncating mutation (including p. Arg2034Ter in some reports)	c.72+2T>C + c.6100C>T (p. Arg2034Ter)
Onset age	Mostly 1–3 years (gait instability)	3 years (youngest), 5 years (middle, elder)
Neurological course	Rapid progression to severe ataxia; early wheelchair use	Slower in youngest; elder child had normal development until age 5 before regression
Telangiectasia onset	Often before 6 years	Present in middle child at 5 years; absent in youngest
AFP elevation	Almost universal after age 2	Present in all three siblings (including youngest)
Cerebellar atrophy	Early and progressive	Eldest: marked vermian atrophy; others: clinical signs without imaging yet
Immunodeficiency	Common; recurrent infections	Mild recurrent infections, no severe immunodeficiency documented yet

4. Conclusion

We describe three siblings with identical compound heterozygous ATM mutations but markedly different ages of onset and progression. Compared to published cases, our patients exhibited delayed onset and slower deterioration. This case emphasizes the heterogeneity of A-T, the importance of AFP and genetic testing in early diagnosis, and the need for individualized surveillance.

Compliance with ethical standards

Acknowledgments

We thank the family for their participation.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of ethical approval

The present research work does not contain any studies performed on animals or human experimentation by the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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