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Clinical Correlation of Ataxia Telangiectasia-Like Disorder 1 with A Variant of Uncertain Significance in the *MRE11* Gene: A Case Report

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ABSTRACT

Introduction: Ataxia telangiectasia-like disorder (ATLD) is a rare autosomal recessive disorder caused by mutations in the MRE11 gene. The diagnosis of patients with ataxia telangiectasia-like disorder and Ataxia telangiectasia may be challenging due to similar clinical manifestations. In the present study, we describe a patient with a homozygous variant of uncertain significance (VUS) in the MRE11 gene correlated clinically with ATLD.

Methods: We performed a brain MRI scan to find the cause of the patient's ataxia. There was no clinical change after ventriculoperitoneal shunting due to obstructive hydrocephalus; therefore, we carried out whole exome sequencing. In addition, the variants were classified using several databases and predicted according to the ACMG 2015 guidelines.

Results: A 2-year-6-month-old boy with ataxia, tonic seizure, and speech delay was found during studies. The WES and in silico analysis identified a homozygous variant of uncertain significance in the MRE11 NM_005591.4 (MRE 11): c.173 G>T (p. GIv58Val).

Conclusion: This case report highlights that genetic testing can be helpful for precise diagnosis when clinical manifestations are not associated with MRI results. Furthermore, based on clinical features, we could categorize a variant in the MRE11 gene from VUS to likely pathogenic.

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Introduction

Ataxia telangiectasia-like disorder is a sporadic autosomal recessive disease with defects in the DNA damage response (DDR) (1). Several diseases, such as ataxia telangiectasia (AT), Nijmegen Breakage Syndrome (NBS), and ataxia telangiectasia-like disorder (ATLD), are associated with defects in the DNA damage response (2). A wide range of clinical characteristics among the diseases are caused by defects in DNA repair, including neurological degeneration, immunodeficiency, and/or cancer predisposition (3). Given that ATLD is such a rare disease, the

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phenotype is challenging to understand. The *ATM* gene is essential to DDR signaling (4). Patients with classical ataxia telangiectasia exhibit homozygous or compound heterozygous mutations in the *ATM* gene (5). At the same time, advancements in next-generation sequencing technologies enable genetic diagnosis of atypical AT cases with new genes. For instance, patients with ataxia and ATM-negative are diagnosed as ATLDs. ATLD1 is associated with mutations in the *MRE11A* gene (6). The protein that the *MRE11* gene produces has nuclease and intrinsic DNA-binding properties, which form the MRN (MRE11-RAD50-NBS1) complex and are involved in DNA recombination, cell-cycle checkpoints, and double-strand break sensing (7,8). Due to similarities in clinical manifestations and cellular characteristics, ATLD is compared to AT (9). The clinical feature that identifies A-T and ATLD is progressive cerebellar ataxia. Although ATLD1 and AT have similar neurological symptoms, related immunodeficiency of ATLD1 is not as severe. In general, ATLD demonstrated mild and later symptoms and a slower progression rate than AT (10). Here, we report a boy who presented with ataxia without telangiectasia. Exome sequencing displayed a homozygous variant of uncertain significance (VUS) in the *MER11* gene linked to ataxia-telangiectasia-like disorder 1, which has not been reported.

Case report

We reported a 2-year-6-month-old boy who was born to consanguineous parents who previously experienced a spontaneous abortion (Figure 1).

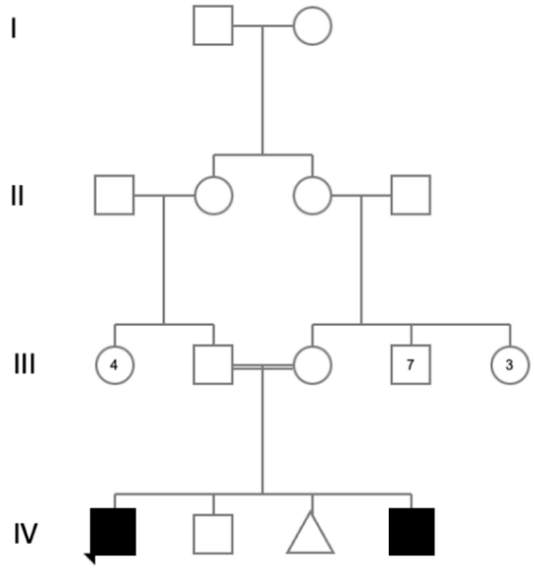

Figure 1. Pedigree analysis of the patient's family. Black squares (male) indicate family members affected by the disease, while open circles or squares indicate unaffected members. The arrow indicates the proband. The open triangle indicates spontaneous abortion.

The patient presented ataxia during his first visit at the age of 2 years and 4 months. His birth weight was 3.2 kg, his head circumference was 49 cm, and his APGAR score was normal. There was no evidence of scoliosis, pes cavus, tendon xanthomas, cataracts, or oculocutaneous telangiectasia. At the age of one, he experienced a tonic seizure accompanied by a high fever. He began walking at two years old but had an unbalanced gait ever since. The brain magnetic resonance imaging (MRI) scan exhibited moderate ventricular dilatation, especially in lateral ventricles and V3. Moreover, there was an abnormally high signal intensity in the high parietal lobe on the left side (Figure 2). At the age of two, the ventriculoperitoneal shunt was placed; nonetheless, it did not improve his ataxia. In addition, the retinal examination was normal. At two years and six months old, he weighed 11.8 Kg, his speaking ability was limited to 30 words, and his attention was not so bad. Moreover, he exhibited a slightly wide-based and ataxic gait, and he was affected by a variety of sinopulmonary diseases. Whole exome sequencing (WES) was performed using DNA extracted from the proband's blood. According to bioinformatic workflow, base calling, primary filtering of low-quality reads and probable artifacts, and annotation of variants were performed. We categorized variants using private and public databases, such as NCBI 1000 genomes, NHLBI Exome Sequencing Project, Exome Aggregation Consortium, and HGMD®. The 2015 American College of Medical Genetics and Genomics (ACMG) guidelines were used to assess the pathogenicity of the variants. We found a homozygous variant of uncertain significance (VUS) in the *MRE11* NM_005591.4 (*MRE 11*): c.173 G>T (p. GIv58Val). This variant is associated with ATLD1.

Discussion

In this report, we present the first Iranian case with a homozygous variant of unknown significance (VUS) in the *MRE11* gene, which was found to be clinically associated with

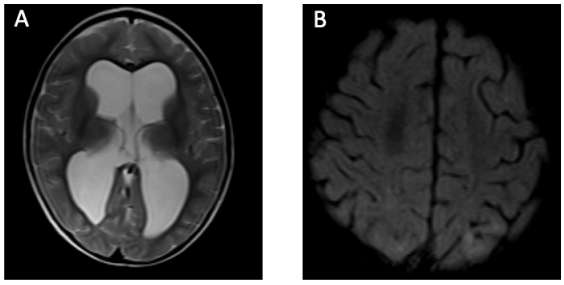

Figure 2. Brain MRI of case. MRI images show moderate ventricular dilatation, especially in lateral ventricles and V3 (A). Also, there is abnormal high signal intensity in the high parietal lobe on the left side (B).

ATLD1. ATLD is a disease that includes defects in the DNA damage response (1). In addition, studies have demonstrated that DDR-related genes cause certain monogenic disorders. For example, ataxia-telangiectasia (A-T, MIM #208900), ataxia-telangiectasia-like disorder 1 (ATLD1, MIM #604391), and Nijmegen breakage syndrome (NBS, MIM #251260) can be caused by pathogenic variants of the *ATM, MRE11A*, and *NBN* (*NBS1*) genes (11,12). Previous research has indicated that mutations in the *MRE 11* gene can result in a variety of clinical symptoms, such as dystonia, global cerebral hypoplasia, facial deformities, and microcephaly NBS-like (13–15). The clinical features of ATLD1 include dystonia, choreoathetosis, radiosensitivity, abnormal eye movements, and cerebellar ataxia. Rarely, ATLD1 can be associated with microcephaly, facial dyskinesia, neuropathy, short stature, and cognitive impairment (16). The most common oculomotor abnormalities in ATLD1 are also slow and dysmetric saccades, oculomotor apraxia, delayed convergence, and gaze-evoked nystagmus (1,15). Nonetheless, the ATLD phenotype is unexpected and difficult to explain due to the disease's rarity. The neurological appearance of ATLD patients is very similar to that of AT patients. ATLD and AT are two separate diseases that share some similarities. Both conditions are caused by mutations in genes that encode proteins involved in the same cellular pathway. However, the particular genes that cause each disease are different; *MRE11* causes ATLD, while *ATM* causes A-T (17,18). For instance, in two siblings with ATLD, researchers discovered an inherited variant of the *MRE11* gene that resulted in a type of A-T that shares many of the clinical traits of A-T but frequently without telangiectasias, moderate radiosensitivity, delayed disease onset and progression, longer survival, and no tumor recurrence (17). Research unveiled a novel missense mutation of the *MRE11* gene in 10 patients from three distinct Saudi families with early-onset, slowly progressive ataxia and ophthalmoplegia. The study shed light on the presence of these symptoms in the affected individuals, suggesting a potential genetic link within the families (19). The *MRE11* gene codes for the protein Mre11, which has nuclease and DNA-binding activities. In response to DNA damage, the MRN complex, consisting of the proteins Mre11, Rad50, and Nbs1, interacts with ATM kinase to activate it and initiate the cellular signaling network(20). Therefore, the connection between the MRN complex and ATM activation provides a possible explanation for the phenotypic similarities observed between individuals with ATLD1 and AT (21–23).

Conclusion

This report highlighted the importance of genetic testing as a diagnostic tool in scenarios where clinical symptoms, such as ataxia, do not align with MRI findings. Furthermore, it was demonstrated how genetic testing could provide a more precise diagnosis, aiding in the identification of underlying genetic causes responsible for the observed symptoms. Moreover, the results of this investigation may boost knowledge of important variants with uncertain significance in the *MRE11* gene in patient ATLD1. In the future, molecular studies of VUS with pathogenic clinical features may lead to targeted medical management and counseling. Furthermore, we want to highlight that VUS is now classified as likely pathogenic when specific phenotypic traits are present.

Conflict of interest

All the authors declare no competing financial interests.

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