Neuroscience Letters 611 (2016) 112–115

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

Novel ATM mutations with ataxia-telangiectasia

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HIGHLIGHTS

- We report three Chinese patients who demonstrated ataxia, oculomotor apraxia, choreoathetosis, myoclonus and telangiectasias of the eyes.
- Sequence analysis of ATM revealed two known missense mutations c.8287C > T and c.9139C > T in the siblings. Intrafamilial clinical heterogeneity was observed in the siblings.
- The other patient was compound heterozygote for ATM: c.8911C > T and c.7141_7151delAATGGAAAAAT, both of which were new and not found in 200 controls.
- This study widens the spectrum of mutations and phenotypes in ataxia telangiectasia.

ARTICLE INFO

Article history:
Received in revised form 28 October 2015
Accepted 22 November 2015
Available online 25 November 2015

Keywords:
Ataxia telangiectasia
ATM
Myoclonus
Novel mutation

ABSTRACT

Ataxia telangiectasia is an autosomal recessive multisystem disorder characterized by progressive cerebellar ataxia with onset in childhood, oculocutaneous telangiectasia, increased serum alpha-fetoprotein, immunodeficiency, chromosomal instability, and radiation hypersensitivity. Ataxia-telangiectasia mutated gene (ATM) is one of the known genes to be associated with ataxia telangiectasia. We reported the clinical and genetic findings of three early-onset Chinese patients who demonstrated ataxia, oculomotor apraxia, choreoathetosis, myoclonus and telangiectasia of eyes. Sequence analysis of ATM revealed two known nonsense mutations c.8287C > T and c.9139C > T in the siblings. Though the siblings carried the same mutations, they showed different clinical features involving strephenopodia, exotropia, torsion dystonia, myoclonus and extrapyramidal impairments. The other patient was compound heterozygotes for ATM: c.8911C > T and c.7141_7151delAATGGAAAAAT, both of which were not reported previously and not found in 200 control chromosomes. This study widens the spectrum of mutations and phenotypes in ataxia telangiectasia.

1. Introduction

Ataxia-telangiectasia (AT, MIM 208900) is an autosomal recessive multisystem disorder which affects the nervous system, immune system, and other systems, caused by mutation in the ataxia-telangiectasia mutated gene (ATM, MIM 607585) [3,10]. Typical AT phenotype is caused by null mutations that truncate or severely destabilize the ATM protein [6]. AT occurs at a frequency ranging from 1 in 40,000 to 1 in 100,000 people worldwide.

As a master regulator of the DNA damage response, ataxia-telangiectasia mutated protein kinase coordinates checkpoint activation, DNA repair, and metabolic changes in eukaryotic cells in response to DNA double-strand breaks and oxidative stress [6]. Cerebellar cells involved in coordinating movements are particularly affected by loss of the ATM protein. Consequently, the hallmarks of AT is a progressive loss of cerebellar neuron resulting in debilitating ataxia as well as dilation of blood vessels. Other variable features include myoclonus, dystonia, oculomotor apraxia, slurred speech, immunodeficiency and endocrine dysfunctions. In addition, AT is characterized by clinical and cellular hypersensitivity to ionizing radiation and by a high rate of malignancies.

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http://dx.doi.org/10.1016/j.neulet.2015.11.036
0304-3940/

2. Materials and methods

2.1. Subjects

Three patients as well as their parents were enrolled in this study. Two hundred genetically unrelated healthy volunteers were recruited from the medical examination center of our hospital with the same Han Chinese ethnic background. Written informed consents were obtained from all subjects. The protocol was approved by the Ruijin Hospital Ethics Committee, Shanghai Jiao Tong University School of Medicine.

2.2. Methods

They underwent extensive clinical and laboratory evaluation. Molecular genetic studies were performed as follows:

Genomic DNA was extracted from peripheral blood through the standardized phenol/chloroform extraction method. The coding region of ATM (NM_000051) was sequenced in three patients. Molecular genetic studies were performed as described previously. The primers flanking the entire coding exons and intron–exon boundaries of above-mentioned genes were designed using the web based Primer 3.0 program. Polymerase chain reaction (PCR) was carried out at appropriate annealing temperature. The purified PCR products were sequenced on an ABI 3730 XL sequencer (Applied Biosystems and Life Technologies, USA). The obtained sequences were compared with the published sequences using SeqMan software (DNASTAR, Madison, WI, USA), and sequence variations were confirmed by analyzing both DNA strands.

3. Results

3.1. Clinical report

Case 1: The patients (II:1) were two siblings from a Han Chinese family without consanguinity (Fig. 1A). The siblings were born at term without neonatal problems and reached their early mile stones for motor and speech development at an appropriate age. As a proband, the elder sister (II:1) is currently 25 years old. Slurring of speech as well as bucking were noticed since her first speaking at 18 month. She could walk independently at the age of 14 months, but often wrestle with a broad-based gait. Over the next years, gait impairment progressed continuously and strephenopodia was present. She lost the ability of independent ambulation by the age of 9 and was confined in a wheelchair thoroughly until age 24. Bilateral conjunctival telangiectasia were obvious since the age of 4 (Fig. 2A). She presented with turning of neck and twisting of trunk toward right and left side by the age of 5. Shortly afterwards, torsion spasm was more and more frequent, and gradually accompanied with myoclonic jerks involving the four limbs, and achieved improvement with cervical botulinum toxin A injections. She had primary amenorrhoea and the secondary sexual characters developed normally. Cognitive function was preserved. Her scholastic performance was at a moderate level.

Laboratory investigations revealed normal hemogram, serum electrolytes, hepatic function and electrocardiogram. The serum alfafetoprotein (AFP) level was 318.61 ng/ml (ref., <13.4 ng/ml) in her serum. Neurological examination disclosed increased muscle tone, marked involuntary shaking in the four limbs and severe cerebellar dysfunction (dysdiadochokinesis, dysarthria). She had cervical dystonia resulting in retrocollis and laterocollis. Deep tendon reflexes were normal. During goal-directed movements, horizontal nystagmus were noted in both eyes. Brain MRI showed severe cerebellar atrophy bilaterally.

Case 2: The other member, affected from this family (Fig. 1A), was the 15-year-old brother (II:2) and presented overlapping features such as classical cerebellar ataxia, oculomotor ataxia, dysarthria, telangiectasia (Fig. 2B), cerebellar atrophy and elevated AFP level (426.33 ng/ml) with the exception of drooling and a left exotropia. In addition, neurological examination showed decreased deep tendon reflexes, normal muscle tone, without involuntary shaking or myoclonus in the limbs or trunk, and without strephenopodia, which performed milder clinical symptom than those of his elder sister.

Case 3: The 14-year-old boy (II:1), from another Han Chinese family (Fig. 1B) with no consanguinity, showed normal developmental milestones without perinatal problems. Slurring of speech as well as walking with a broad-based gait and a pigeon-toed pose existed initially at 18 months. Obvious balance problems were noticed at the age of 9. A neurological examination at that time showed mild ataxia, involuntary shaking in the four limbs, and there had been a subsequent gradual deterioration in balance. By

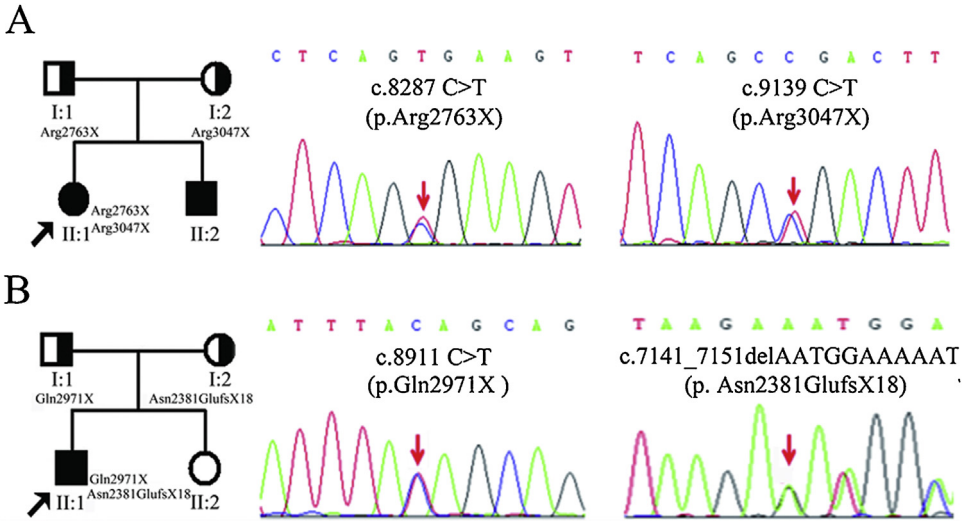

Fig. 1. Pedigree and sequencing chromatograms of three cases. The pedigrees are shown in the left half, and the corresponding chromatograms are shown in the right half. The one marked with the arrow is the proband. (A) Case 1 and case 2 displayed two mutations: c.8287C > T (p.Arg2763X) and c.9139C > T (p.Arg3047X) inheriting from their father and mother respectively. (B) Case 3 displayed two mutations: c.8911C > T (p.Gln2971X) inheriting from his father and c.7141_7151delAATGGAAAAAT (p.Asn2381GlufsX18) inheriting from his mother.