

Clinical, radiologic, and genetic features of Korean patients with Mucopolysaccharidosis IVA

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Purpose: Mucopolysaccharidosis IVA (MPS IVA; Morquio A syndrome) is rare lysosomal storage disorder caused by *N*-acetylgalactosamine-6-sulfatase (GALNS) deficiency. Only a few MPS IVA cases have been reported in the Korean literature; there is a paucity of research about clinical or radiologic findings for this disorder. Therefore, we studied clinical findings, radiological features, and genetic data of Korean MPS IVA patients for determining factors that may allow early diagnosis and that may thus improve the patients' quality of life.

Method: MPS IVA was confirmed via assay for enzymatic activity of leukocytes in 10 patients. The *GALNS* gene was analyzed. Patients' charts were retrospectively reviewed for obtaining clinical features and evaluated for radiological skeletal surveys, echocardiography, pulmonary function test, and ophthalmologic test results.

Result: Nine patients had severe clinical phenotype, and 1 had an intermediate phenotype, on the basis of clinical phenotype criteria. Radiologic findings indicated skeletal abnormalities in all patients, especially in the hips and extremities. Eight patients had an odontoid hypoplasia, and 1 showed mild atlantoaxial subluxation and cord myelopathy. Genetic analysis indicated 10 different *GALNS* mutations. Two mutations, c.451C>A and c.1000C>T, account for 37.5% (6/16) and 25% (4/16) of all mutations in this samples, respectively.

Conclusion: An understanding of the clinical and radiological features involved in MPS IVA may allow early diagnosis of MPS IVA. Adequate evaluations and therapy in the early stages may improve the quality of life of patients suffering from skeletal abnormalities and may reduce life-threatening effects of atlantoaxial subluxation.

Key words: Mucopolysaccharidosis IVA, *GALNS*, Atlantoaxial subluxation, Morquio A syndrome

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Introduction

Mucopolysaccharidosis IVA (MPS IVA; Morquio A syndrome)

is an autosomal recessive lysosomal storage disease caused by a deficiency in *N*-acetylgalactosamine-6-sulfatase (*GALNS*)^{1,2}. *GALNS* is one of several sulfatases required to degrade the glycosa-

minoglycan (GAG), keratan sulfate (KS) and chondroitin-6-sulfate (C6S). It is encoded by the *GALNS* gene³. In the absence of this enzyme, the stepwise degradation of KS and C6S is blocked, resulting in the intracellular accumulation of the respective GAG in the lysosomes of a wide range of tissue⁴. It manifests mainly as short stature and skeletal dysplasia⁵ with bone deformity being the most common initial symptom⁶. Additional compromised systems include the visual, auditory, digestive, cardiovascular, and respiratory system⁷.

MPS IVA is a rare disorder, and the incidence of MPS IVA varies among different populations; reported rates range from 1 in 76,000 live births in Northern Ireland⁸ to 1 in 640,000 live births in western Australia⁹. In Japan, the incidence was 1 per 625,000 live births for five years⁴.

Like other lysosomal storage disorders, phenotypes of MPS IVA patients vary from the classical form with severe bone dysplasia, short trunk dwarfism, hearing loss, heart valve involvement, corneal opacity, and a life span of 20 to 30 years, to the mild form with fewer manifestations^{3,7}. A broad spectrum of clinical severity in MPS IVA suggests allelic heterogeneity^{10,11}. The *GALNS* cDNA is 2,339 bp in length with a 1,566 bp open-reading frame encoding 522 amino acids¹², and the *GALNS* gene is split into 14 exons spanning approximately 50 kb¹³. To date, about 150 different mutations have been identified (Human Gene Mutation Database, www.hgmd.org).

Currently, no effective therapies exist for MPS IVA patients with severe bone dysplasia. Supportive care is used to treat the clinical manifestations of this disorder. Hematopoietic stem cell transplantation has been attempted in some patients, and enzyme replacement therapy for MPS IVA with recombinant human *GALNS* is now under way.

There have only been a few MPS IVA case reports conducted in Korean¹⁴, and there is a need for more research on clinical and genetic findings. In particular, the radiologic findings of Korean MPS IVA have rarely been studied even though the predominant clinical features of MPS IVA are skeletal problems. The purpose of this study was to better understand the characteristics of Korean patients with MPS IVA by studying the clinical, laboratory and particularly radiological findings of 10 patients diagnosed with MPS IVA at the Samsung Medical Center.

Materials and methods

Ten patients with MPS IVA were diagnosed between July 2004 and December 2010 at the Samsung Medical Center. Patients' charts were retrospectively reviewed for clinical features and previous medical history. Findings on physical examinations were

obtained from the physicians' notes on admission or the outpatient department. Patients' radiological skeletal surveys, including skull (anteroposterior [AP] and lateral), chest (AP), spine (AP and lateral), pelvis (AP), tubular bones (AP), and hands and feet (AP), were evaluated. All radiologic findings were reading from one radiologist. Echocardiography, pulmonary function tests, and speech audiometry were also performed. For screening of corneal abnormalities, slit lamp examinations were performed by ophthalmologists.

Based on previous research^{15,16}, we classified our patients into three phenotypes by clinical manifestations determined from the physical examination, radiology, and clinical course. The criteria for each clinical phenotype is shown in Table 1.

1. Biochemical analysis

We measured urinary GAG levels using the cerylpyridinium chloride (CPC) precipitation test. To confirm MPS IVA, we performed thin layer chromatography in urine and determined the N-acetylgalactosamine-6-sulphatase activity in either peripheral blood leukocytes or skin fibroblasts. N-acetylgalactosamine-6-sulphatase activity was measured using the fluorophotometry method with artificial 4MU-beta-D-Galactopyranoside-6-sulphate substrate.

2. Mutation analysis of the *GALNS* gene

Genomic DNA was isolated from peripheral blood leukocytes. The 14 exons of the *GALNS* gene, along with their flanking intronic regions, were amplified by polymerase chain reaction (PCR). Five

Table 1. Criteria for Clinical Phenotypes of Patients with Mucopolysaccharidosis IVA^{15,16}

	Clinical course and radiologic findings
Severe	Growth retardation (adult height <125 cm) Early symptoms (before 3.5 years of age) of (one or more) Genu valgum Kyphosis Waddling gait with a tendency to fall Radiographs of typical skeletal changes include of (one or more) Odontoid Hypoplasia with atlantoaxial instability Deformities of the metacarpals Ovoid deformities of vertebrae
Intermediate	Fall between those seen in the severe and the mild phenotype
Mild (attenuated)	Grow normally until age 5 (adult height >150 cm) Mild skeletal anomalies do not have Short neck Genu valgum Radiographs of the hands and the odontoid process show almost no abnormal findings

microliters of the amplification product were treated with 10 U shrimp alkaline phosphatase and 2 U exonuclease I (USB Co., Cleveland, OH, USA). Direct sequencing of the DNA was performed using the ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) with the BigDye Terminator Cycle Sequencing-Ready Reaction Kit (Applied Biosystems). The cDNA nucleotide sequences of the *GALNS* gene examined were numbered according to their respective GenBank accession numbers of NM_000512.4 for *GALNS*. Our mutation nomenclature follows the recommendations of the Human Genome Variation Society (<http://www.hgvs.org/mutnomen/>), with nucleotide +1 corresponding to the A of the ATG translation initiation codon. All novel mutations were confirmed via sequencing of 100 control chromosomes. To avoid misinterpretation of the reading frames, we used both forward and reverse sequencing. We also investigated the mutational status of the patients' family members by PCR and sequencing.

Results

1. Clinical findings

Ten patients (eight males, two females) from eight families were involved in the study. The clinical findings are shown in Table 2. The median age at onset of disease-related initial symptoms was one year and seven months (ranging from nine months to three years and

three months) and median age at diagnosis was five years and seven months (ranging from one year and nine months to nine years).

All patients had uneventful birth histories and appeared normal at birth. The common disease-related initial symptoms were bony deformities (knee, spine, and ribs), short stature, and gait disturbance. At the time of clinical diagnosis, nine patients had genu valgum, and four patients (P2, P4, P6, and P10) had undergone a hemiepiphyodesis operation. All patients had hip joint dysplasia when diagnosed and two patients (P1 and P4) had undergone hip capsulotomy and capsular placcation operations. The consequence of these skeletal changes in most patients was restricted mobility of the large joints (especially the hips, knees, and elbows). Four patients (P1, P3, P8, and P9) were unable to walk, and five patients (P2, P4, P5, P6, and P7) had a waddling gait and a tendency to fall. But, No one had undergone a cervical spine operation.

All patients had growth retardation. At their current age, the heights of eight patients ranged from -12 to -3.4 standard deviation (SD) when compared to the height of age and gender-matched healthy children¹⁷⁾. Compared with the Morquio growth chart, the heights of our patients ranged from -1.1 to 1 SD¹⁸⁾. Two patients (P8 and P9) were unable to check their height because they could not stand. Two patients (P1 and P8) had previously undergone a ventilation tube insertion operation because of recurrent otitis media. Patient 3 received at-home ventilation care due to restrictive lung disease. Based on our

Table 2. Clinical Findings of Korean Patients with Mucopolysaccharidosis IVA

	P1	P2	P3	Family 1		P6	P7	Family 2		P10
				P4	P5			P8	P9	
Age at diagnosis (yr)	9.0	5.1	3.0	5.1	1.8	8.1	2.8	7.8	6.2	7.6
Age at onset of Sx (yr)	3.3	0.9	1.7	0.8	1.8	3.0	2.0	NA	NA	1.4
Current age (yr)	18	12.5	21	9.1	5.1	12.4	5.7	17.8	16.2	8.5
Sex	F	F	F	F	F	F	F	M	F	M
Height (cm)	142	115.7	97	98.6	92.8	99.2	87	NA	NA	90.3
Normal growth, SD	-3.8	-4.9	-12	-5.2	-3.4	-7.2	-5.7			-6.0
Morquio chart, SD	1.3	0.4	-0.7	-0.2	-0.1	-0.5	-1.3			-1.3
Weight (kg)	41.8	20.7	19.8	18.9	17	21.3	12.8	22.6	23.5	16.8
Normal growth, SD	-1.6	-2.6	-4.5	-1.8	-0.6	-2.5	-2.8	-4.3	-4.0	-2.6
Morquio chart, SD	0.4	-0.7	-1.1	-0.1	1	-0.6	-1.1	-1.1	0	-0.8
Growth retardation*	+	+	+ [†]	+	+	+	+	+ [†]	+ [†]	+
Protrusion of the chest	+ [†]	+	+	+	+ [†]	-	+	+	+	+
Knocked knee	-	+ [†]	+	+ [†]	+	+ [†]	+	+	+	+ [†]
Gait abnormality	+	+	+	+	+	+	+ [†]	+	+	-
Coarsening of facial feature	-	-	+	-	-	+	-	+	+	-
Corneal clouding	+	+	+	+	+	+	-	-	-	-
Respiratory problem	-	-	+	-	-	-	-	-	-	-
Recurrent AOM	+	-	+	-	-	-	+	-	-	+

P, patient; Sx, symptom; NA, not available; SD, standard deviation; AOM, acute otitis media.

*Height < 3th percentile normal population. [†]Disease related initial symptom of patient.

criteria, nine patients were classified as having the severe form and one patient was classified as having the intermediate form of the disease.

2. Radiologic findings

Skeletal abnormalities were present in all patients. The radiographic results are shown in Table 3. In the skull, no one had abnormal J-shaped sella turcica; seven patients had thickened diploic space. Roentgenographic findings of the chest included barrel chest deformities in eight patients and paddle-shaped ribs in eight patients.

The AP radiographic view of the spine showed thoraco-lumbar scoliosis in five patients; the lateral view demonstrated thoraco-lumbar kyphosis with irregular, platyspondyly and anterior beaking vertebrae in all patients (Fig. 1). In the cervical spine, eight patients had an odontoid hypoplasia and two patients had an atlantoaxial instability that increased the predentate space more than 5 mm in the neck flexion and extension views. Patients 8 and 9 were uncooperative and

did not complete the test. Six patients had spine magnetic resonance imaging (MRI) or computed tomography to gather further information and obtain an accurate evaluation of the cervical spine. All six showed spinal canal stenosis. Spinal stenosis was defined as a ratio of the spinal canal and vertebra that is below 0.8. One patient (P10) showed mild atlantoaxial subluxation and subtle signal changes in the spine MRI, which suggested cord myelopathy (Fig. 2).

Of note, almost all of the patients' radiologic findings indicated severe bony dysplasia of the limbs. In the hip joint, all patients showed inferior tapering of the iliac bones with flared iliac wings. Acetabular and femoral head dysplasia were also observed in all patients. Even worse, coxa valga was present in seven patients and hips subluxation was observed in nine patients (Fig. 3). In the knee joint, eight patients had genu valgum and four patients had patella dislocation. In the upper extremities, eight patients had a Madelung deformity and seven patients had mesomelic shortening. In the hands, seven patients

Table 3. Radiologic Findings of Korean Patients with Mucopolysaccharidosis IVA

		P1	P2	P3	Family 1		P6	P7	Family 2		P10
					P4	P5			P8	P9	
Skull	Thickening diploic space	-	+	+	+	+	-	+	+	+	-
Thorax	Canoe paddle shaped ribs	-	-	+	+	+	+	+	+	+	+
	Barrel chest	-	+	+	+	-	+	+	+	+	+
	Thick and short clavicle	-	-	+	+	-	+	-	-	+	-
Spine	Kyphosis	+	+	+	+	+	+	+	+	+	+
	Scoliosis	+	+	+	+	+	-	-	-	-	-
	Platyspondyly	+	+	+	+	+	+	+	+	+	+
	Ant. Beaking appearance	+	+	+	+	+	+	+	+	+	-
	Atlantoaxial subluxation	-	-	-	-	-	-	-	-	-	±
	Atlantoaxial instability*	-	-	-	+	+	-	-	NA	NA	-
	Odontoid hypoplasia	+	+	+	+	+	+	+	NA	NA	+
	Spinal canal stenosis [†]	+	+	+	+	NA	+	NA	NA	NA	+
	Spinal cord myelopathy	-	-	NA	-	NA	NA	NA	NA	NA	+ [‡]
Hip	Inf. tapering of iliac bones with flared iliac wings	+	+	+	+	+	+	+	+	+	+
	Acetabular dysplasia	+	+	+	+	+	+	+	+	+	+
	Dysplastic femoral heads	+	+	+	+	+	+	+	+	+	+
	Coxa valga	+	-	-	+	+	-	+	+	+	+
	Hips subluxation	+	-	+	+	+	+	+	+	+	+
Knee	Genu valgum	-	+	+	+	+	+	+	+	-	+
	Patella dislocation	-	-	+	-	-	-	+	+	+	-
Forearm	Madelung's deformity	-	+	+	+	+	+	+	+	+	NA
	Mesomelic shortening	-	+	+	+	-	NA	+	+	+	NA
Hand	Metacarpal bone short and thick	-	+	NA	+	+	+	+	+	+	NA
	Metacarpal bone proximally pointed	+	+	NA	+	+	+	+	+	-	NA
	Hypoplastic and irregular carpal bone	+	+	NA	+	+	+	+	+	+	NA
Osteopenia	+	+	+	+	+	+	+	+	+	+	+

P, patient; NA, not available.

*Increase in the predentate space of greater than 5 mm. [†]A ratio of the spinal canal and vertebra that is below 0.8. [‡]Subtle signal change of spinal cord.



Fig. 1. Lateral radiograph of the thoracolumbar spine of patient 4 shows platyspondyly, anterior beaking, and posterior scalloping of the vertebral bodies, as well as thoracolumbar kyphotic deformity.

had proximally pointed metacarpal bones that appeared short and thickened. Hypoplastic and irregular carpal bone changes were observed in eight patients (Fig. 4).

In addition, all patients had mild to severe osteopenia.

3. Extraskkeletal findings

Echocardiography was done in eight patients. One patient (P1) had normal echocardiogram findings, and the other patients showed mild abnormal findings like minimal mitral or tricuspid valve regurgitation or thickening of the aortic or the mitral valve. The size of the left ventricle of three patients (P4, P7, and P10) was enlarged. However, none had decreased left ventricular contractility. Pulmonary function tests were performed in five patients (P1, P2, P4, P6 and P10). All five had a normal range of forced vital capacity and forced expired volume in one second in spirometry test, and a normal flow volume curve. Because one patient (P3) was using an at-home ventilator, the test was not performed. Others could not exam due to noncooperation.

Ophthalmologic testing was performed on six patients by slit lamp examination. Five patients (P1, P2, P4, P5, and P6) had mild corneal opacity and one patient (P3) had severe opacity. Of the four patients who did not take this ophthalmologic test, corneal clouding was not

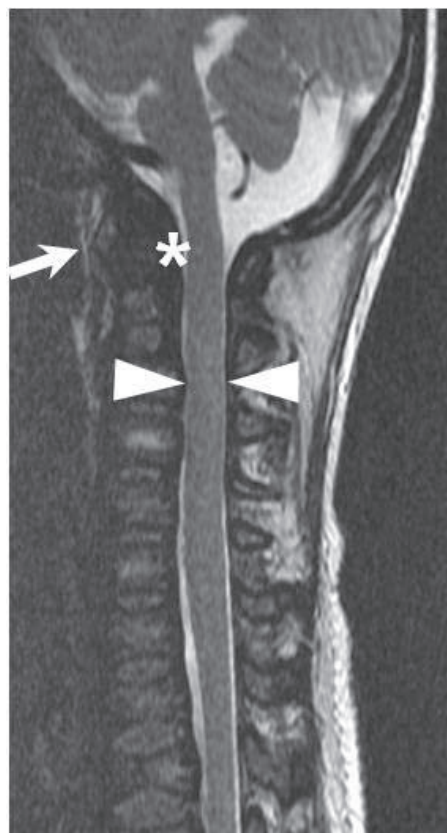


Fig. 2. Sagittal T2-weighted image of patient 10 shows mild atlantoaxial subluxation (arrow), a thickened soft tissue replacing the odontoid process (asterisk). Platyspondyly (arrowheads) and compromised cerebrovascular fluid space of the cervical spinal canal are also noted.



Fig. 3. Anteroposterior radiograph of the pelvis of patient 10 shows flared iliac wings, acetabular dysplasia, and inferior narrowing of the iliac bones. Dislocation of both hip joints with flattened femoral heads and coxa valga deformity are also observed.

observed in their general physical examinations. Four patients (P2, P6, and P10) received a speech audiometry test. One patient (P3) had a sensory neural hearing loss. Other patients couldn't test due to



Fig. 4. Anteroposterior radiograph of the left arm of patient 9 shows Madelung's deformity and severe bowing deformity of the radius, resulting in radiocapitellar dislocation. Mesomelic shortening of upper extremity is also observed. The image shows metacarpal bones and periarticular osteopenia.

noncooperation. No patients had significant cognitive problems.

4. Biochemical and genetic analysis

The biochemical and genetic data are shown in Table 4. The urine KS concentration was elevated in all MPS IVA patients ranging from 133.3 CPC unit/g creatinine to 585 CPC unit/g creatinine compared with normal control values. Normal ranges of GAG levels are <175 CPC unit/g creatinine (age, 1 to 9 years,) and <85 CPC unit/g creatinine (age, >9 years,) in random urine.

Nine patients showed severely reduced GALNS activity ranging from not detected to 8.27 pmol/min/mg protein in leukocytes (normal range, 39 to 166 pmol/min/mg protein), and the remaining patient exhibited 3.1 pmol/min/mg protein of enzyme activity in skin fibroblasts (normal range, 18 to 72 pmol/min/mg protein).

From the *GALNS* gene analysis, total of 16 mutant alleles from 8 families were identified, corresponding to 10 different mutations (Table 4); seven missense mutations of c.218A>G (6.3%, 1/16), c.415G>A (12.5%, 2/16), c.451C>A (37.5%, 6/16), c.725C>G (6.3%, 1/16), c.752G>A (6.3%, 1/16), c.1156C>T (6.3%, 1/16), c.1568A>G (12.5%, 2/16), one nonsense mutation of c.1000C>T (25%, 4/16), one deletion mutation of c.853_855delTTTC (6.3%, 1/16), and one splice site mutation of c.1243-1G>A (6.3%, 1/16). The c.725C>G and c.752G>A mutations were in exon 7, and the other mutations were scattered in different exons or introns. The c.451C>A and c.1000C>T account for 37.5% (6/16) and 25% (4/16) of the total number of mutant alleles in the Korean patients with MPS IVA, respectively.

One mutation of c.1568A>G (p.Y523W) in patient 6 was a novel homozygous mutation. But we didn't have approval of family study in this patient.

Table 4. Biochemical and Genetic Characteristics of Korean Patients with Mucopolysaccharidosis IVA

	Phenotype	GAG level* (CPC unit/g creatinine)	Leukocyte GALNS Activity† (pmol/min/mg protein)	<i>GALNS</i> mutation
P1	Intermediate	195.4	0.3	c.218A>G (p.Y73C), c.725C>G (p.S242C)
P2	Severe	585.2	3.1‡	c.752G>A (p.R251Q), c.451C>A (p.P151T)
P3	Severe	133.3	0.2	c.1243-1G>A (IVS11 1G>A), c.451C>A (p.P151T)
P4	Severe	192.7	<0.1	c.451C>A (p.P151T), c.1000C>T (p.Q334X)
P5	Severe	472.5	0.3	c.451C>A (p.P151T), c.1000C>T (p.Q334X)
P6	Severe	230.4	0.2	c.1000C>T (p.Q334X), c.1156C>T (p.R386C)
P7	Severe	420	0.78	c.1568A>G (p.Y523W) [§] , c.1568A>G (p.Y523W) [§]
P8 [¶]	Severe	NA	8.27	c.451C>A (p.P151T), c.415G>A (p.G139S)
P9 [¶]	Severe	NA	6.4	c.451C>A (p.P151T), c.415G>A (p.G139S)
P10	Severe	167.5	1.43	c.1000C>T (Q334X), c.853_855delTTTC (p.F285)

P, patient; GAG, glycosaminoglycan; CPC, cerylpyridinium chloride; NA, not available.

*Normal ranges of GAG level are <375 CPC unit/g creatinine (age, <1 year), <175 CPC unit/g creatinine (age, 1 to 9 years) and <85 CPC unit/g creatinine (age, >9 years) in random urine. †Normal ranges of GALNS activity are 39 to 166 pmol/min/mg protein in leukocytes and 18 to 72 pmol/min/mg protein in skin fibroblasts. ‡Skin fibroblast GALNS activity. §Novel mutation. ¶Family 1. ¶Family 2.

Discussion

In our study, nine patients were classified as having the severe phenotype and one patient was classified as intermediate. All patients had growth retardation and their height at current age ranged from -12 to -3.4 SD when compared to the height of age and gender-matched healthy children. And all patients showed severe skeletal dysplasia on radiologic findings, especially in their hips and limbs. Consequently, some patients had flexion deformities of the arms, were unable to walk, and underwent knee or hip joint operations. However, MPS IVA patients are usually not evaluated for unusual skeletal features until their second or third year of life. Thus, the average diagnostic age differs significantly from the age of onset⁶.

Compared with other patients who have MPS, patients with MPS IVA tend to have greater spine involvement with scoliosis, kiphosis, and severe gibbus¹⁹. Odontoid hypoplasia is the most critical skeletal feature in any patient with Morquio syndrome. In fact, both mortality and morbidity are related primarily to atlantoaxial subluxation resulting from the instability of the odontoid process¹⁹. Therefore, several studies have suggested that patients who have an increased risk of developing symptoms of spinal cord compression require the application of a brace or an early prophylactic posterior cervical fusion^{20,21}. One MPS IVA patient, who was diagnosed at Samsung Medical Center but not included in this study, expired due to atlantoaxial subluxation, which occurred while she was washing her hair. All patients included in our study, except two patients who were unable to be fully examined, had odontoid hypoplasia, and two patients had atlantoaxial instability. In addition, one patient showed mild atlantoaxial subluxation and cord compression in a spine MRI, but he had no neurologic symptoms like cord paralysis or sphincter dysfunction. In our study, the cervical instability and subluxation were less common than previous study⁴ reported that 90% of the MPS IVA patients had cervical instability and cervical spine operations were the most frequent surgical procedure in MPS IVA patients.

The genetic analysis, 10 different *GALNS* mutations were identified. The p.R386C mutation was the most common mutation worldwide, and it has been found in 34 alleles from 25 patients of American (Caucasian), Argentine, Brazilian, British, Chilean, Colombian, German, Italian, Japanese, Mexican, Polish, and Turkish origin²². In our study, the p.R386C mutation accounted for only 6.3% (1/16) of all mutations. However, p.P151T and p.Q334X mutations accounted for 37.5% (6/16) and 25% (4/16) of all mutations in this sample, respectively. These two mutations have been found in Korean patients (Pack et al., unpublished data).

A limitation of this study was the small number of patients involved, which can be explained by the fact that MPS IVA is an extremely rare disease and accounts for about 4 percent of all Korean patients with

MPS²³. Additionally, we were unable to determine the correlation between phenotype and biochemical data because nine patients had a severe phenotype, only one patient was intermittent, and no patients showed a mild phenotype.

As shown above, the Korean patients with MPS IVA had severe skeletal problems and almost all had a severe phenotype by the time they were diagnosed. This means that those patients with mild symptoms or deformities did not suspect MPS, thus did not take the MPS screening test. With a more accurate understanding of clinical and radiological features of MPS IVA, however, we can identify the symptoms earlier. This will lead to more patients being diagnosed earlier, so proper therapy can be provided and irreversible damage can be prevented. Furthermore, as with other types of MPS, research on enzyme replacement therapy in MPS IVA is currently in progress^{24,25}.

Patients with MPS IVA can be distinguished from patients with other MPSs because their intelligence is preserved, but they have severe skeletal abnormalities²⁴. Therefore, adequate evaluations and therapy in the early stages of the disease can greatly improve the quality of life of patients suffering from skeletal abnormalities. Moreover, such early detection and intervention can reduce the mortality rate of those with atlantoaxial subluxation.

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