A case of Smith-Lemli-Opitz syndrome confirmed by molecular analysis: Review of mutation spectrum of the DHCR7 gene in Korea

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Introduction

Smith-Lemli-Opitz syndrome (SLOS) is a rare autosomal recessive disorder caused by 7-dehydrocholesterol reductase deficiency. The characteristic clinical features are syndactyly of the second and third toes, facial dysmorphism, multiple malformations, and intellectual disability. Few cases of SLOS have been reported in Korea. We observed a male patient with SLOS who presented with typical facial features, undescended testes, microcephaly, bilateral syndactyly of the second and third toes, and cardiac defects, including patent ductus arteriosus and atrial septal defect. Mutation analysis of the DHCR7 gene identified compound heterozygous mutations of c.907G>A (p.Gly303Arg) and c.1055G>A (p.Arg352Gln). In a review of the literature, c.1054C>T (p.Arg352Trp) was the most common mutation reported in Far East Asian countries. This report describes the clinical features, biochemical data, molecular characteristics, and clinical outcome of a Korean patient with SLOS.

Key words: Smith-Lemli-Opitz syndrome, 7-Dehydrocholesterol reductase, DHCR7.
confirmed by molecular analysis of the DHCR7 gene. Here, we describe the clinical features, biochemical data, and molecular characteristics of this case, with a review of the literature.

Case

The patient was born at 40 weeks of gestation, by cesarean section because of fetal distress and placental abruption. The patient weighed 2,700 g (−1.55 standard deviation score [SDS]) at birth and was the first child born to nonconsanguineous parents. As the triple marker test was abnormal at 16 weeks of gestation, amniocentesis was carried out, and the karyotype was 46,XY.

At birth, the patient displayed transient tachypnea and weak crying; this improved spontaneously after several days. Low-set and large ears, bilateral syndactyly of the second and third toes, a grade 2 systolic murmur at the left sternal border, developmental dysplasia of both hips, and ambiguous genitalia with hypospadias were noted. Patent ductus arteriosus (diameter, 1.5 mm) and a secundum atrial septal defect (ASD; diameter, 6 mm) were identified by echocardiography. Pelvic ultrasonography revealed the right testis in the peritoneum and left testis in the inguinal canal, without a uterus or ovaries. Auditory evoked potential measurements showed a sensorineural hearing defect in both ears (70 dB discrepancy in the right, 100 dB discrepancy in the left). At the age of 3 months, the patient was hospitalized because of pneumonia and pulmonary edema. Upon follow-up echocardiography, an almost common atrium, due to a large ASD (diameter, >8 mm), and a dilated right ventricle were observed. The patient was treated with intravenous antibiotics and diuretics.

The patient was referred to our institute for evaluation of multiple congenital anomalies at 1.6 years of age, when his height, weight, and head circumference were 77.6 cm (−1.81 SDS), 6.3 kg (−5.57 SDS), and 40.5 cm (−4.50 SDS), respectively. He manifested bilateral Y-shaped partial syndactyly of the second and third toes, micropenis, bilateral undescended testes, and facial dysmorphism such as bilateral epicanticular folds, large ears, and strabismus. The serum cholesterol level was 17 mg/dL (normal range, 45–182 mg/dL). Subsequently, he underwent ASD closure surgery using fresh autologous pericardium for a large ASD (diameter, 17.1 mm). Direct sequencing of the DHCR7 gene, using genomic DNA isolated from peripheral blood leukocytes, identified compound heterozygous mutations of c.907G>A (p.Gly303Arg) and c.1055G>A (p.Arg352Gln) (Fig. 1), which were already reported to be pathogenic [13]. Mutation analysis of the patient's parents was not carried out.

Discussion

This study described a case of SLOS, which was confirmed by molecular analysis of the DHCR7 gene. Two missense mutations in our case, p.Gly303Arg and p.Arg352Gln, were previously reported to be pathogenic in Japanese SLOS patients [13]. SLOS was first described in 1964 by David Smith, Luc Lemli, and John Opitz, as distinctive facial appearance, microcephaly, broad alveolar ridges, hypospadias, severe feeding disorder, and developmental delay [2]. Tint et al. [14] reported that SLOS patients had an increased plasma concentration of 7-DHC, suggesting a deficiency in the 7-DHC reductase the final step of the cholesterol biosynthesis pathway. In 1998, it was discovered that defects in the DHCR7 gene located on chromosome 11q13.4 cause SLOS [6].

The DHCR7 gene contains 9 exons and 8 introns within
### Table 1. Previously reported patients with Smith-Lemli-Opitz syndrome in Korea

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Facial dysmorphism</th>
<th>Syndactyly of the 2nd and 3rd toes</th>
<th>Genitourinary anomaly</th>
<th>Heart defect</th>
<th>Other findings</th>
<th>Cholesterol (mg/dL)</th>
<th>7-DHC (μg/mL)</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010 [7]</td>
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<td></td>
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<tr>
<td>Lee et al.,</td>
<td>Female</td>
<td>Hypertelorism, long cilia, low-set ears, short nasal root with anteverted nares, cleft palate, bifid uvula</td>
<td>Bilateral</td>
<td>-</td>
<td>-</td>
<td>Failure to thrive, feeding intolerance, irritability, sleep disorder</td>
<td>64</td>
<td>3,493</td>
<td>p.Gly303Arg and p.Arg352Trp</td>
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<td>2010 [8]</td>
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<tr>
<td>Park et al.,</td>
<td>Male</td>
<td>Flat supraorbital ridge, cleft lip and palate, micrognathia</td>
<td>-</td>
<td>Ambiguous genitalia, undescended testes</td>
<td>Tetralogy of Fallot with severe pulmonary atresia</td>
<td>Club foot, postaxial polydactyly of toes, cholestasis, cataract, feeding intolerance</td>
<td>12</td>
<td>-</td>
<td>p.Arg352Gln homozygote</td>
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<td>2008 [9]</td>
<td></td>
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<tr>
<td>Chae et al.,</td>
<td>Female</td>
<td>Cleft palate, ptosis, short nasal root</td>
<td>Bilateral</td>
<td>-</td>
<td>-</td>
<td>Failure to thrive, developmental delay, feeding intolerance, hypotonia</td>
<td>47-63</td>
<td>176</td>
<td>p.Lys376Argfs*37 and p.Arg352Trp</td>
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<td>2007 [10]</td>
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<tr>
<td>Ko, 2014</td>
<td>Female</td>
<td>Microcephaly, short nasal root with anteverted nares, bifid uvula</td>
<td>Bilateral</td>
<td>-</td>
<td>-</td>
<td>Failure to thrive</td>
<td>107</td>
<td>-</td>
<td>p.Arg352Trp homozygote</td>
</tr>
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<td>[11]</td>
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<tr>
<td>Ko, 2014</td>
<td>Male</td>
<td>Microcephaly, cleft palate, short nasal root with anteverted nares, micrognathia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Developmental delay, feeding intolerance, failure to thrive</td>
<td>119</td>
<td>-</td>
<td>p.Arg352Trp homozygote</td>
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<td>[11]</td>
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<tr>
<td>Jeong et al.,</td>
<td>Female</td>
<td>Microcephaly, ptosis, epicanthic folds, cleft palate, micrognathia</td>
<td>Bilateral</td>
<td>-</td>
<td>-</td>
<td>Feeding intolerance, ventriculomegaly</td>
<td>64</td>
<td>3,493</td>
<td>p.Gly303Arg and p.Arg352Trp</td>
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<tr>
<td>2014 [12]</td>
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</table>

注: 7-DHC, 7-dehydrocholesterol.
7-DHC is an important clue for the diagnosis of SLOS [3], and of SLOS patients [5]. Therefore, high serum concentration of serum cholesterol value can be normal in approximately 10% infants have hypocholesterolemia (<40 mg/dL). However, the is helpful for the diagnosis of SLOS, because most affected case reported here [3,18]. The serum concentration of cholesterol genital anomalies and congenital heart defects, including the of SLOS patients. Approximately 50-60% of SLOS patients had syndactyly, developmental delay, microcephaly, and postnatal mild clinical phenotype.

Both the c.907G>A (p.Gly303Arg) and c.1055G>A (p.Arg352Gln) mutations in our case are located in the TM region, indicating a mild clinical phenotype. Although it is difficult to establish a correlation between genotype and phenotype, some genotypes are known to cause a severe phenotype. Witsch-Baumgartner et al. [15] grouped mutations into 4 classes: nonsense and splice-site mutations resulting in putative null alleles, missense mutations in the transmembrane domain (TM), mutations in the fourth cytoplasmic loop (4L), and mutations in the carboxy-terminal endoplasmic reticulum domain (CT). They reported that patients with null and 4L mutations had severe clinical phenotypes, while patients with TM and CT mutations had mild clinical phenotypes. Both the c.907G>A (p.Gly303Arg) and c.1055G>A (p.Arg352Gln) mutations in our case are located in the TM region, indicating a mild clinical phenotype.

Common clinical findings in SLOS were second and third toe syndactyly, developmental delay, microcephaly, and postnatal growth retardation; each finding was observed in at least 80% of SLOS patients. Approximately 50–60% of SLOS patients had genital anomalies and congenital heart defects, including the case reported here [3,18]. The serum concentration of cholesterol is helpful for the diagnosis of SLOS, because most affected infants have hypocholesterolemia (<40 mg/dL). However, the serum cholesterol value can be normal in approximately 10% of SLOS patients [5]. Therefore, high serum concentration of 7-DHC is an important clue for the diagnosis of SLOS [3], and mutation analysis of the DHCR7 gene is helpful for confirmatory diagnosis.

Although therapeutic options for SLOS are limited, cholesterol supplementation might improve clinical symptoms such as irritability, hyperactivity, sleep disorders, and growth retardation. Supplementation of dietary cholesterol not only raises blood cholesterol to normal levels, but also often prevents the accumulation of 7-DHC via feedback inhibition. The estimated daily cholesterol requirement during infancy is 30–40 mg · kg⁻¹ · day⁻¹, which decreases to 10 mg · kg⁻¹ · day⁻¹ in adults; experimental treatment protocols included 30 mg · kg⁻¹ · day⁻¹ of egg yolk or 150–300 mg · kg⁻¹ · day⁻¹ of cholesterol suspension [3,19].

Low maternal concentration of unconjugated estriol could suggest the possibility of SLOS [18]. Fetal ultrasound findings of intrauterine growth retardation; major malformation of the brain, heart, kidneys, or limbs; and ambiguous genitalia may be helpful for prenatal diagnosis of SLOS. When SLOS is suspected, the elevated 7-DHC and/or decreased cholesterol level in the amniotic fluid is a helpful biomarker for diagnosis. In addition, molecular sequencing of the DHCR7 gene, using chorionic villus tissue or amniocytes, can be considered for prenatal diagnosis [1,5,20].

In conclusion, we have reported the case of a patient with SLOS who carried heterozygous mutations of c.907G>A (p.Gly303Arg) and c.1055G>A (p.Arg352Gln) in the DHCR7 gene, and described the mutation spectrum of DHCR7 in Korea via a review of available literature. As the clinical features and biochemical findings of SLOS are variable, molecular analysis of the DHCR7 gene is useful for confirmation of its diagnosis.

References

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