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Clinical Characterization and Mutation Analysis of 13 Iranian Ataxia Telangiectasia Patients: Introducing Two Novel Mutations

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ABSTRACT

Ataxia Telangiectasia (A-T) is a rare autosomal recessive neurodegenerative disease caused by mutations in the ataxia telengiectasia mutated (*ATM*) gene. The gene is on chromosome 11q22-23 and codes for the protein kinase ATM, which plays an essential role in DNA damage repair. In this study, we review the clinical characteristics of 13 A-T patients, 2 of whom displayed novel mutations.

Thirteen patients with ataxia-telangiectasia from 10 unrelated families were referred to Immunology, Asthma and Allergy Research Institute, Tehran, Iran. After clinical confirmation, blood samples were collected from the patients and their parents. Genetic analysis for 8 patients was conducted using whole-exome sequencing; in the other 3 patients, polymerase chain reaction was used, followed by sequencing.

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We identified 11 different mutations in the *ATM* gene. Two patients had mutations as compound heterozygous, while 9 other patients were homozygous for the mutations. Among these, 2 likely pathogenic mutations (ie, c.2639-1G>A and c.7940_7970delTTCCAGCAGA CCAGCCAATTACTAAACTTAA) have not been reported.

Our study highlights the significance of next-generation sequencing techniques in identifying novel *ATM* mutations in A-T patients. Although all reported A-T mutations reside in 1 gene, the absence of a mutation hotspot for this gene necessitates the use of next-generation sequencing techniques. Specifically, we identified 2 mutations that have not been reported previously, emphasizing the importance of continued research in this area. This study provides new insights into the genetic underpinnings of A-T and underscores the potential clinical implications of identifying novel mutations.

Keywords: Ataxia-telangiectasia; Ataxia telangiectasia mutated proteins; Cerebellar ataxia; Iran; Mutation; Primary immunodeficiency diseases; Whole exome sequencing

INTRODUCTION

Ataxia-telangiectasia (A-T, OMIM 208900) is an autosomal recessive disorder that affects multiple organ systems and causes immunodeficiency (in 75% of the patients), progressive neurodegeneration (manifesting by cerebellar ataxia, oculomotor apraxia, dysarthria, chorea, and dystonia), telangiectasias, radiosensitivity, and increased risk of malignancies. A-T affects a broad spectrum of immune system components, encompassing cellular and humoral immunity. At the humoral level, it affects antibody production through class-switching recombination, leading to hypogammaglobulinemia, particularly immunoglobulin (Ig) A and IgG deficiencies. At the cellular level, it can affect both the count and function of $CD4^+$ and $CD8^+$ T cell lineages; B and T cell lymphomas are also associated with the disease. The concentration of alpha-fetoprotein (AFP) increases in the serum of patients with A-T.[1]

A-T affects approximately 1:40 000 to 1:300 000 children in different populations.[1] Mutation in the *ATM* gene is responsible for all A-T cases identified to date. The gene is on chromosome 11q22-23 and spans approximately 150 kb of genomic DNA. It consists of 64 exons, produces a 150-kb transcript, and codes for a 3056-amino acid protein. The ATM protein comprises at least 3 domains and 1 region. The domains include FAT (FRAP, ATM, and TRRAP; amino acids 1940–2566), phosphatidylinositol 3-kinase (PI3K) (amino acids 2712–2962), and FATC (amino acids 3024–3056). The region (amino acids 1373–1382) interacts with ABL1.[2] ATM is a serine/threonine protein kinase that phosphorylates various proteins involved in the cell cycle and double-stranded DNA break repair.[3] ATM is also necessary for class-switching recombination and normal immunoglobulin production.

More than 1700 mutations in the *ATM* gene have been previously described, most of which are single-nucleotide substitutions, including missense, nonsense, and splicing site mutations, followed by small and gross deletions.[4] Due to the length and number of exons in the *ATM* gene, the whole exome sequencing (WES) technique followed by confirmation using Sanger sequencing is the gold standard method to analyze patients suspected to be affected with A-T.

This study provides detailed clinical and genetic information on 13 patients with A-T, which include 2 novel mutations.

MATERIALS AND METHODS

Thirteen Iranian A-T patients referring to the Immunology, Asthma and Allergy Research Institute (IAARI), Tehran, Iran, between 2018 and 2022, were enrolled in this study.

The European Society for Immunodeficiencies (ESID) criteria[5] were used to determine the diagnosis of A-T, which include ataxia and at least 2 of the following: oculocutaneous telangiectasia, elevated alpha-fetoprotein (10-fold the upper limit of normal), lymphocyte A-T karyotype (translocation 7;14), and cerebellum hypoplasia on MRI.

Genomic DNA was extracted from peripheral blood using the Blood Genomic DNA Extraction Kit (Pars Tous, Iran). WES was performed for 10 patients (P1 to P7, and P11 to P13). The polymerase chain reaction

(PCR) of all exons was performed to analyze the mutation of *ATM* in patient P8; this patient's siblings (P9 and P10) were also analyzed for the same mutation. To confirm the WES results in the patients and their parents by Sanger sequencing, the primers flanking the entire coding exons and intron-exon boundaries of *ATM* were used, according to the article by Sandoval et al.[6] PCR was carried out at appropriate annealing temperatures, followed by sequencing.

RESULTS

Demographic and Clinical Characteristics

The patients enrolled in our study included 5 males and 8 females, ages 2 to 16 years old (median age 8 years old). The time from the appearance of the first symptom to the patients' referral ranged from 5 months up to 9 years. The diagnosis of A-T was made by a clinical immunologist according to the ESID criteria; the status of each patient regarding the criteria is summarized in Table 1. Consanguinity was observed in 11 patients. The family histories were significant for malignancy in 1 patient whose older brother had died of leukemia at age 6.

All patients in this study were referred by their primary healthcare provider or a neurologist for further diagnostic workup. The referrals were based on a range of manifestations, which can be categorized into 3 main groups: neurological, immunological, and hematological.

Neurological symptoms were the most common, with 10 patients presenting with ataxic gait, 3 with developmental motor delays, and 1 with writing apraxia.

Immunologic manifestations were also prevalent, primarily in the form of recurrent infections. These included recurrent sinusitis in 7 patients, gastroenteritis requiring hospitalization in 4, pneumonia in 2, oral candidiasis in 1, gingivitis in 2, and severe oral aphthous ulcers in 2 patients.

Hematologic disturbances were observed in 3 patients, each presenting with a different condition: 1 with lymphopenia, 1 with transient thrombocytopenia, and 1 with pancytopenia.

Additionally, 2 patients exhibited dermatological manifestations: 1 with vitiligo and another with alopecia totalis. Table 2 summarizes the associated symptoms for each patient.

AFP levels were increased in all patients; however, this data was not available for 1 patient (P13). Table 3 shows the immunological lab results, including the immunoglobulin and CD marker values for each patient.

One of the patients (P1) had presentations distinct from the others: he was a 5-year-old boy referred for a prolonged fever of 5 days duration, pancytopenia, hepatosplenomegaly, a history of recurrent infections, and manifestations of ongoing sepsis. A diagnosis of hyper-IgM syndrome was entertained after a complete sepsis workup, serum protein electrophoresis, immunotyping, and bone marrow aspiration and biopsy (revealing reactive myeloid hyperplasia). WES was performed to confirm the diagnosis, upon which a mutation in *ATM* was revealed.

Genetic Analysis

Genetic analysis was carried out using WES in 10 families and PCR in the other family (3 siblings). The analysis revealed 11 different mutations (Table 4), including 2 novel mutations.

Eleven patients had homozygous mutations, and 2 patients (P3 and P6) with unrelated parents each showed 2 compound heterozygous mutations. The 9 previously reported mutations were as follows:

1) A nonsense mutation (c.6658C>T) in exon 46 in patients P1, P12, and P13, which introduces an amino acid change at codon 2220 of the reading frame resulting in a premature stop codon (p.Gln2220Ter).

2) A nonsense mutation, c.4864G>T in patient P2 creates a stop codon at position 1622 of *ATM* instead of glutamic acid.

3) The second mutation was a nonsense mutation (c.8907T>G) in exon 62 of patient P3, producing a stop codon at position 2969 (p.Tyr2969Ter). This mutation was seen in P3 along with a novel mutation as compound heterozygous.

4) A nonsense mutation (c.829G>T) was found in exon 7 of patient P4. This mutation leads to an amino acid change at codon 277 of the protein, changing glutamic acid to a premature stop codon (p.Glu277Ter).

5 and 6) Patient P6 inherited two nonsense mutations as compound heterozygous: c.1537C>T in exon 10 that changes glutamine 513 to a stop codon (from the father) and c.8050C>T in exon 55 that changes glutamine 2684 to a stop codon (from the mother).

7) One homozygous splice-site defect, c.2921+1G>T, was detected in intron 19 of the *ATM* gene in P7. This mutation targets the splice donor site leading to loss of exon 19 due to abolished normal splicing.

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8) The c.5712dupA mutation was found in exon 38 in 3 patients in one family (P8, P9, and P10). This mutation causes a frameshift in the open reading frame (ORF), leading to a premature stop codon at the 26th position after the mutated amino acid (p.Lys1904fsTer26).

9) The last reported mutation, c.8494C>T, was a missense mutation found in exon 58 in P11. This mutation changes the amino acid arginine at position 2832 to cysteine (p.Arg2832Cys).

The 2 novel mutations reported in this study include 1 splice site defect and 1 deletion. These include:

1) Patient P3 was heterozygous for a novel splice site defect (c.2639-1G>A) from her father and a reported nonsense mutation (c.8907T>G) from her mother. c.2639-1G>A occurs on intron 17 (Figure 1A) and prevents the formation of exon 17. Both mutations produce abnormal proteins.

2) A 31-base-pair nucleotide deletion (c.7940_7970delTTCCAGCAGACCAGCCAATTAC-TAAACTTAA) was found in exon 54 of the *ATM* gene in patient P5 (Figure1B). This deletion leads to a frameshift in the ORF and produces a truncated 2650-amino acid protein that is unstable and degrades.

All the patients' parents were heterozygous for the abovementioned mutations.

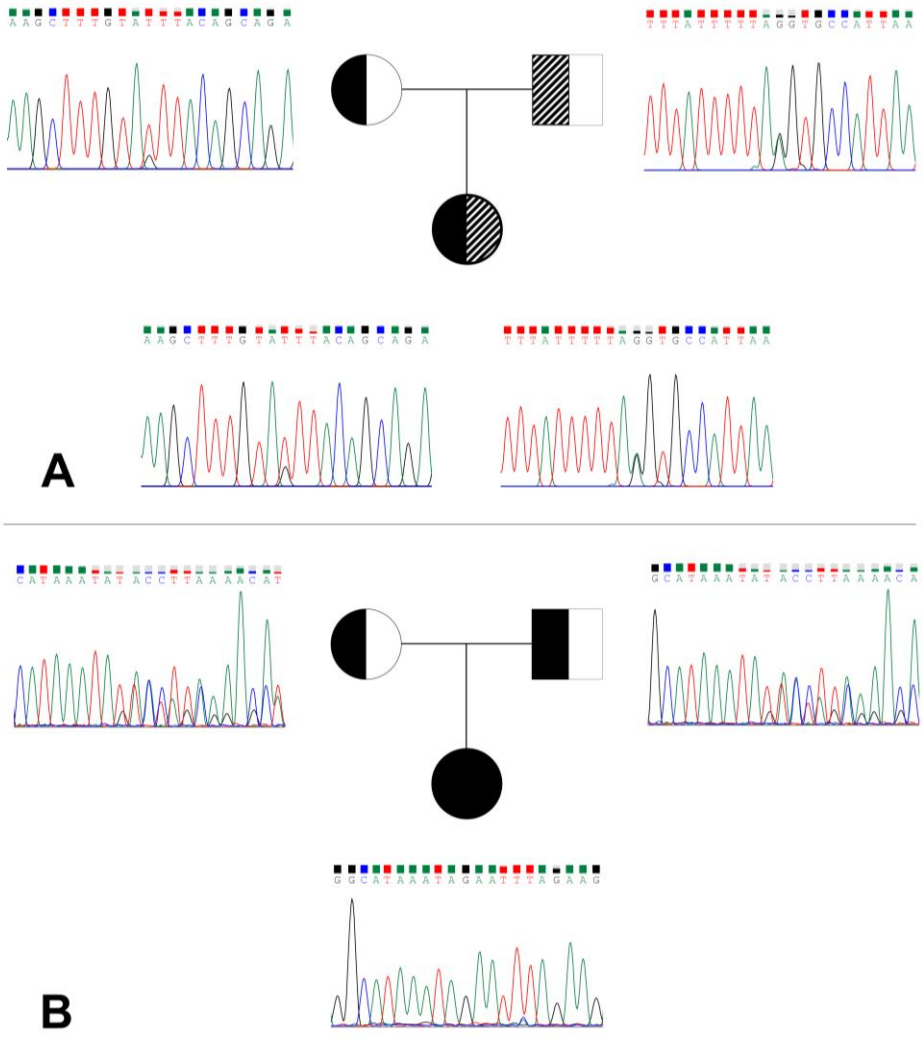

Figure 1. Genetic analysis results of the 2 patients with novel mutations. A. Patient P3 (c.2639-1G>A); B. Patient P5 (c.7940_7970delTTCCAGCAGACCAGCCAATTACTAAACTTAA).

Table 1. Demographic characteristics of the 13 A-T patients with their corresponding states according to the European Society for Immunodeficiencies criteria for the diagnosis of ataxia-telangiectasia

Families	Patients	Gender	Delay in diagnosis, y*	Current age, y	Consanguinity	Serum AFP (ng/mL)	History of recurrent infections	Cerebellar atrophy	Telangiectasia
F1	P1	Male	<1	6	Yes	70	Yes	NA	Yes
F2	P2	Female	<1	5	Yes	73	Yes	Yes	Yes
F3	P3	Female	1	11	No	150.6	Yes	NA	Yes
F4	P4	Female	3	12	Yes	113.5	Yes	NA	Yes
F5	P5	Female	5	14	Yes	553	Yes	Yes	Yes
F6	P6	Female	9	17	No	96	Yes	NA	Yes
F7	P7	Male	5	10	Yes	120	Yes	Yes	Yes
F8	P8	Female	7	10	Yes	291	No	NA	Yes
F8	P9	Male	4	7	Yes	271	No	NA	Yes
F8	P10	Female	1	4	Yes	92	No	NA	Yes
F9	P11	Male	2	3	Yes	49.8	No	NA	Yes
F10	P12	Male	4	9	Yes	309	Yes	NA	Yes
F10	P13	Female	<1	2	Yes	NR	Yes	NA	Yes

AFP: alpha-fetoprotein; NA: data not available. *Delay in diagnosis in years, refers to the time between the appearance of disease manifestations and the confirmation of diagnosis.

Table 2. Patients' primary manifestations of the disease

Patient	Neurological manifestation(s)	Recurrent or opportunistic infections	Visual disturbances	Developmental motor delay	Telangiectasia (on presentation)*	Hematologic disturbances	Other
P1	NR	Prolonged fever and a rash	NR	NR	NR	Pancytopenia	NR
P2	Ataxia	Recurrent sinusitis, oral candidiasis, gingivitis	NR	NR	NR	Lymphopenia	NR
P3	Ataxia	None	NR	NR	NR	NR	NR
P4	Seizures	Recurrent sinusitis, gastroenteritis	NR	NR	+	NR	NR
P5	Ataxia	Recurrent sinusitis	+	NR	NR	NR	NR
P6	NR	Recurrent sinusitis	+	NR	NR	NR	Alopecia totalis
P7	Ataxia, writing apraxia, head tremor	Recurrent sinusitis	NR	Delay in speech	+	NR	NR
P8	Ataxia, speech disturbances	None	NR	NR	+	NR	Vitiligo
P9	Ataxia, dysarthria	None	NR	NR	+	NR	NR
P10	Ataxia	None	NR	NR	+	NR	NR
P11	Ataxia, dysarthria	None	NR	Delay in walking	+	NR	NR
P12	Ataxia	Recurrent sinusitis, otitis media. pneumonia, gastroenteritis, severe oral aphthous ulcers	NR	NR	+	Transient thrombocytopenias	NR
P13	Ataxia	Gastroenteritis, severe oral aphthous ulcers	NR	Delay in walking	+	NR	NR

NR: not reported

Table 3. Paraclinical data of the ataxia-telangiectasia patients presented in the study

Patient	IgA (mg/dL)	IgE (IU/mL)	IgG (mg/dL)	IgM (mg/dL)	CD3 (%)	CD4 (%)	CD8 (%)	CD19 (%)	CD16 (%)	CD56 (%)
P1	NR	NR	NR	NR	12	6.8	8	20	NR	NR
P2	43 (14–123)	6.3 (<135)	263 (295–1156)	124 (37–184)	42	22	20	15	37	34
P3	48 (14–106)	Undetectable	150 (345–1213)	100 (43–173)	44	21	28	11	25	25
P4	42 (22–159)	0.5 (<68)	935 (441–1135)	85 (47–200)	50	17	40	8	32	22
P5	68 (48–345)	<5 (<91)	706 (500–1300)	48 (40–160)	7	4	3	2	5	4
P6	Undetectable	0.5 (0.98–570.6)	Undetectable	Undetectable	74	30	39	2	20	4
P7	130 (33–202)	1.4 (<1015)	528 (468–1680)	70 (38–251)	33	24	16	13	44	44
P8	97 (45–236)	0.6 (0.98–570.6)	320 (608–1572)	111 (52–242)	NR	NR	NR	NR	NR	NR
P9	209 (33–202)	2.3 (1.03–161.3)	2.3 (633–1280)	133 (48–207)	NR	NR	NR	NR	NR	NR
P10	3.4 (22–159)	0.1 (<68)	186 (295–1156)	110 (37–184)	52	35	21	9	29	21
P11	41 (19–220)	5 (0–378)	899 (500–1300)	94 (40–180)	58	35	21	16	16	16
P12	9.3 (45–236)	NR	869 (608–1527)	1660 (52–242)	58	26	10	20	20	20
P13	11.3 (14–123)	NR	184 (424–1051)	148 (48–168)	NR	NR	NR	NR	NR	NR

The normal ranges for immunoglobulins varied with the patient's age and the technique used; we have therefore included them in parentheses separately for each value; CD values are expressed as the percentages of lymphocytes carrying the marker. CD: cluster of differentiation; Ig: immunoglobulin; NR: not reported.

Table 4. Results of DNA mutation analysis and the resulting protein alterations

Patient	Exon/intron	cDNA mutation	Protein alteration	Mutation reference	ACMG score
P1	Exon 46	c.6658C>T	p.Gln2220Ter	Reported	Pathogenic
P2	Exon 32	c.4864G>T	p.Glu1622Ter	Reported	Pathogenic
P3	Intron 17 / Exon 62	c.2639-1G>A / c.8907T>G	Splicing Site Defect/ p.Tyr2969Ter	Novel / Reported	Splicing Acceptor Site: 0.99
P4	Exon 7	c.829G>T	p.Glu277Ter	Reported	Pathogenic
P5	Exon 54	c.7940_7970delTTCCAGCAGA-CCAGCCAATTACTAAACTTAA	p.Ile2647fsTer3	Novel	Pathogenic
P6	Exon 10 / Exon 55	c.1537C>T / c.8050C>T	p.Gln513Ter/ p.Gln2684Ter	Reported	Pathogenic/ Pathogenic
P7	Intron 19	c.2921+1G>T	Splicing Site Defect	Reported	Splicing Donor Site: 0.85
P8	Exon 38	c.5712dupA	p.Lys1904fsTer26	Reported	Pathogenic
P9	Exon 38	c.5712dupA	p.Lys1904fsTer26	Reported	Pathogenic
P10	Exon 38	c.5712dupA	p.Lys1904fsTer26	Reported	Pathogenic
P11	Exon 58	c.8494C>T	p.Arg2832Cys	Reported	Pathogenic
P12	Exon 46	c.6658C>T	p.Gln2220Ter	Reported	Pathogenic
P13	Exon 46	c.6658C>T	p.Gln2220Ter	Reported	Pathogenic

ACMG: American College of Medical Genetics.

DISCUSSION

Here we presented the clinical manifestations of 13 Iranian A-T patients and their mutation analysis of the *ATM* gene. Several studies have previously reported the clinical manifestations of Iranian A-T patients.[7-9]

Ataxia was the primary manifestation of the disease in all patients except one (P1) due to his young age at the time of onset. Rather, recurrent infections and sepsis were the primary symptoms. Instead, recurrent infections and sepsis were the primary presentations. This picture, together with abnormal bone marrow aspiration/biopsy and serum protein immunotyping results, had pointed the physicians toward a diagnosis of hyper-IgM syndrome. Cases of A-T patients presenting with a hyper-IgM syndrome phenotype have been reported in the literature. The humoral component of the immune system affected by A-T commonly involves IgG and IgA, and approximately 10% of these patients are expected to have increased IgM levels.[10,11] Since the presentation of infections usually precedes the hallmarks of A-T (ie, ataxia and telangiectasias), this group is commonly misdiagnosed with hyper-IgM syndrome. Even though it is expected for these patients to have a worse prognosis than other A-T patients,[12] our patient has been clinically stable while receiving regular intravenous immunoglobulin.

Autoimmune diseases are also expected to manifest in patients with immunodeficiency. This report included 2 A-T patients with autoimmune skin conditions: alopecia and vitiligo. Several studies have also reported this association with A-T. Alopecia can be viewed from the two perspectives of autoimmunity or a progeric effect commonly associated with A-T.[13] The patient in this study (P6) had developed alopecia areata, which is more appropriately explained by an autoimmune process.[14] Vitiligo is a rare manifestation of ataxia-telangiectasia, which was observed in one of the patients (P8). Only several case reports exist in the literature that describe such a cooccurrence. It is still an open question whether A-T is linked with vitiligo or other polyglandular autoimmune syndromes.[15]

In this study, although not all patients initially presented with ataxia, the signs of ataxia and telangiectasias eventually appeared in all patients.

While a definitive diagnosis of A-T can be made without genetic testing, such testing offers several benefits. It clarifies inheritance patterns for family planning, identifies asymptomatic carriers, and facilitates enrollment in clinical trials for new therapies. Moreover, a confirmed genetic diagnosis provides clarity and support for patients and their families, enhancing their emotional and psychological well-being.

ATM mutations are rather evenly distributed along with its 64 exons, and no hot spots are assumed for the gene. Several studies have previously characterized *ATM* mutations in Iranians in exons 39, 54, 55, 59,[16] 43, 28, and 62.[17] In this study, 9 out of the 11 mutations were single-nucleotide substitutions, followed by 1 deletion and 1 duplication. Eleven patients were homozygotes for the mutations, and two (P3 and P6) displayed compound heterozygosity. We searched several gene mutation databases, including the Human Gene Mutation Database (HGMD), ClinVar, Varsome, and Iranome (an Iranian mutation database) for *ATM* mutations. So far, more than 1700 mutations have been reported for the *ATM* gene in HGMD, most of which consist of single-nucleotide substitutions followed by small deletions.[4]

Considering that 9 mutations in the present study lead to truncated proteins, they are expected to get degraded by the nonsense-mediated mRNA decay (NMD) mechanism-an inherent mechanism of cells for removing abnormal gene products-and have deleterious effects on the protein structure.[18] Moreover, the critical domains of *ATM*, such as PI3K, are located in the C-terminal end of the protein-which is highly conserved-therefore, even if a truncated protein is formed, the shortened protein product would not be functional.[19]

The mutation c.7940_7970delTTCCAGCAGA-CCAGCCAATTACTAAACTTAA in P5 has not been previously reported. This mutation results in a frameshift in the ORF, which produces a premature stop codon at position 2650 of the protein. The resulting protein lacks kinase activity.

Two of the mutations (c.2921+1G>T in intron 19 and c.2639-1G>A in intron 17) affect *ATM* at the 5′ (GT) and 3′ (AG) splicing sites, respectively. Therefore, any substitution in these nucleotides would prevent the interaction between pre-mRNA and spliceosomes. Consequently, mutations c.2921+1G>T and c.2639-1G>A lead to single exon skipping of exons 19 and 17, respectively.

The mutation c.4864G>T in exon 32 results in a premature stop codon and truncates the original full-length protein to a 1622-residue protein. This shortened protein is unstable and is degraded by the NMD mechanism.

As the function of ATM depends on the C-terminal domains, the 2 mutations c.829G>T and c.1537C>T (affecting the N-terminus) and c.5712dupA (before the FAT domain) produce proteins with no catalytic sites and are hence nonfunctional. Mutation c.6658C>T is located on the FAT domain and impairs the interaction of ATM with other proteins. Mutation c.8050C>T (p.Gln2684Ter) is situated between the FAT and PI3K domains and results in a truncated nonfunctional protein.

In the nonsense mutation c.8494C>T, arginine is substituted by cysteine, classified in a different group of amino acids, and has highly dissimilar properties relative to arginine. Mitui et al showed that c.8494C>T causes a mild phenotype of A-T—caused by low levels of ATM—compared with other A-T patients with no detectable ATM.[20]

Lastly, although the presence of all A-T mutations on a single gene has made it easier for us to target the gene, no hotspots can be considered for such mutations; this makes the identification of such mutations without WES an arduous task. Indeed, we found 11 different mutations in exons 7, 10, 32, 38, 46, 54, 55, 58, 62, and introns 17 and 19, which span a broad region of the gene. All mutations reported in this study prevented the production of a full-length functional protein.

The limitations of this study include the lack of functional analysis of identified *ATM* mutations, which should be addressed in future studies.

In conclusion, these results have implications for the diagnosis and management of A-T in Iranian patients. It is crucial for clinicians to consider A-T as a differential diagnosis in patients presenting with ataxia, recurrent infections, and hyper-IgM syndrome phenotype. Early diagnosis and genetic counseling can help improve the quality of life and survival of affected individuals and their families.

Overall, this study contributes to the growing body of knowledge on A-T and highlights the importance of continued research to improve our understanding of this debilitating disorder.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Immunology, Asthma and Allergy Research Institute, Tehran, Iran (IR.TUMS.IAARI.REC.1397.008).

Written informed consent was obtained from all the patients' parents. The patients underwent extensive clinical and laboratory evaluation.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Data Availability

The genetic sequence analyses for the patients and their parents are accessible from: https://doi.org/10.17632/4s6pbz6bsd.1

AI Assistance Disclosure

Not applicable.

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