Case Report
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The Effect of Combined Growth Hormone and a Gonadotropin-Releasing Hormone Agonist Therapy on Height in Korean 3-M Syndrome Siblings

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3-M syndrome is a rare autosomal recessive growth disorder characterized by severe growth retardation, low birth weight, characteristic facial features, and skeletal anomalies, for which three causative genes (*CUL7*, *OBSL1*, and *CCDC8*) have been identified. We herein report two Korean siblings with 3-M syndrome caused by two novel *OBSL1* mutations, and describe the effect of a combined treatment with growth hormone (GH) and a gonadotropin-releasing hormone (GnRH) agonist. A 7-year-old girl with short stature (-3.37 standard deviation score, SDS) and breast budding presented with subtle dysmorphic features, including macrocephaly, frontal bossing, a triangular face, prominent philtrum, full lips, a short neck, and fifth-finger clinodactyly. GnRH stimulation test revealed a pubertal pattern and advanced bone age of 8 years and 10 months. Her older sister, aged 10 years and 9 months, had experienced an early menarche, and had an advanced bone age (13.5 years) and predicted adult height of 142 cm (-4.04 SDS). Targeted exome sequencing identified that the siblings had two heteroallelic mutations in *OBSL1*. Both siblings underwent a combination therapy with GH and a GnRH agonist. A height gain was noted in both siblings even after short-term treatment. To fully elucidate the effects of the combined therapy, a larger cohort should be analyzed following a longer treatment period. However, such an analysis would be challenging due to the rarity of this disease.

Key Words: Short stature, precocious puberty, growth hormone, 3-M syndrome, *OBSL1*

INTRODUCTION

First described by Miller, McKusick, and Malvaux in 1975,[1] 3-M syndrome (MIM 273750, 612921, and 614205) is a rare autosomal recessive growth disorder characterized by severe growth retardation, low birth weight, characteristic facial features, and skeletal anomalies.[1-4] This syndrome is mainly caused by loss-of-function mutations in the genes encoding cullin 7 (*CUL7*), obscurin-like 1 (*OBSL1*), and coiled-coil domain containing 8 (*CCDC8*) proteins.[2,3,5] Any defect in these causative genes (*CUL7*, *OBSL1*, or *CCDC8*) leads to pre- and postnatal growth failure due to resistance to the growth hormone (GH) and insulin-like growth factor (IGF) axes.[1-3] However, the detailed mechanism underlying the growth impairment associated with 3-M syndrome remains to be elucidated.[1-4] We herein report two precociously pubertal Korean sisters with 3-M syndrome caused by two novel heteroallelic *OBSL1* mutations.

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CASE REPORT

A 7-year-old girl (Case 1) with short stature and early breast budding visited our clinic. She was born with a weight of 2.74 kg at 38 weeks of gestation (10–25th percentile, -1.45 standard deviation score, SDS). Her height at birth was 46 cm (-2.52 SDS). The heights of her father and mother were 167 cm (-1.1 SDS) and 143 cm (-3.8 SDS), respectively, and her mother had expe-

rienced her menarche at 11 years of age. The midparental height was estimated at 148.5 cm (-2.55 SDS). The girl had a height of 108.6 cm (-3.37 SDS), body weight of 21.5 kg (-0.38 SDS), head circumference of 50 cm (-0.37 SDS), and arm span of 109 cm. She did not have a goiter. She had Tanner-stage-II breasts, whereas her pubic hair was of Tanner stage I. She presented with macrocephaly, frontal bossing, a triangular face, prominent philtrum, full lips, a short neck, fifth-finger clinodactyly, and prominent heels (Fig. 1). Nevertheless, she had no developmental issues, except that her bone age (BA) was advanced to 8 years and 10 months (height for BA: -5.11 SDS). Skeletal survey revealed lumbar lordosis, brachydactyly, and a narrowed pelvic cavity (Fig. 2). Laboratory tests for chemistry and thyroid hormone showed normal levels. The serum IGF-1 and IGF-binding protein-3 (IGFBP-3) levels were 232.0 ng/mL (0.1 SDS) and 4670 ng/mL (3.5 SDS), respectively. GH provocation test showed normal peak GH levels (10.3 and 18.9 ng/mL), and gonadotropin-releasing hormone (GnRH) stimulation test revealed a pubertal pattern (luteinizing hormone peak: 10.7 IU/L). Her karyotype was also normal.

Her older sister (Case 2, 10 years and 9 months of age) visited our clinic with a concern of early menarche. She had experienced menarche when she was 9 years and 10 months old. She was born with a weight of 2.82 kg (50–75th percentile, -1.26 SDS) at 36 weeks of gestation. Her facial features resembled those of her younger sister, and the typical prominent heel form was observed (Fig. 1). Her height, weight, and head circumference at presentation were 137 cm (0.01 SDS), 44 kg (0.97 SDS), and 54.5 cm (2.58 SDS), respectively. Breasts and pubic hair were of Tanner stages IV and III, respectively. Her BA was advanced to 13 years and 6 months (height for BA: -3.03 SDS), and her predicted adult height was 142 cm (-4.04 SDS) as per the Greulich-Pyle criteria.

Targeted exome sequencing was performed to assess for genetic abnormalities. Genetic testing revealed two heteroallelic mutations (transheterozygosity) in *OBSL1* (NM_015311.2)—c.2135-3_2135-2del and c.3341G>A (p.Trp1114*) (Fig. 3A). It should be noted that this is the first time these two mutations have been identified in patients with 3-M syndrome. The population allele frequencies of c.2135-3_2135-2del and c.3341G>A

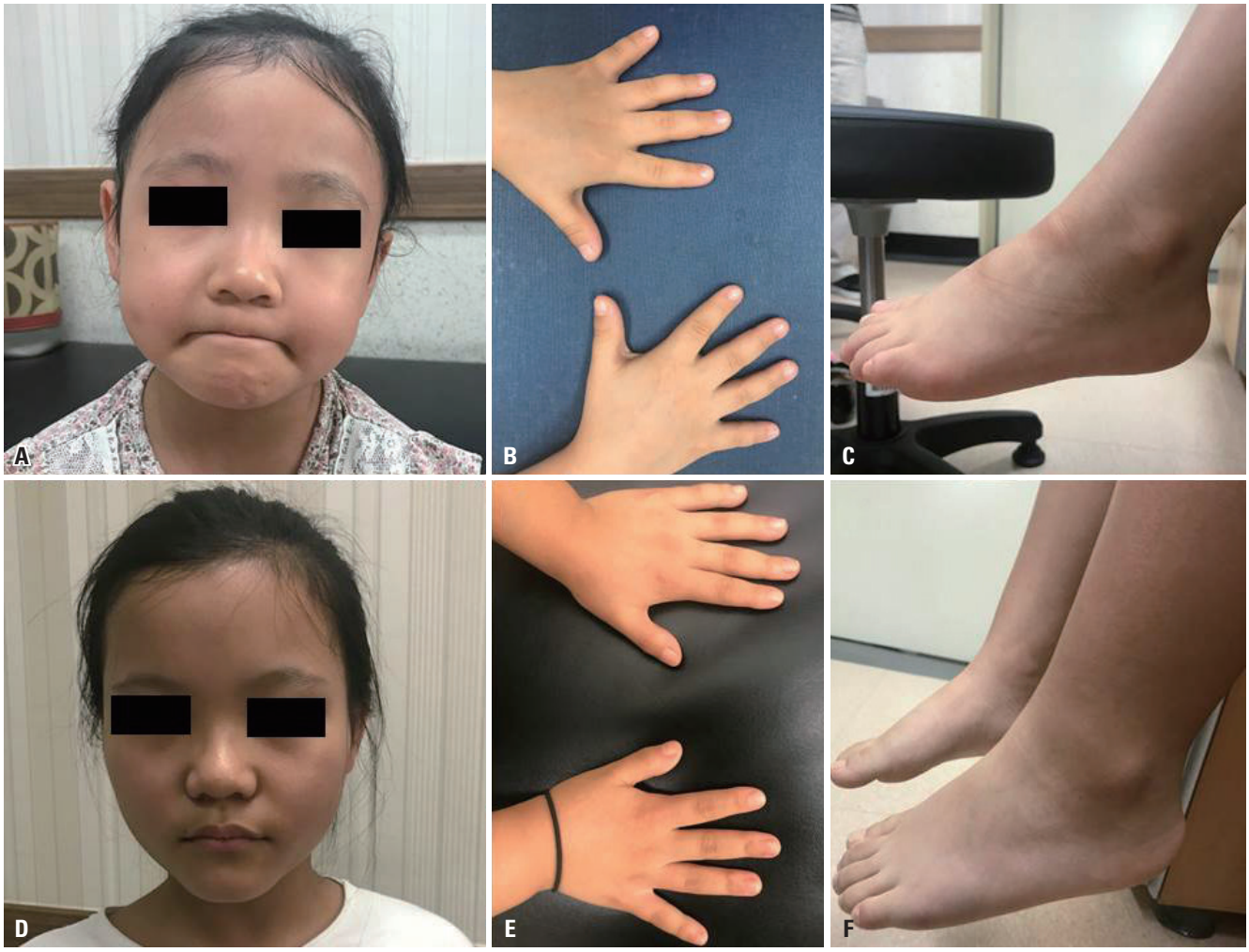

Fig. 1. Clinical photos of (A-C) Case 1 and (D-F) Case 2, showing typical features of 3-M syndrome. A and D: Photos showing frontal bossing, a triangular face, prominent philtrum, a fleshy nose, and full lips. B and E: Photos showing fifth-finger clinodactyly. C and F: Photos showing prominent heel.

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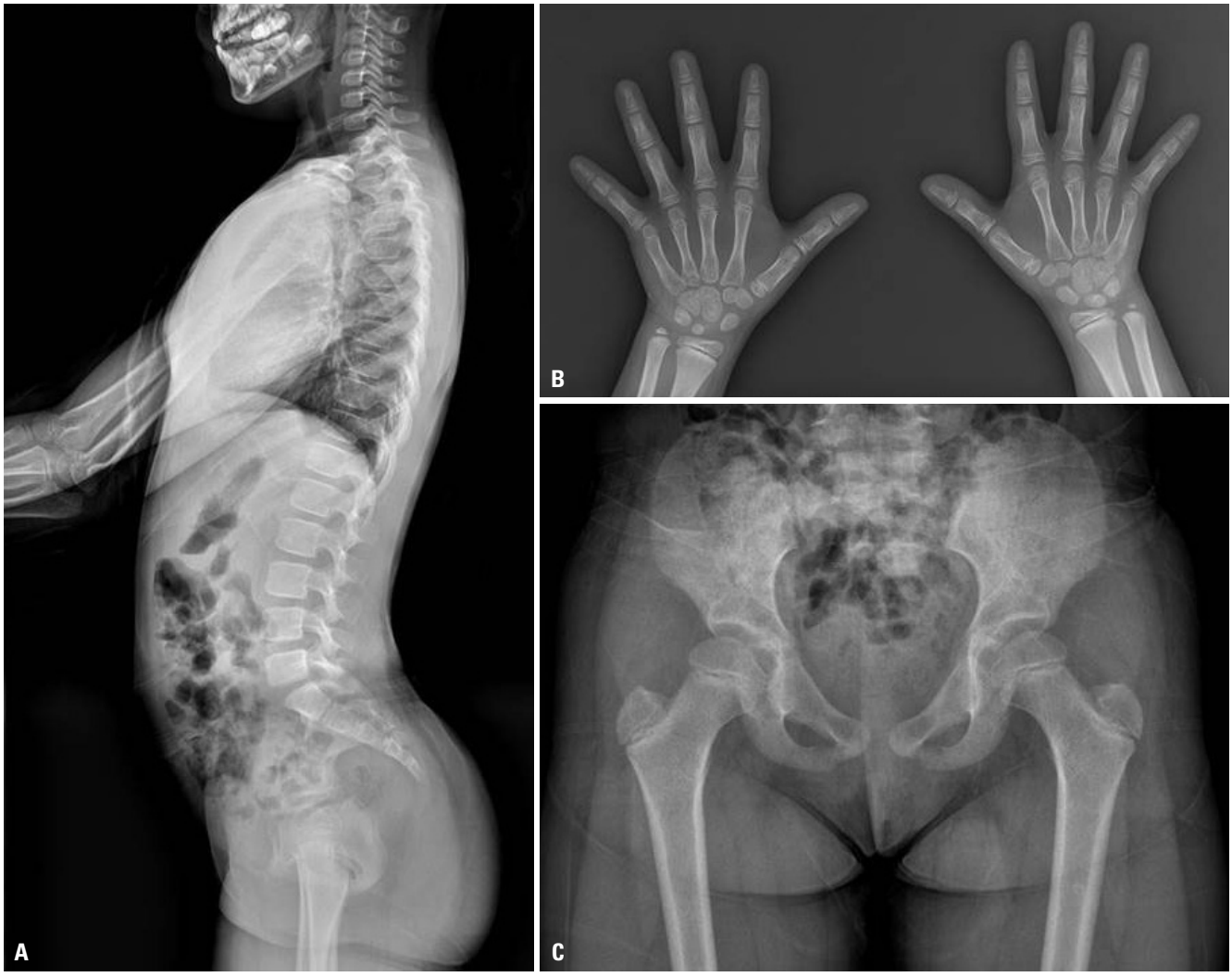


Fig. 2. Simple radiographs of Case 1 with 3-M syndrome showing (A) hyperlordosis, (B) advanced bone age and brachydactyly, and (C) narrowing pelvic cavity.

(p.Trp1114*) are reported as 0.0006 and 0.0001 in the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/), respectively.

The two sisters showed central precocious puberty, which occurred incidentally independent of 3-M syndrome. To date, no association between 3-M syndrome and precocious puberty has been reported. Despite the central precocious puberty, the sisters were treated with GH and a GnRH agonist for their pathological short stature and precocious puberty. Following 22 months of combination therapy with GH and GnRH (at 9 years and 8 months of age), the height gain of Case 1 was 12.6 cm (height: 121.2 cm, -2.3 SDS), and her BA was advanced to 10.5 years (height for BA: -2.91 SDS). Case 2, on the other hand, received 3 months of GH therapy alone, and then 6 months of the combination therapy with GH and GnRH agonist. Although the age of Case 2 was over the optimal age for GnRH-agonist therapy, we nevertheless subjected her to this therapy to delay the menarche and lengthen the GH treatment duration. After 9 months, her height gain was 4 cm (height: 141 cm), and her BA was advanced to 14 years (height for BA: -2.86 SDS). The doses of GH and GnRH agonist were 0.27 mg/kg/week and 11.75 mg/12 weeks, respectively.

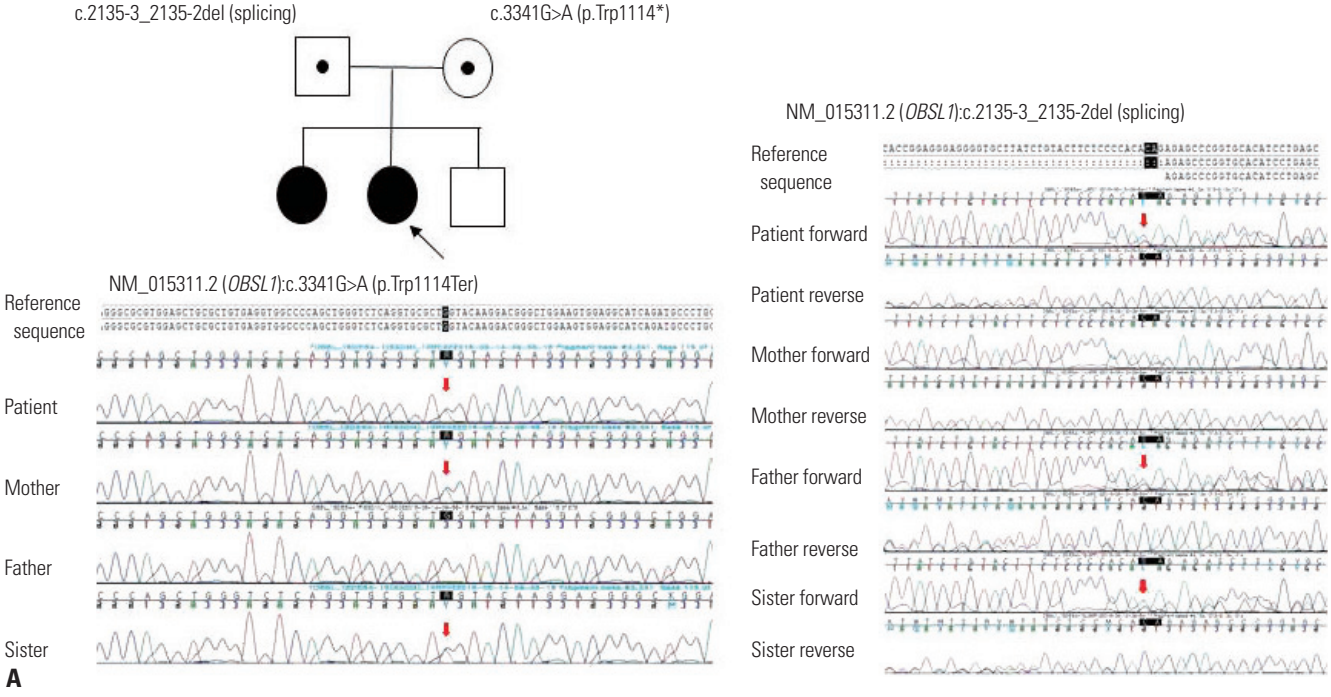
After the combination therapy, height SDS values for the BA of Case 1 and 2 improved from -5.11 and -3.03 to -2.91 and -2.86, respectively.

Informed consent was obtained from the patients regarding the reporting and publication of this case report. Since this was not a clinical trial and no off-label drugs were used, the ethical approval is not required for this case report.

DISCUSSION

We identified novel heteroallelic (compound heterozygous) mutations of *OBSL1* [NM_015311.2; c.2135-3_2135-2del and c.3341G>A (p.Trp1114*)] in two Korean sisters with short statures and precocious puberty. Among the three causative genes of 3-M syndrome, *CUL7* accounts for 77.5%, *OBSL1* for 16.3%,

and *CCDC8* for less than 5% of the cases.[5-8] To date, only 38 patients with 3-M syndrome and 24 *OBSL1* variants have been reported.[2,7-14] In total, seven missense, two splicing, and 15 small deletion/insertion mutations have been identified. These mutations reside within the first eight exons encoding the Ig domains of OBSL1 proteins (Fig. 3B). *OBSL1* is a homolog of the



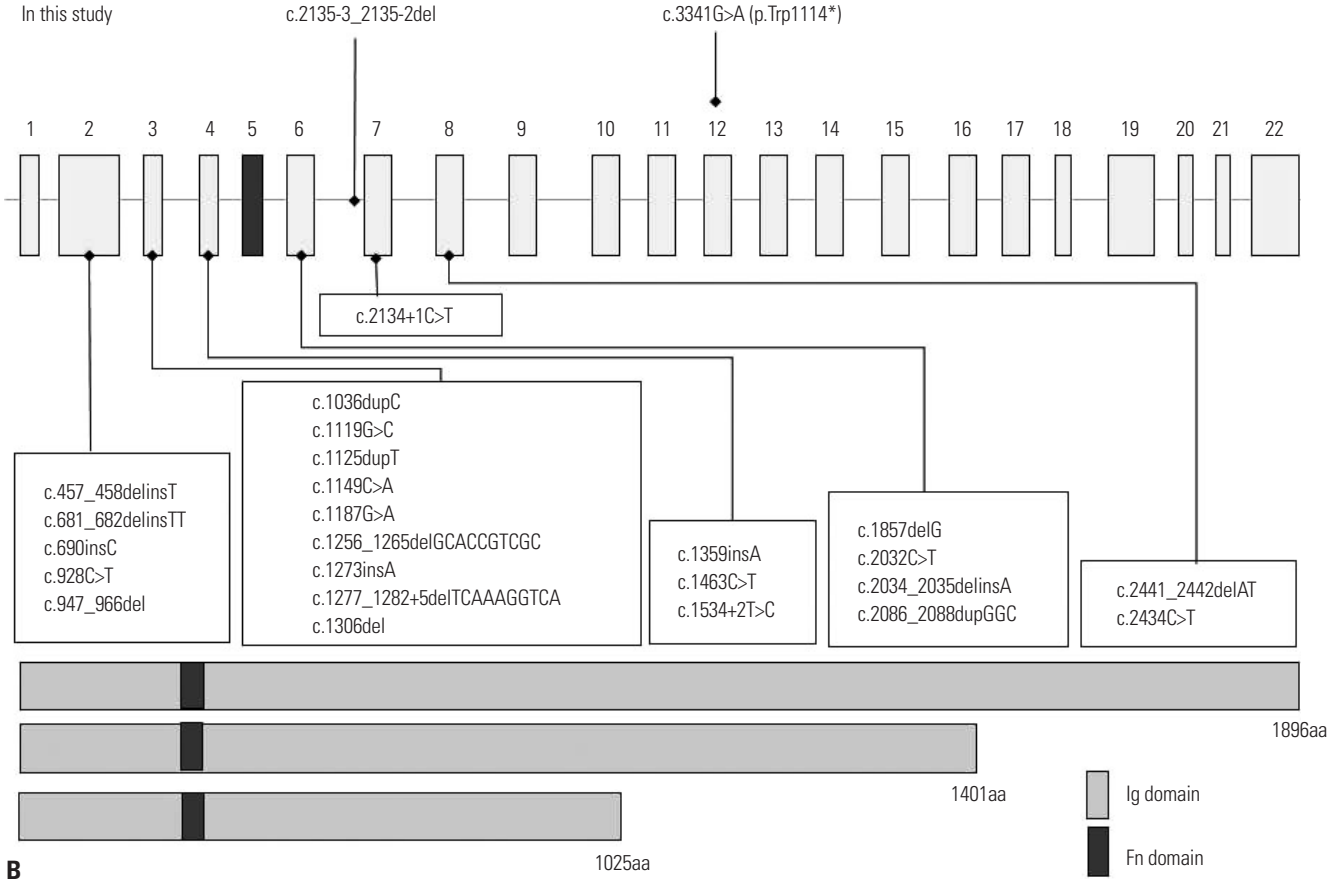


Fig. 3. Partial genomic DNA sequences of OBSL1 (NM_015311.2) both (A) in this study and (B) in previously reported mutations.

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muscle protein obscurin,[3] which contributes to growth retardation by modulating the expression of IGFBPs (IGFBP-2 and IGFBP-5) and downregulating CUL7.[2,3]

Patients with 3-M syndrome exhibit significantly different height SDS values depending on the mutation (-5.7, -4.7, and -4.1 for *CUL7*, *OBSL1*, and *CCDC8*, respectively).[2,4,11] However, the effects of GH treatment on the symptoms caused by these three different mutations are still unknown, and only a few cases have been reported. Keskin, et al.[11] have reported the case of a 16-month-old girl who was small for a gestational age girl [67 cm tall (-3.6 SDS)] and had a homozygous p.T45Nfs*40 (c.1273 dupA) mutation in the *OBSL1* gene. After 6 months of treatment with GH at a dose of 0.25 mg/kg/week, a growth increment of 7 cm was achieved.

In this study, we treated our patients with GH and a GnRH agonist, whereby a height gain and decreased rate of bone advancement were achieved. Further studies involving longer treatments and larger cohorts are needed to fully elucidate the effect of the combination therapy with a GnRH agonist and GH on 3-M syndrome.

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AUTHOR CONTRIBUTIONS

Conceptualization: Yoo-Mi Kim. Data curation: In Kyung Lee and Yoo-Mi Kim. Formal analysis: all authors. Funding acquisition: Yoo-Mi Kim. Investigation: In Kyung Lee and Yoo-Mi Kim. Methodology: In Kyung Lee and Yoo-Mi Kim. Project administration: Yoo-Mi Kim. Resources: Yoo-Mi Kim. Software: In Kyung Lee. Supervision: Yoo-Mi Kim. Validation: Yoo-Mi Kim. Visualization: In Kyung Lee and Yoo-Mi Kim. Writing—original draft: In Kyung Lee and Yoo-Mi Kim. Writing—review & editing: Yoo-Mi Kim and Han Hyuk Lim. Approval of final manuscript: all authors.

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