First Identified Korean Family with Sotos Syndrome Caused by a Novel Intragenic Mutation in NSD1

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Abstract. Sotos syndrome (SS) is a congenital overgrowth syndrome. NSD1 mutations are identifiable in most SS patients. There have been a few reports of familial inheritance of SS worldwide, but no familial cases have been reported in Korea. A 6-month-old girl had tall stature and macrocephaly with mild ventricular enlargement, and showed mild delay in motor and language development. Her mother also had tall stature and a long narrow face. The baby and her mother were suspected of having familial SS. Chromosome 5q35 microdeletion was first ruled out by fluorescence in situ hybridization analysis, and direct sequencing of NSD1 revealed a novel heterozygous mutation in exon 22 (c.6356delA; p.Asp2119Valfs*31). This report describes, for the first time, a Korean family with two generations of SS resulting from a novel intragenic NSD1 mutation.

Key words: NSD1, overgrowth, Sotos syndrome

Introduction

Sotos syndrome (SS, OMIM 117550) is an autosomal dominantly inherited congenital malformation syndrome characterized by four cardinal features: pre- and postnatal overgrowth, typical facial dysmorphism, macrocephaly, and variable degrees of mental retardation [1,2]. Additional clinical features include neonatal jaundice, congenital heart defects, brain anomalies, neonatal hypotonia, skeletal anomalies, and increased incidence of malignancy [1,3,4].

Since NSD1 was found as the causative gene, more than 90% of cases have been shown to involve this gene and more than 350 kinds of NSD1 mutations have been reported (HGMD, http://www.hgmd.org/) [5]. In the European population, more than 80% of people with SS have an intragenic mutation; this contrasts with microdeletions of chromosome 5q35 as the major cause of SS in Japan [6–8]. A recent report of SS in Korea also documented that 53% of patients had a 5q35 microdeletion, a result that is similar to that in Japan [9]. Most SS cases are sporadic, and there is a low recurrence rate in siblings. SS is associated with reduced reproductive fitness. Although there have been at least 16 cases of familial SS associated with an intragenic mutation in NSD1 worldwide [10], no familial SS case has been reported in Korea.

In this report, we describe the first identified Korean case of familial SS involving a mother and her daughter, who both have a novel intragenic mutation in NSD1.

Case Report

Patient 1 (daughter). A 6-month-old girl visited the pediatric clinic at St. Vincent Hospital for evaluation of delayed development. She was born at 40 weeks weighing 3.3 kg weight (50th percentile) and with a birth length of 53 cm (90–95th percentile). She was delivered by Cesarean section because of a breech presentation. She was the first baby for her parents. She had a history of breast milk jaundice in her neonatal period. She was diagnosed with right-sided sensorineural hearing loss at the age of 3 months and had been followed up. Her father’s height was 171.5 cm (25–50th percentile), and he had no specific history of illness. On her first visit, the baby’s body length was 74.8 cm (>97th percentile), weight was 11 kg (>97th percentile), and head...
circumference was 46 cm (>97th percentile). She had a round face with a broad forehead, pointed chin, and down-slanted eyes (Figure 1). She also showed a high arched palate and eight teeth. Abdominal organomegaly was absent, and other physical and laboratory findings were normal.

Conventional chromosomal analysis of peripheral blood leukocytes showed the normal female karyotype, 46,XX. Her bone age was about 9 months when she was 6 months of age. Brain imaging by computed tomography showed mild ventricular enlargement without other structural malformations. Cardiac and renal evaluations with ultrasonography and echocardiography found no renal or cardiac structural anomalies. Her developmental milestones were evaluated using Bayley Scales of Infant and Toddler Development at the age of 9 months, and the result showed a 2-month delay in receptive language and a 6-month delay in expressive language. Cognitive development was also slightly delayed by about 2 months for her age. Motor developmental status was about the level of a 7-month-old, and she could roll over in both directions and sit alone without support.

Patient 2 (mother). The patient’s mother was 32 years old. She was the third child of her parents, and all of her siblings are of normal height and intelligence. She was tall (174 cm in height, >97th percentile) and had big hands, macrocephaly (55 cm head circumference, >97th percentile) with a long face, broad forehead, down-slanted eyes, and a low-pitched voice (Figure 1). She denied any specific history of illness and did not have any problems in receptive language. However, she stuttered when she spoke and had difficulty with expressive language. Although we did not perform an intelligence test, she had graduated from a regular high school without any problems. She had been taller than her peers since early childhood, and her tall stature had been evaluated for a suspicion of acromegaly several years before. However, there was no hormonal abnormality including growth hormone.

Cytogenetic and molecular genetic analysis. The patient and her mother were suspected of having familial SS based on the medical history and findings of the physical examinations, and genetic analyses for SS were performed. Written consent was obtained from participants, and the Institutional Review Boards of Seoul National University hospital approved this study (H-1208-129-423). First, fluorescence in situ hybridization analysis was performed to identify a 5q35 microdeletion was conducted using an NSD1 probe in patient 1, and no deletion was revealed. Therefore, NSD1 sequencing analysis was performed using genomic DNA isolated from peripheral blood leukocytes. All coding exons and exon–intron boundaries of the NSD1 gene were amplified by polymerase chain reaction, and direct sequencing was performed. A novel deletion mutation in exon 22 of the NSD1 gene, c.6356delA (p.Asp2119Valfs*31), was detected in the daughter (patient 1). The mother (patient 2) was also found to carry the same mutant allele (Figure 2). Therefore, familial SS was confirmed in both the mother and the daughter.

Discussion

SS is a representative congenital overgrowth syndrome along with Beckwith–Wiedemann syndrome. The incidence of SS is estimated at 1 in 15,000 worldwide. Since haploinsufficiency of NSD1 on chromosome 5q35 was identified as a cause of SS in 2002 [11], NSD1 is the only causative gene identified to date. Although the exact role of the NSD1 protein has not been identified, it is suggested that NSD1 enables the regulation of both negative and positive transcription [12]. A study of the genetic basis of SS in Korea, which
analyzed the whole *NSD1* gene, was reported recently [9]. This study found that the 5q35 microdeletion was detected more frequently as the cause of SS compared with *NSD1* intragenic mutations. This finding is similar to data on SS in Japan [6,13].

In this study, we describe the first Korean SS family of a mother and her daughter with a novel intragenic mutation in *NSD1*. Although SS can be transmitted in an autosomal dominant manner, since the first familial case of SS was described in 1976 [13], 95% of cases have been shown to be caused by a de novo mutation, and there have been few cases of familial SS [15,16]. Because the disease recurrence rate in families with SS is low, it has been suggested that SS might be associated with reduced reproductive fitness [8]. However, reports of familial SS do not agree with this hypothesis. Familial inheritance of SS may be caused by a different type of mutation from that causing sporadic disease. Although no mutational hot spots and no correlation between the mutation position and clinical phenotype have been identified, some clinical differences between patients with the 5q35 microdeletion and intragenic mutations have been suggested. A chromosome 5q35 microdeletion might have a more detrimental effect on fertility than would an *NSD1* intragenic mutation [6]. All of the reported familial cases involve an intragenic mutation, and no instances of familial inheritance of a 5q35 microdeletion have been reported. Among the various types of intragenic mutations, people with familial SS are more likely to have a missense mutation than are those with sporadic SS [7]. SS with a 5q35 microdeletion also tends to have more severe clinical manifestations including cardiac and renal anomalies than does SS caused by an intragenic mutation [17]. More severe learning disability and less prominent overgrowth have been observed in patients with a microdeletion [15,18].

Although our patients had a heterozygous deletion of one base pair causing premature termination of the *NSD1* protein, the affected mother and daughter showed mild physical phenotypes without major organ anomalies. The location of the mutation identified in our study is on the 22nd exon of a total of 23 exons of *NSD1*, and the length of the mutant protein was 2149 of 2696 amino acids in the wild-type *NSD1* protein. Therefore, the mutant protein might have some residual function and may be associated with a milder phenotype, as shown in these patients. Although the mother’s intelligence was not assessed, she had difficulty only in expressive language. By contrast, the affected daughter had a more prominent delay in expressive language even...
at a very young age. This phenotype discrepancy between the affected mother and daughter with the same mutation can be explained by the variable expression of SS.

As in other congenital overgrowth syndromes, SS has an increased relative risk of tumor development during childhood regardless of the type of mutation. Malignant tumors including neuroblastoma, sacrococcygeal teratoma, and hematological malignancies have been reported in people with SS [7,17,19]. Therefore, a patient with SS should be evaluated regularly to provide surveillance of malignancy development.

Here, we report on the first identified Korean family with SS resulting from a novel NSD1 mutation who show mild clinical phenotypes. Although SS is a rare disease that mainly occurs sporadically, it can also be transmitted as an autosomal dominant condition, and other familial recurrences have been reported. Considering the concerns about tumor development and that early rehabilitation is helpful in providing a catch-up in development, an accurate diagnosis followed by appropriate management and genetic counseling should be provided to these patients.

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References