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Novel variants of *IDS* gene, c.1224_1225insC, and recombinant variant of *IDS* gene, c.418+495_1006+1304del, in Two Families with Mucopolysaccharidosis type II

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In this report, the phenotypes of three patients from two families with mucopolysaccharidosis type II (MPS II) are compared: a novel variant and recombinant variant of *IDS* gene. The results of urine in patients showed a pronounced increase in glycosaminoglycan excretion with decreased iduronate-2-sulfatase enzyme activity in leukocyte, leading to a diagnosis of MPS II. A patient has a novel variant with 1 bp small insertion, c.1224_1225insC in exon 9, which caused frameshifts with a premature stop codon, and two patients have a recombination variant, c.418+495_1006+1304del, leading to the loss of exons 4, 5, 6, and 7 in genomic DNA, which is relatively common in Korean patients. They had different phenotypes even in the same mutation. The patients have now been enzyme replacement therapy with a significant decrease in glycosaminoglycan excretion. Further study on residual enzyme activity, as well as experience with more cases, may shed light on the relationship between phenotypes in MPS II and gene mutations.

Key words: Mucopolysaccharidosis type II, Iduronate-2-sulfatase, Enzyme replacement therapy

CASE REPORT

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INTRODUCTION

Mucopolysaccharidosis type II (MPS II) is a rare inborn error of metabolism that affects every organ of the body [1]. It is caused by a deficiency of the lysosomal enzyme, iduronate-2-sulfatase (IDS), which catalyses the degradations of the glycosaminoglycan (GAG) dermatan sulfate and heparan sulfate [1, 2]. As a result, lysosomal accumulation of upstream metabolites affects a variety of organ systems, including the visceral organs, connective tissue, skeleton, and the central nervous system [3, 4]. The incidence of MPS II is 1 per 162,000 births [5]. Its common phenotypes are: coarse facial features, upper airway obstruction, cardiac valve regurgitation, restrictive lung disease, hepatosplenomegaly, hernias, joint contractures, and reduced quality of life [6]. Variation of mutations in *IDS* gene results in differences in clinical symptoms among patients [7]. In this study, two families with MPS II which have variants of small insertion or recombination mutation in *IDS* gene were reported: c.1224_1225insC or c.418+495_1006+1304del.

PATIENTS REPORT

Patient 1 presented with stunted growth at 9 years of age. The boy was born at 40 weeks of gestation, with a birth weight of 3,700 g. He is the second child of healthy, non-consanguineous Korean parents. His neonatal period was unremark-

able. He had episodes of recurrent acute otitis media after 3 years. At 4 years of age he underwent adenoid-tonsillectomy. His height was between the 10th and 25th percentiles. Coarse facial features, including macrocephaly were noted. He had hepatosplenomegaly and dysostosis multiplex. In addition, he had high tone sensorineural hearing loss, reduced pulmonary function, and carpal tunnel syndrome. He showed high intelligence (IQ score 140). He showed elevated urinary GAG level (220.06 mcg/ml; reference range (RR), <36 mcg/ml) and decreased IDS enzyme activity (1.03 nmol/4 hr/mg protein; RR, 18-57 nmol/4hr/mg protein) in leukocyte. He has now been on enzyme replacement therapy (ERT) for 24 months, resulting in improvement of urinary GAG, liver/spleen volume, 6-Min Walk Test, passive joint range of motion, and growth velocity.

Patient 2 complained of intellectual disability (second grade level) at 3 years of age. He had hepatosplenomegaly, dysostosis multiplex and Mongolian spots. His height was normal (75-90th percentile). He had undergone an umbilical hernia operation at two years of age, and had markedly elevated urinary GAG level (535.0 mcg/ml; RR, <36 mcg/ml) and reduced IDS enzyme activity (0.1 nmol/4hr/mg protein; RR, 18-57 nmol/4 hr/mg protein) in leukocyte. During the treatment with ERT in patient 2, his older brother (patient 3) was admitted to evaluate growth and development. He complained of intellectual disability (first grade level) at 3 years of age. Physical examination showed he had a profound short stature (<3th percentile), hepatosplenomegaly, and dysostosis multiplex. He underwent a meningomyelocele operation at age three years, and showed a highly elevated urinary GAG level (927.0 mcg/ml; RR, <36 mcg/ml) and reduced IDS enzyme activity (0.03 nmol/4 hr/mg protein; RR, 18-57 nmol/4 hr/mg protein). He showed severe cognitive impairment (IQ score 40) at the age of 5 year

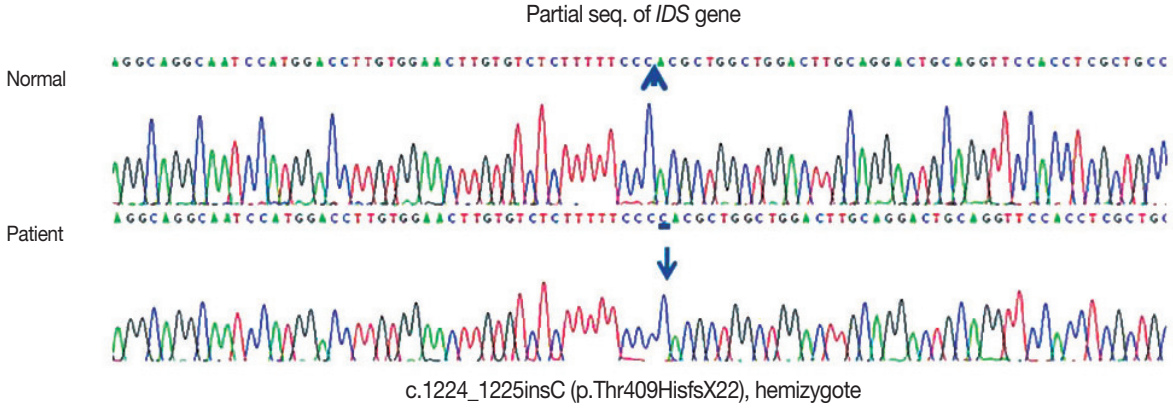

Fig. 1. Novel c.1224_1225insC (p.T409Hfs*22) mutation in exon 9 of *IDS* gene.

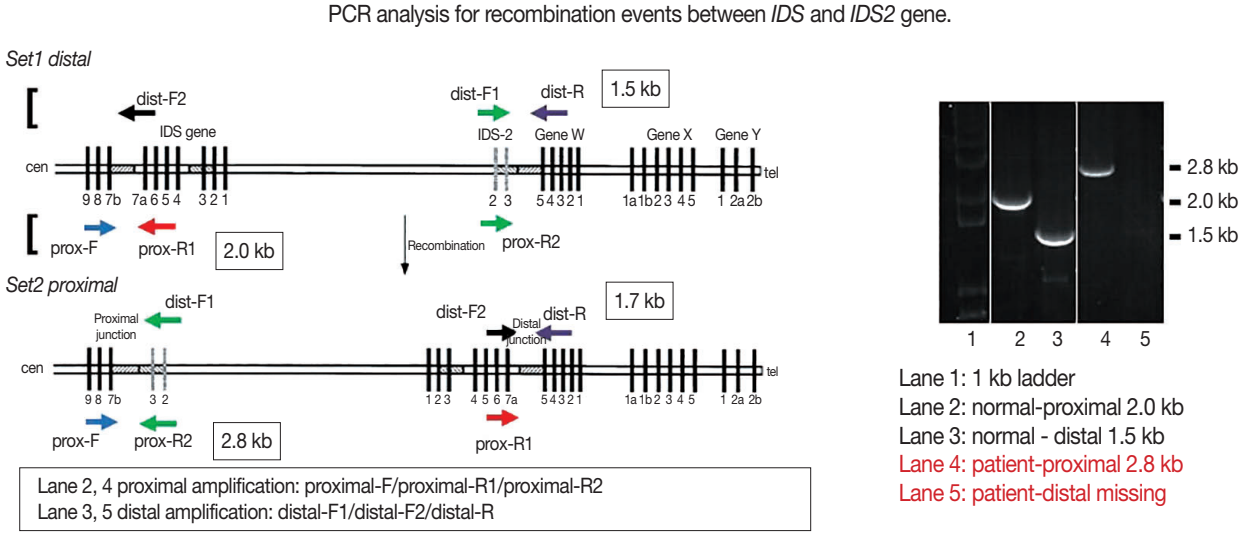

Fig. 2. PCR analysis for recombination events between IDS and *IDS2* gene.

old. The sibling patients have been on ERT for 24 months, resulting in improvement of urinary GAG, liver/spleen volume, passive joint range of motion, and growth velocity without experiencing further aggravation of neurological deficit.

IDS Genetic Analysis

Analysis of the *IDS* gene was performed for definitive analysis of the type of MPS in these patients. By direct sequencing, patient 1 revealed a variant with 1 bp insertion in exon 9 (NM_000202.4), c.1224_1225insC (p.T409Hfs*22), which caused frameshifts starting from codon 409 with a premature stop codon (Fig. 1). This hemizygous mutation was derived from his mother and has not been reported previously. His older brother showed symptom and had no mutation of *IDS* gene. According to 2015 ACMG guideline, this variant was regarded as pathogenic. The PCR-based recombination detection method of patient 2 and 3 was shown an *IDS-IDS2* recombination mutation, c.418+495_1006+1304del in intron 3 and 7, leading to the loss of exons 4, 5, 6, and 7 in genomic DNA (Fig. 2). Informed consent was obtained from patients and their family.

DISCUSSION

In these cases of MPS II, the T409Hfs*22 mutation in exon 9 was identified which has never previously been reported, and recombination mutation of *IDS* and *IDS2*, which is relatively common in Korean patients. The T409Hfs*22 mutation leads to the introduction of a premature termination codon and might cause subsequent non-sense mediated mRNA decay of mutant *IDS* mRNA. The patient 1 in present study presented with stunted growth. The laboratory results of urine and blood analysis suggested that this case was a metabolic disease of MPS II, and the patient was treated with ERT. Before the start of ERT, the urine GAG level was 220.06 mcg/ml, as compared with 66.3 mcg/mL after treatment. Two sibling patients (patient 2 and patient 3) also showed significant decrement in urine GAG level (535.0 mcg/mL vs. 136.3 mcg/mL and 927.0 mcg/mL vs. 114.2 mcg/mL, respectively) after ERT. Of interest, sibling patients with the same mutation had different clinical manifestation. Patient 3 had a profound short stature and underwent a meningomyelocele surgery. However, patient 2 had a normal stature and MRI scan of the brain was normal. This result suggested the clinical heterogeneity of MPS II even in the same genotype. Although the phenotype of MPS II depends on the mutation types at the *IDS* gene [8, 9] as well as residual enzyme activity, no strict relationship between genotype and clinical phenotype has been established [10]. In MPS II patients, more than 400 different genotypic variations have been documented in the *IDS* gene, which is approximately 24 kb with 9 exons [7]. The patients with the *IDS-IDS2* recombination mutation in the present study had severe MPS II phenotypes, which were most frequently observed in Korean patients [11]. The recombination mutation identified in our patients involves homologous recombination between intron 3, 7 of the *IDS* gene and the homologous region of its closely related pseudogene (*IDS2*), and leads to the loss of exons 4, 5, 6, and 7 in genomic DNA. The deletion spanned a region of 13,807 bp that comprised the half of the region of *IDS* gene. Ultimately, *IDS-IDS2* recombination was identified by a PCR-based recombination deletion method, resulting in a definitive diagnosis of MPS II. The limitations of this study is that functional study about a novel variant detected was not conducted.

Taken together, urine glycosaminoglycan and enzyme activity study of specific lysosomal storage disease can help diagnosis. A high index of suspicion is the most important factor for diagnosing lysosomal storage disease, and if the symptoms suggest a specific diagnosis, a genetic test is helpful to take genetic counseling for families at risk and prenatal diagnosis. Further experience with more cases may shed light on the relationship between gene mutations and phenotypes in MPS II.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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