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Case report

A novel *ATM* frameshift mutation (c.3613dup) leading to ataxia-telangiectasia with early-onset severe immunodeficiency: A case report and literature review

Xin-Ru Wang and Rong Lu*

Department of Pediatrics, Yanan University Affiliated Hospital, Yanan, 716000, China

* **Correspondence:** Email: 81727839@qq.com.

Abstract: Background: Ataxia-telangiectasia (A-T) is a rare, autosomal recessive, multisystem disorder caused by mutations in the *ATM* gene. Atypical presentations that lack classic ocular telangiectasias or present predominantly with early-onset movement disorders pose significant diagnostic challenges and frequently lead to misdiagnosis during early childhood. Case Presentation: We reported a 6-year-old Chinese boy who was presented with delayed motor milestones and dysarthria since 1 year of age. Brain magnetic resonance imaging (MRI) revealed distinct cerebellar atrophy. Notably, classic oculocutaneous telangiectasias were absent; instead, atypical hypopigmented macules were observed on the skin. Whole-exome sequencing identified compound heterozygous mutations in the *ATM* gene: A known pathogenic missense variant (c.8110T>G) and a novel, maternally inherited frameshift mutation (c.3613dup, p.Arg1205Profs*24) were found in exon 25. In silico analysis predicted that this novel variant triggers nonsense-mediated mRNA decay (NMD), potentially leading to loss of the ATM protein kinase catalytic domain, which aligns with his mild-to-moderate neurological and severe immunological phenotypes. Conclusion: This case highlights that progressive cerebellar involvement and profound immunological compromise can manifest in A-T patients even in the absence of classic telangiectasias. The identification of the novel c.3613dup mutation broadens the genotypic spectrum of the *ATM* gene. Furthermore, it underscores the critical importance of integrating early genetic screening for atypical childhood-onset movement disorders to prevent diagnostic delays and facilitate timely multidisciplinary management.

Keywords: ataxia-telangiectasia; *ATM* gene; frameshift mutation; nonsense-mediated mRNA decay; movement disorders; case report

1. Introduction

Ataxia-telangiectasia (A-T) is a rare, autosomal recessive, multisystem disorder caused by mutations in the *ATM* gene, classically characterized by the triad of progressive cerebellar ataxia, oculocutaneous telangiectasia, and immunodeficiency [1–3]. However, an increasing number of variant or atypical A-T cases have been recognized, broadening the clinical spectrum significantly [4,5]. These atypical presentations may initially lack the hallmark telangiectasias or present predominantly with extrapyramidal movement disorders (such as dystonia, chorea, and apraxia) rather than classic ataxia [6–8]. Such phenotypic variations pose a significant diagnostic challenge, frequently leading to delayed diagnoses or misdiagnoses, such as cerebral palsy, during early childhood, and can dangerously mask underlying primary immunodeficiencies [9,10].

2. Case presentation

2.1. Clinical data

A 6-year-old boy was admitted to the emergency department of Yanan University Affiliated Hospital presenting with "recurrent severe infections for 6 years and fever for 4 days." Tracing his medical history, the patient was delivered full-term via normal vaginal delivery. He developed intermittent pulmonary infections starting 16 days after birth, with a history of 3–4 hospitalizations per year due to infections. His condition has worsened over the past year, requiring multiple emergency resuscitations at local hospitals for severe pneumonia and multi-pathogen infections. Motor developmental delay and dysarthria were noted at 1 year of age. As he grew older, he gradually developed progressive susceptibility to fatigue, drooling, and an abnormal gait (toe-walking). The parents are non-consanguineous. His mother has vitiligo, and his 1.5-year-old younger sister is healthy. There is no reported family history of similar genetic disorders.

2.2. Physical examination

Vitals: Temperature 38.5 ℃, weight 18.4 kg (3rd percentile), and height 119 cm (10th–25th percentile). The patient was conscious but lethargic. Multiple scattered hypopigmented macules, approximately 0.5–2 cm in diameter, were observed on the trunk and extremities. These presented as flat white patches with relatively clear borders and without skin atrophy or telangiectasia at the lesions. No obvious telangiectasia was observed on the systemic skin or bulbar conjunctiva. The pharynx was hyperemic, gums were swollen, and dense white ulcers were visible on the oral mucosa and tongue surface. Neurological examination revealed dysarthria. Muscle strength and tone in all four limbs were within normal limits, and tendon reflexes were symmetrically elicited.

2.3. Auxiliary examinations and clinical course

Emergency routine blood tests upon this admission showed a white blood cell (WBC) count of 22.75 × 10^9/L, with 84.1% neutrophils and extreme lymphopenia (10.90%). High-sensitivity C-reactive protein (hs-CRP) was 49.95 mg/L. Chest radiography revealed no significant abnormalities. The clinical diagnosis was severe mixed infection (sepsis complicated by herpetic stomatitis).

Review of key historical examinations: 1. Imaging: Brain MRI clearly indicated cerebellar atrophy. 2. Baseline immunological evaluation: Performed at Peking Union Medical College Hospital prior to any exogenous immunoglobulin infusion, testing demonstrated profound combined humoral and cellular immunodeficiency, characterized by severe hypogammaglobulinemia (predominantly IgA, IgG3, and IgG4), marked B-cell lymphopenia, an inverted $CD4^+/CD8^+$ ratio, and striking depletion of naive $CD4^+$ T cells (Table 1).

Table 1. Baseline immunological evaluation of the patient (prior to IVIG replacement therapy).

Category	Parameters	Patient result	Reference range
Humoral Immunity	IgG (g/L)	10.99	7.00–17.00
	IgA (g/L)	**0.12 (↓)**	0.70–4.00
	IgM (g/L)	0.93	0.40–2.30
	IgG1 (mg/L)	10218	3604–11638
	IgG2 (mg/L)	1750	670–3946
	IgG3 (mg/L)	**79 (↓)**	160–950
	IgG4 (mg/L)	**<15 (↓)**	32–1699
Lymphocyte Subsets	**B cells ($CD19^+$, %)**	**1.2 (↓)**	8.5–14.5
	NK cells ($CD16/56^+$, %)	40.4 (↑)	9.5–23.5
	Total T cells ($CD3^+$, %)	**57.8 (↓)**	62.6–76.8
	$CD4^+$ T cells (%)	**22.1 (↓)**	30.0–46.0
	$CD8^+$ T cells (%)	33.6 (↑)	19.2–33.6
	$CD4^+/CD8^+$ ratio	**0.66 (↓)**	0.95–2.13
CD4+ T Cell Subsets	Memory $CD4^+$ T cells (%)	91.7 (↑)	45.6–68.4
	Naive $CD4^+$ T cells (%)	**1.9 (↓)**	31.6–54.4
	$CD4^+CD28^+/CD4^+$ (%)	**72.9 (↓)**	85.0–100.0
CD8+ T Cell Subsets	$CD8^+CD28^+/CD8^+$ (%)	39.7	37.2–60.4
	$CD8^+DR^+/CD8^+$ (%)	**67.5 (↑)**	6.3–23.8

(Note: Laboratory tests were performed at the Department of Laboratory Medicine, Peking Union Medical College Hospital on August 26, 2025. Bold values indicate highly abnormal immunological parameters. RTEs, recent thymic emigrants.)

2.4. Immunological characteristics

The baseline immunological profile displayed a characteristic T-B-NK+ phenotype driven by defective V(D)J recombination, a direct consequence of impaired ATM-dependent DNA double-strand break repair. As summarized in Table 1, this underlying defect manifests as: (1) B-cell

developmental arrest, evidenced by profound B-cell lymphopenia and hypogammaglobulinemia, explaining the patient's susceptibility to recurrent sinopulmonary infections; and (2) thymic output failure, marked by near-complete depletion of naive $CD4^+$ T cells, which serves as a sensitive cellular hallmark distinguishing A-T from common variable immunodeficiency (CVID). Given this severe immune collapse, high-dose intravenous immunoglobulin (IVIG) pulse therapy was promptly administered, successfully controlling the acute systemic infection.

2.5. Treatment and clinical course

Considering the profound compromise of the patient's underlying immune barrier and the extremely poor response to conventional antimicrobial therapies, high-dose IVIG pulse therapy and immunomodulatory support were administered. Following this intervention, the patient's temperature gradually normalized, and the severe infection was effectively controlled. Based on previous consultation recommendations from Peking Union Medical College Hospital, the patient was strongly advised to undergo lifelong, regular IVIG infusions for passive immune replacement therapy upon discharge.

2.6. Molecular genetics analysis

A review of the genetic testing report from an external institution (Beijing Children's Hospital) revealed that the patient underwent proband-only whole-exome sequencing (WES) using a peripheral blood sample in December 2024. Subsequently, Sanger sequencing was performed on the proband and his parents to validate the candidate pathogenic variants within the pedigree. The results demonstrated that the patient harbors compound heterozygous mutations in the ATM gene (see Figure 1). The novel frameshift mutation, c.3613dup, is predicted in silico to impair or abolish ATM protein kinase activity, thereby potentially triggering a pathophysiological cascade involving multiple systems, including the neurological, immunological, and dermatological systems (See Figure 2).

(1) c.8110T>G (p.Cys2704Gly): A missense mutation in exon 55 (FAT domain). Sanger sequencing confirmed its paternal inheritance. This variant is a recognized hotspot mutation within the Chinese population.

(2) c.3613dup (p.Arg1205Profs*24): A frameshift mutation in exon 25. Sanger sequencing confirmed its maternal inheritance. This variant is predicted to cause a frameshift starting at arginine residue 1205, leading to a premature termination codon 24 amino acid downstream, thereby potentially severely impairing ATM protein kinase function. Furthermore, the premature translation termination is predicted to trigger nonsense-mediated mRNA decay (NMD), potentially resulting in the loss of the ATM protein kinase catalytic domain.

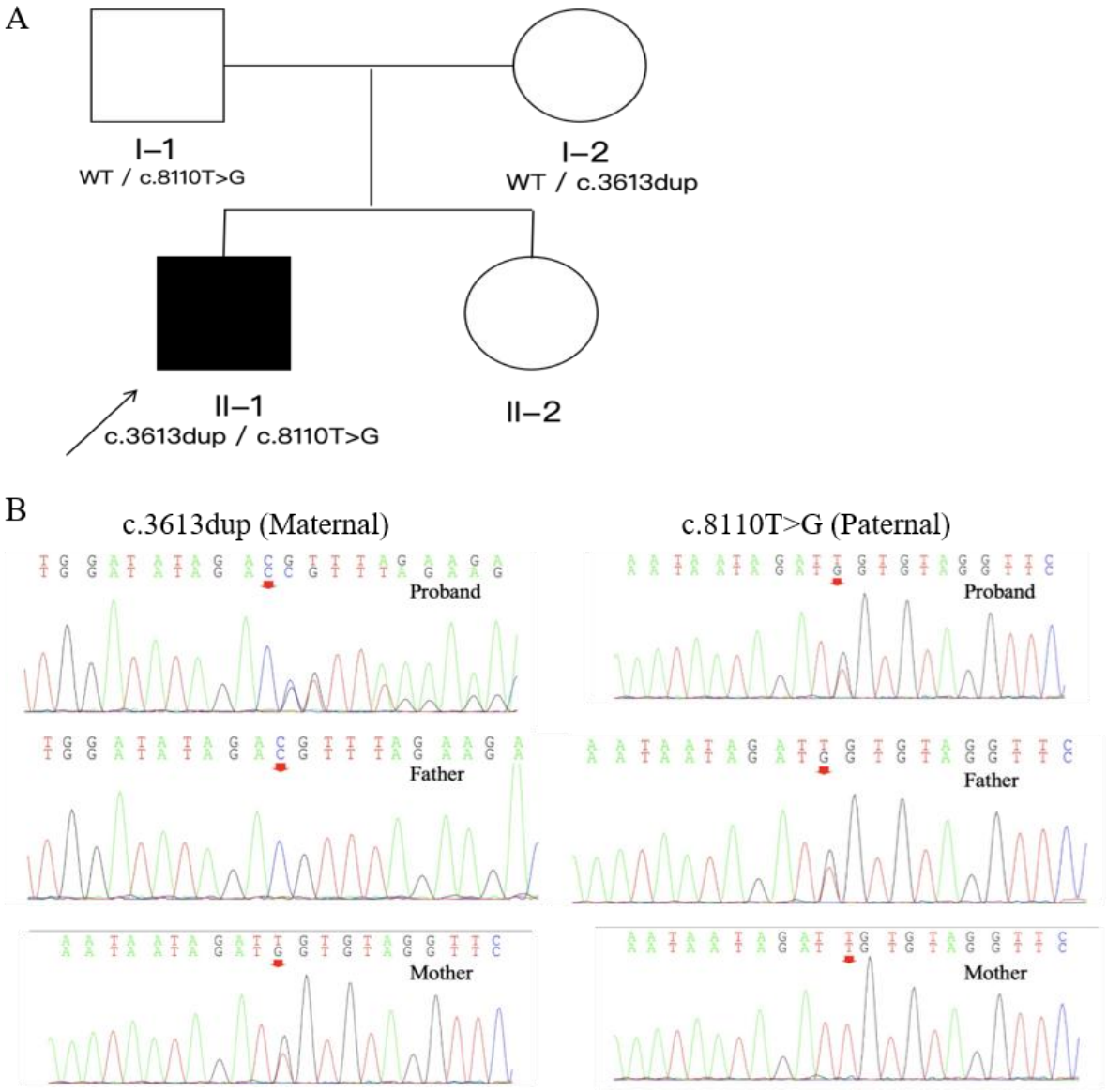


Figure 1. Pedigree and Sanger sequencing validation of ATM gene mutations. (A) Pedigree of the family. The black arrow indicates the proband (II-1, the 6-year-old patient). (B) Sanger sequencing chromatograms of the proband and his parents. The results confirmed that the proband carries compound heterozygous mutations in the ATM gene: A maternally inherited frameshift mutation c.3613dup (p.Arg1205Profs24) in exon 25, and a paternally inherited missense mutation c.8110T>G (p.Cys2704Gly) in exon 55.

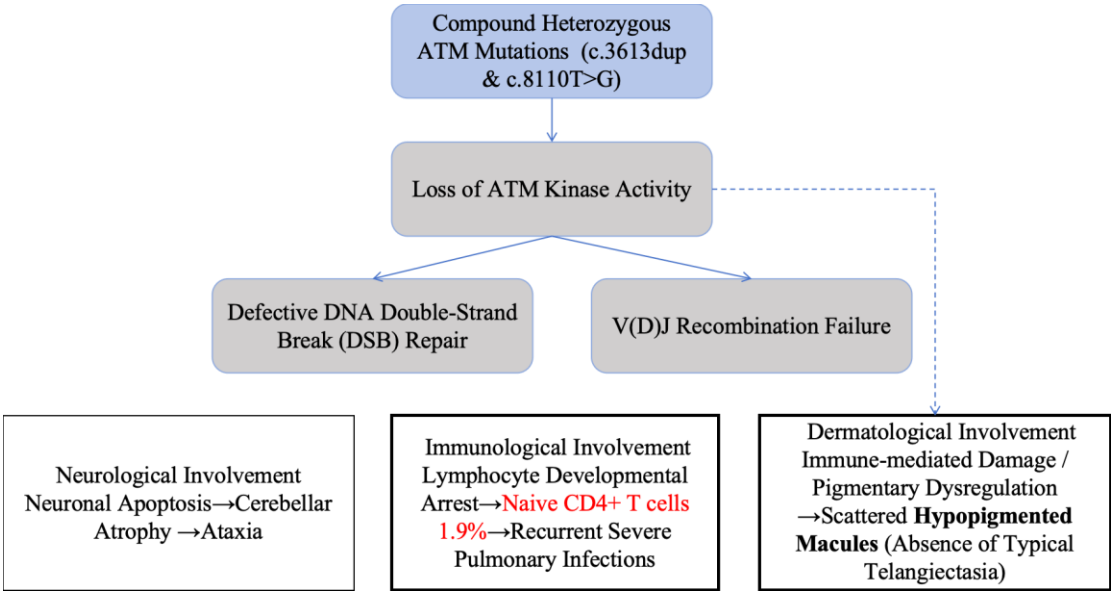


Figure 2. Schematic diagram of the hypothesized pathophysiological cascades driven by compound heterozygous ATM mutations. The flowchart illustrates how these mutations are predicted to impair ATM kinase activity, triggering three core pathological processes: (1) Defective DNA double-strand break repair induces neuronal apoptosis, manifesting as cerebellar atrophy and ataxia; (2) V(D)J recombination failure causes lymphocyte developmental arrest, characterized by a drastic depletion of naive $CD4^+$ T cells (1.9%) and recurrent severe infections; and (3) Immune-mediated damage or pigmentary dysregulation results in the atypical hypopigmented macules specific to this case. Note: The loss of kinase activity and downstream molecular consequences represent in silico predictions, as functional assays were not performed.

3. Discussion

The patient in this study presented with delayed motor milestones, dysarthria, and MRI-confirmed cerebellar atrophy, aligning with the natural history of A-T. However, a clinically cautionary aspect is the complete absence of classic ocular telangiectasias even at 6 years of age. Instead, the patient exhibited atypical hypopigmented macules. As illustrated in our pathophysiological model (Figure 2), the loss of ATM kinase activity can trigger immune-mediated damage or pigmentary dysregulation, resulting in these variant dermatological manifestations rather than classic telangiectasias [11,12]. Dermatological manifestations in A-T extend beyond classical telangiectasia; pigmentary abnormalities such as café-au-lait macules, hypopigmented patches, and vitiligo-like depigmentation, as well as cutaneous granulomas, have been occasionally described in patients with ATM deficiency. These pigmentary changes are hypothesized to reflect genomic instability in dermal lineages or underlying immune dysregulation. Nevertheless, because the patient's mother had vitiligo, a familial predisposition to autoimmune pigmentary alterations cannot be ruled out. Therefore, while clinically noteworthy, hypopigmented macules cannot be definitively attributed to ATM deficiency based on this single case. The absence of hallmark skin lesions, combined with early-onset movement disorders, frequently misleads clinicians toward idiopathic developmental delay [8,9]. To mitigate such

diagnostic delays, routine screening of serum alpha-fetoprotein (AFP) is highly recommended [2,11]. AFP is persistently elevated in approximately 95% of A-T patients after two years of age, serving as a crucial initial screening biomarker long before pathognomonic telangiectasias become visible [11]. A growing body of literature indicates that A-T exhibits marked phenotypic heterogeneity [12,13]. Non-classical or atypical forms often lack cardinal manifestations, such as oculocutaneous telangiectasias or recurrent sinopulmonary infections, and may initially present with isolated movement disorders, early-onset combined immunodeficiency, or autoimmune and inflammatory complications (Bartsch et al. [13]; De Nardi et al. [14]). For instance, Bartsch et al. [13] reported an atypical A-T case featuring profound motor delay, severe oligoarthritis, and normal cranial MRI findings without classic respiratory infections or telangiectasia, where diagnosis was guided by elevated AFP and confirmed by compound heterozygous ATM mutations and acquired chromosomal rearrangements. Similarly, De Nardi et al. [14] described an atypical A-T patient presenting with chronic polyarthritis, interstitial lung disease, and hepatic granulomas, which initially masqueraded as an autoinflammatory disorder before genetic confirmation. Such variant presentations pose significant diagnostic hurdles and are frequently misdiagnosed as cerebral palsy, juvenile idiopathic arthritis, or primary immunodeficiency disorders, leading to considerable diagnostic delay [9,10]. Our patient, who manifested progressive cerebellar involvement and recurrent severe infections in the absence of classic telangiectasias, fits within this expanding spectrum of variant A-T and reinforces the imperative role of early genetic testing [4,5].

At the genotypic level, the c.8110T>G missense variant is a confirmed pathogenic hotspot in the Chinese cohort. Concurrently, the maternally inherited c.3613dup is a novel frameshift mutation in exon 25. This variant is predicted to trigger nonsense-mediated mRNA decay (NMD), potentially resulting in a truncated protein. While truncating frameshift variants are generally predicted to cause loss of kinase function through nonsense-mediated decay, the patient's clinical phenotype reflects the compound heterozygous interaction of both alleles; the novel truncating c.3613dup and the known pathogenic missense variant c.8110T>G. Given that functional expression studies were not conducted and this report is based on a single patient, genotype–phenotype associations must be interpreted cautiously, and disease severity should not be ascribed solely to the novel frameshift allele. Pathophysiologically, the profound loss of ATM catalytic function fundamentally impairs DNA double-strand break (DSB) repair [15]. As depicted in our schematic (Figure 2), this defective DSB repair directly induces neuronal apoptosis, which clinically manifests as the progressive cerebellar atrophy and ataxia observed in this patient [15]. Furthermore, chronic ATM deficiency exacerbates mitochondrial dysfunction and oxidative stress, further accelerating this process and driving premature cellular senescence [16].

Beyond neurodegeneration, the most striking feature of this case is the early-onset severe immunodeficiency. The ATM kinase is indispensable for resolving DSBs generated during lymphocyte gene rearrangements [2,17]. The complete loss of ATM function directly disrupts V(D)J recombination, causing severe lymphocyte developmental arrest [17]. Consequently, as highlighted in our model, the patient exhibited a drastic depletion of naive $CD4^+$ T cells (only 1.9%), alongside severe B-cell deficiency. This failure in thymic output and B-cell maturation elucidates the patient's heightened susceptibility to recurrent severe pulmonary infections [17]. Moreover, this profound genomic instability and immune collapse significantly elevate the long-term risk of lymphoid malignancies, such as Hodgkin's lymphoma [18]. Given this severe immunological profile, proactive multidisciplinary management, including continuous IVIG replacement and rigorous immunological monitoring, is critical to preserve overall survival [17].

4. Conclusions

A-T is highly susceptible to missed diagnosis in its early clinical stages. When pediatricians encounter children presenting with "developmental delay or cerebellar atrophy" combined with "early-onset, refractory respiratory infections," they must avoid the diagnostic pitfall of waiting for "telangiectasia" to appear. Absolute lymphocyte counts and precise subset subtyping (especially the evaluation of naive T cells) should be performed as early as possible. Furthermore, the proactive application of WES is recommended to achieve early diagnosis, prompt intervention, and improved long-term prognosis for these patients.

5. Limitations

Despite the comprehensive clinical and genetic evaluation, this study has limitations. First, as a single case report, the clinical phenotypic spectrum associated with these compound heterozygous mutations requires further observation in larger patient cohorts. Second, although the pathogenicity is strongly supported by genetic principles (in silico-predicted nonsense-mediated mRNA decay) and the patient's profound immunological defects, we did not perform *in vitro* functional assays (such as Western blotting to assess ATM protein expression or functional kinase assays) due to laboratory resource constraints. Future functional studies are warranted to fully elucidate the molecular downstream mechanisms underlying this variant. We acknowledge that functional assays (e.g., Western blot or kinase activity assays) were not performed; therefore, the predicted molecular consequences require experimental validation in future studies.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Author contributions

Xin-Ru Wang contributed to the clinical data collection, literature review, and drafted the manuscript. Rong Lu supervised the study, critically revised the manuscript for important intellectual content, and takes full responsibility for the integrity of the data. Both authors read and approved the final manuscript.

Conflict of interest

All authors declare no conflicts of interest in this paper.

Ethical statement and informed consent

This research has received ethical approval by the Ethics Commission of Yanan University Affiliated Hospital (IIR-R-2026150). Written informed consent was obtained from the patient's legal guardians (parents) for the participation in this study, the collection of clinical data and biological samples, and the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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