Novel compound heterozygous mutations of *ATM* in ataxia-telangiectasia: A case report and calculated prevalence in the Republic of Korea

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Ataxia-telangiectasia (AT; OMIM 208900) is a rare autosomal recessive inherited progressive neurodegenerative disorder, with onset in early childhood. AT is caused by homozygous or compound heterozygous mutations in *ATM* (OMIM 607585) on chromosome 11q22. The average prevalence of the disease is estimated at 1 of 100,000 children worldwide. The prevalence of AT in the Republic of Korea is suggested to be extremely low, with only a few cases genetically confirmed thus far. Herein, we report a 5-year-old Korean boy with clinical features such as progressive gait and truncal ataxia, both ankle spasticity, dysarthria, and mild intellectual disability. The patient was identified as a compound heterozygote with two novel genetic variants: a paternally derived c.5288_5289insGA p.(Tyr1763*) nonsense variant and a maternally derived c.8363A>C p.(His2788Pro) missense variant, as revealed by next-generation sequencing and confirmed by Sanger sequencing. Based on claims data from the Health Insurance Review and Assessment Service Republic of Korea, we calculated the prevalence of AT in the Republic of Korea to be about 0.9 per million individuals, which is similar to the worldwide average. Therefore, we suggest that multi-gene panel sequencing including *ATM* should be considered early diagnosis.

Key words: Spinocerebellar degenerations, Ataxia telangiectasia, High-throughput nucleotide sequencing, Prevalence.

Introduction

Hereditary ataxia has a variety of causes, one of which is an autosomal recessive disorder associated with defective DNA repair mechanisms known as ataxia-telangiectasia (AT; OMIM 208900) [1-4]. AT is primarily characterized by progressive cerebellar ataxia beginning between 1 and 4 years of age, abnormal eye movements, other neurological abnormalities, oculocutaneous telangiectasias, immune deficiency, and an increased risk for malignancy [1,5,6]. AT is caused by variants in *ATM* (OMIM

607585), which encodes the ATM protein belonging to the phosphatidylinositol (PI)3/PI4-kinase family [2,3]. In the Republic of Korea, only two families with genetically confirmed AT have been reported thus far, suggesting an extremely low prevalence of AT in the Korean population [7,8]. We herein report the clinical and genetic findings of a Korean boy with novel compound heterozygous variants in *ATM* and estimate the prevalence of AT in the Republic of Korea.

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Case

1. Patient

A 5-year-old boy presented with progressive gait unsteadiness since the beginning of independent walking at 12 months of age. He walked on the toes, and the imbalance in walking progressively worsened since the age of 2 years. His perinatal and neonatal histories were unremarkable. He was the third child of healthy, non-consanguineous Korean parents. He had two older siblings, a healthy brother and sister (Fig. 1A). The family history was unremarkable for neurodegenerative disease and cancer. He had no history of recurrent infectious diseases. Physical examination showed normal growth with relative macrocephaly; weight: 16 kg (−1.40 standard deviation [SD]), height: 104.5 cm (−1.07 SD), and head circumference: 52 cm (+0.70 SD). Mild ocular telangiectasia was observed (Fig. 1B), but there was no cutaneous telangiectasia or scoliosis. Neurological examination revealed no nystagmus or oculomotor apraxia. He exhibited progressive slurred speech, progressive gait unsteadiness, truncal ataxia, choreoathetosis, and ankle plantar flexor and extensor spasticity with normal muscle strength. Babinski sign was not shown, and deep tendon reflex was not elicited. He

exhibited mild intellectual disability with a Full Scale Intelligence Quotient of 61, as measured by the Korean-Wechsler Preschool and Primary Scale of Intelligence. Serially checked brain magnetic resonance imaging suggested diffuse cerebellar atrophy with enlarged cerebellar sulci and compensatory dilation of posterior fossa (Fig. 1C). Serum immunoglobulin (Ig) levels (IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgE, and IgM) were all within normal limits. His serum concentration of alpha-fetoprotein was markedly elevated (182.4 ng/mL, normal range <10 ng/mL).

After genetic confirmation, he started physical therapy to reduce the risk for contractures and scoliosis. He needs careful monitoring of pulmonary function and other signs of pulmonary disease and early signs of malignancy, particularly leukemia and lymphoma.

2. Genetic analysis results

The G-banding of the chromosomes from the patient's peripheral blood lymphocytes was normal (46, XY). DNA was obtained from family members (patient and parents), and whole-exome sequencing (WES) was performed for the patient. Genomic DNA was extracted from peripheral blood leukocytes, and sequencing was performed on the Illumina NextSeq500

Fig. 1. (A) Pedigree of the family with ataxia-telangiectasia. The shaded circle indicated by the black arrow indicates the patient, "II-3". Symbols marked with dots are definite carriers. Stars indicate sampled subjects. (B) Conjunctival telangiectasia in the right eye (black arrow) was observed but not prominent. (C) Serial brain magnetic resonance imaging in the patient at the age of 3, 4, and 5 years. The upper row shows sagittal T1-weighted images and the lower row shows axial T2-weighted images. These show diffuse decreased cerebellar volume with enlargement of cerebellar sulci, hemisphere atrophy, and compensatory enlarged posterior fossa due to enlarged cisterna magna.

platform (Illumina Inc., San Diego, CA, USA) at GC Genome (Yongin, Korea). Alignment of sequence reads, indexing of the reference genome (hg19), and variant calling with a pipeline based on GATK Best Practice was performed by the genomic bioinformatics team of GC Genome. Two heterozygous variants in *ATM* were identified—a c.5288_5289insGA p.(Tyr1763*) nonsense variant and a c.8363A>C p.(His2788Pro) missense variant—on the basis of the reference sequence NM_000051.3. The two variants were confirmed by Sanger sequencing in the patient and his parents (Fig. 2). His father was heterozygous for the c.5288_5289insGA p.(Tyr1763*) variant, and his mother was heterozygous for the c.8363A>C p.(His2788Pro) variant. The c.5288_5289insGA p.(Tyr1763*) variant is classified as a pathogenic variant with PVS1 (null variant), PM2 (absent from controls including gnomAD, ExAC, 1000G, and KRGDB), and PM3 (in *trans*), according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) [9]. The c.8363A>C p.(His2788Pro) is a variant of uncertain significance (VUS) with

PM2, PM3, and PP3 (multiple lines of *in silico* analysis support a deleterious effect, including SIFT, PolyPhen-2, MutationTaster, GERP++, and SiPhy) according to ACMG. Interestingly, the heterozygote germline variant of c.8363A>C p.(His2788Pro) was previously reported as a VUS in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/variation/482589/>) associated with hereditary cancer-predisposing syndrome. The novel nonsense variant and known missense variant are suggested to be disease-causing variants responsible for the phenotype observed in our patient. The clinical and genetic characteristics of Korean pediatric patients with genetically confirmed AT are summarized in Table 1.

3. Estimation of ataxia-telangiectasia prevalence in Republic of Korea

According to the public claims data from the Health Insurance Review and Assessment Service (<http://www.hira.or.kr/main.do>), the average prevalence of AT in 2010 to 2016 was estimated to be approximately 0.9 per million individuals. The estimated

Fig. 2. Genomic DNA sequence analysis of *ATM* in the patient and his parents. (A and B-1) The patient was identified as being compound heterozygous for variants in *ATM*: a paternally derived c.5288_5289insGA p.(Tyr1763*) nonsense variant and a maternally derived c.8363A>C p.(His2788Pro) missense variant. (B-2) Conservation analysis of the amino acid sequence; the missense variant site was highly conserved across vertebrate species.

Table 1. Clinical and genetic characteristics of Korean pediatric patients with genetically confirmed ataxia-telangiectasia

	Huh et al. (2013) [7]		Jeong et al. (2014) [8]	Present case
Age at test (yr)/sex	8/male	6/female	18/female	5/male
Age of onset (yr)	4	ND	3	1
Progressive gait and truncal ataxia	+	+	+	+
Progressively dysarthria	ND	ND	+	+
Oculomotor apraxia/nystagmus	+/-	+/-	+/-	-/-
Choreoathetosis	+	+	ND	+
Ocular telangiectasia	-	-	+	+
Cutaneous telangiectasia	-	-	-	-
Frequent infections	+	ND	-	-
Intellectual disability	-	-	-	mild
Serum level of alpha-fetoprotein	Elevated (119.68 IU/mL)	ND	Elevated (77.1 ng/mL)	Elevated (182.4 ng/mL)
Serum immunoglobulin	ND	ND	normal	normal
CD4 and CD8 T lymphocytes	ND	ND	normal	ND
Brain magnetic resonance imaging	Cerebellar atrophy	ND	Cerebellar atrophy	Cerebellar atrophy
Chromosome analysis	40,XY	ND	46,XX,t(7;14)(q32;q11.2) [6]/46,XX,t(7;14) (p15.1;q11.2) [2]/46,XX,inv(7)(p1?q3?) [2]/46,XX[30]	46,XY
Genomic/protein change	c.8546G>C p.(Arg2849Pro) c.2639-19_2639-7del13	c.8546G>C p.(Arg2849Pro) c.2639-19_2639-7del13	c.3154-2A>C p.(Ala1052Phefs*17) c.7090-2A>C p.(Ala2364*)	c.5288_5289insGA p.(Tyr1763*) c.8363A>C p.(His2788Pro)

ND, no data available; CD, cluster of differentiation.

prevalence was slightly higher in men than in women (1:1.14) in the Republic of Korea.

4. Ethics statement

Since this is a case report, approval from the institutional review board was not sought. However, written informed consent for the publication of medical photography and genetic test results was obtained from the patient's parents.

Discussion

The hereditary ataxias are characterized by slowly progressive gait ataxia and often associated with poor coordination of hands, speech, and eye movements [1,2]. Age of onset varies widely but is frequently in childhood in autosomal recessive ataxias, including AT [1,2]. However, diverse phenotypes made it difficult to diagnose our patient who showed progressive spasticity in both ankles, intellectual deficiency, and no history of infectious illness, leading to delayed diagnosis of AT [2,6]. Although curative treatments for AT are lacking, early diagnosis can help prevent malignancies, manage immunodeficiency, and initiate family genetic counseling. Thus, early genetic testing is

useful for AT diagnosis. *ATM* is relatively large, containing 66 exons and spanning approximately 150 kb of genomic DNA. Compared to Sanger sequencing, using molecular genetic tests with next-generation sequencing, which includes multi-genes, is more cost-effective for analyzing large-sized genes with no hot spots and is an efficient tool for differential diagnosis. Although this study was performed using WES, targeted multigene panel testing with a high coverage depth could be more efficient for a clinician than WES.

The worldwide prevalence of AT is estimated to be 0.4 to 1 in 100,000, although this prevalence varies with the degree of consanguinity in a country [1,2]. The prevalence of AT in the Republic of Korea is suggested to be extremely low [7,8]. The precise incidence and genetics of AT in the Republic of Korea are unknown because of a lack of epidemiological surveys. We calculated the prevalence using public claims data, and found it to be similar to the average prevalence worldwide. Thus, pediatric patients presenting with ataxia of unknown etiology in the Republic of Korea should be considered for early genetic testing, including testing for *ATM*.

As mentioned, the heterozygous c.8363A>C p.(His2788Pro) variant was previously reported to be of uncertain significance

associated with hereditary cancer-predisposing syndrome. Our patient and his mother's families had no reported history of cancer disease. This heterozygous variant of c.8363A>C p.(His2788Pro) may increase the cancer risk and interact unpredictably with other genes or environmental factors. However, we suggested that the homozygous variant of the c.8363A>C p.(His2788Pro) or compound heterozygous variants such as in our study caused AT.

In summary, this study reports a Korean boy with two compound heterozygote variants: a c.5288_5289insGA p.(Tyr1763*) nonsense variant and a c.8363A>C p.(His2788Pro) missense variant. Its prevalence in the Republic of Korea was estimated to be similar to the average prevalence worldwide. Considering that the prevalence was not relatively low in the Republic of Korea, early multi-gene panel sequencing including *ATM* should be considered.

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