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Identification of a novel *de novo* nonsense mutation of the *NSD1* gene in monozygotic twins discordant for Sotos syndrome

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ABSTRACT

Introduction: Sotos syndrome is a congenital overgrowth disorder characterized by facial gestalt, excessively rapid growth, acromegalic features and a non-progressive cerebral disorder with intellectual disability.
Methodology: The identical male twins showed somewhat different clinical, cognitive and behavioural phenotypes. Abnormal clinical manifestations including seizures, scoliosis, enlarged ventricles, and attention-deficit/hyperactivity disorder (ADHD) were found in the proband (first twin), but not in the sibling (second twin). We used diagnostic exome sequencing (DES) to identify a heterozygous *de novo* mutation of the *NSD1* gene in monozygotic twins with Sotos syndrome.
Results: DES revealed a novel nonsense mutation c.2596G > T (*p.Glu866**) of the *NSD1* gene in the proband, the first of monozygotic twins. Sanger sequencing analysis of the proband and his family members showed that this nonsense mutation was present in the proband and his sibling, but was absent in their parents, indicating that it occurred with *de novo* origin.
Conclusion: This finding expands the phenotypic spectrum associated with variable expression of the Sotos syndrome caused by *NSD1* mutation, and it adds further support for postconceptual mutation, epigenetic change and/or an environmental factor involved in the cause of the Sotos syndrome.

1. Introduction

Sotos syndrome (MIM # 117550) was first reported in 1964, and its main clinical features, including distinctive craniofacial features, learning disabilities, and overgrowth resulting in a tall stature and macrocephaly, are evident from birth in > 90% of patients [1]. The typical facial characteristics are macrocephaly, prominence of the forehead, down-slanting palpebral fissures, high arched palate small chin, and sparse hairs. Clinically, three phenotypic features, including a distinctive facial appearance, learning disability, and overgrowth are considered as cardinal features of Sotos syndrome and are easily recognizable between one and six years of age. Sotos syndrome is diagnosed in a proband by identifying of a heterozygous *NSD1* pathogenic mutation during molecular genetic testing [2]. The majority of recurrent 1.9-Mb 5q35 microdeletion (up to 50%) encompassing *NSD1* with the same breakpoints and a specific chromatin structure have been reported in most Japanese and some non-Japanese individuals with Sotos syndrome, and there may be an increase in recurrent crossover events and predisposition to recombination hot spots at 5q35 [2–4]. > 250 pathogenic mutations have been described. However no mutational hot spots have been identified [5–8]. In a previous study of the clinical and genetic spectrum of 18 unrelated Korean patients with Sotos syndrome, eight patients (53%) had 5q35 microdeletions, and seven other patients (47%) had seven different *NSD1* intragenic mutations including four novel mutations [9].

Here, we report on a novel mutation of the *NSD1* gene in monozygotic male twins with phenotypic features of Sotos syndrome in South Korea. The different clinical, cognitive and behavioural phenotypes in our monozygotic twins with Sotos syndrome was an interesting finding.

2. Clinical presentation

2.1. The proband

The proband (Fig. 1A, individual II-2), a 5-year-old boy, was

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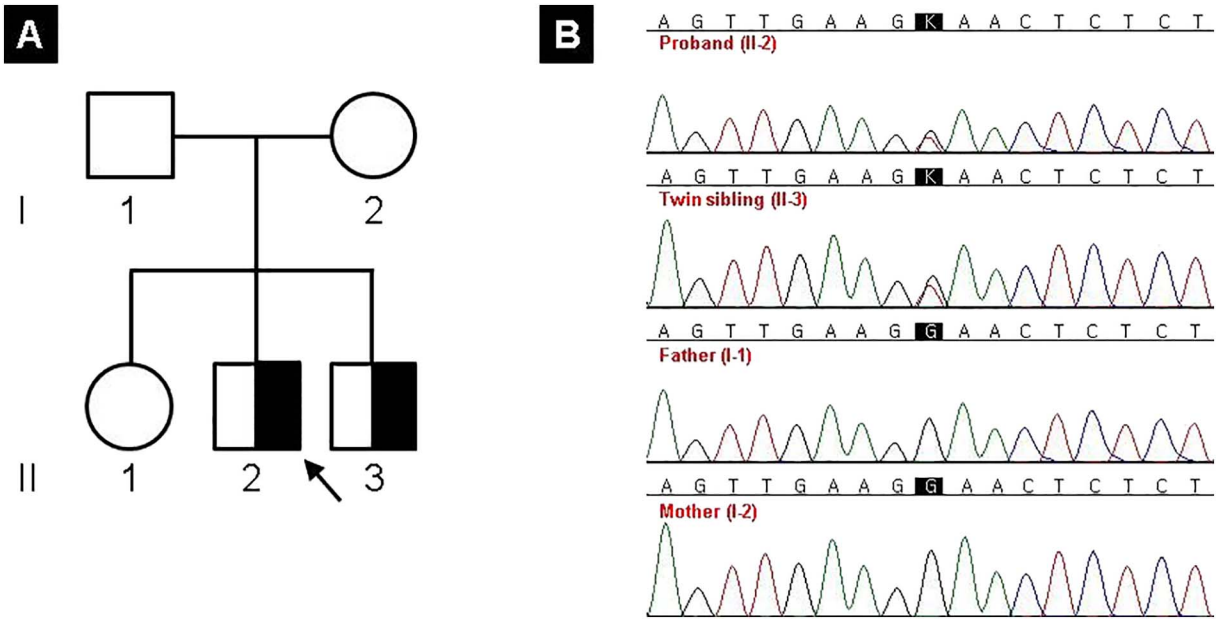

Fig. 1. (A) Pedigree analysis of monozygotic twins diagnosed with Sotos syndrome with a novel *de novo* nonsense mutation c.2596G > T (*p.Glu866**) of the *NSD1* gene. Proband (indicated by the arrow) and affected family member revealed the same mutation in the heterozygous state. (B) Heterozygous nonsense mutation of the *NSD1* gene in the proband and his sibling *via* Sanger sequencing. The monozygotic twins had a novel *de novo* mutation c.2596G > T (*p.Glu866**).

referred to our hospital for genetic counselling to discuss global developmental delay and recurrent febrile convulsions. He is the second child of healthy, non-consanguineous parents and was born at 38 weeks *via* Caesarean section. He was the first of monozygotic twins, and his birth weight was 3000 g. There was no family history of any genetic disorders. Their elder sister was healthy and appeared normal. The proband weighed 21.4 kg (90th percentile) and was 113 cm tall (over 97th centile). Three consecutive yearly height measurements had been over the 97th centile. He grew taller than his peers during infancy and childhood. His hands and feet were also large, and he had disproportionately long limbs. Wrist radiographs taken at the age of 5 showed that his bone age had advanced to that of a 7 years old child.

He had a triangular-shaped face, prominent forehead, high hairline, downward-slanting palpebral fissures, mild micrognathia, high arched palate, fronto-temporal sparse hairs, and large ears. He showed macrodolicocephaly, and his head circumstance was 55 cm (97th percentile). An orthodontic evaluation showed tooth size/arch circumference discrepancies and a narrow, high-arched palate, prognathism of the mandible and premature eruption of the teeth. He revealed pes planus and mild scoliosis. He was not able to sit without support before one year of age. He walked alone at the age of 2 years, and at three years, he could speak several words. At 5 years of age, he attained an intelligence quotient of 60 on the Wechsler Intelligence Scale for Children Revised. His parents had observed behavioural problems since 3 years of age when he first attended kindergarten. A Conner's parent questionnaire and an independent evaluation indicated the presence of attention deficit-hyperactivity disorder and a developmental receptive and expressive language disorder. He exhibited behavioural disturbances with aggressive, willful and avoidant behaviour. Bed wetting was present until the day of presentation. He demonstrated significant temper instability and was aggressive toward other people.

Brain magnetic resonance imaging (MRI) showed venticulomegaly, modest thinning of the corpus callosum and prominent extracereberal fluid-filled spaces (Fig. 2A and B). Audiometry revealed sensorineural hearing loss (Lt. 6dB, Rt. 40B). An ophthalmologic test showed hypermetropia and amblyopia, he had received occlusive treatment. Electroencephalography revealed sharp-and-slow waves on the fronto-central regions. No kidney or genitourinary system abnormalities were detected on ultrasonography. Echocardiography demonstrated no structural abnormalities. The laboratory test including thyroid function test, growth hormone level, and metabolic work-up were normal.

2.2. Silbling of the proband

We saw the proband's sibling (Fig. 1A, individual II-3) for the first time when he was 5.5 years old. He was the second of monozygotic twins, and his birth weight was 3200 g. His birth head circumference (33 cm) and length (59 cm) were within normal limits. He spoke his first word at 14 months and phrases at 2.5 years. His weight, height, and head circumference were always greater than the 90th centile after the birth. He had overgrowth, peculiar facies, and slight intellectual disability. His weight was 23.9 kg (90th centile), his height was 113 cm (90th centile), and his head circumference was 54 cm (90th centile) at 5.5 years-old. Routine blood examination, hormone tests, immunological levels, and abdominal ultrasonography were within normal limits. A wrist radiograph taken at the age of 5.5 showed that his bone age was as advanced as that of a 7 years old child. He had normal hearing and vision. An orthodontic evaluation showed hypodontia, high-arched palate, prognathism of the mandible and dental caries. He had a deficit in language areas, but his coordination was good and he liked to be in touch with friends. Formal psychometric tests at 5 year of age revealed an IQ of 73, and he attends a regular primary school.

Brain MRI did not show any structural anomalies (Fig. 2C and D), and both echocardiogram and abdominal ultrasonography were normal. He revealed no pes planus nor scoliosis. A chromosomal analysis revealed normal male karyotype, and Fragile X testing was negative.

3. Methods

Blood karyotype with G-banding showed normal chromosomes (46, XY) in the proband. A genomic microarray was performed using the SurePrint G3 Human CGH + SNP Microarray 4x180K kit (Agilent Technologies, Inc., Santa Clara, CA, USA), and no abnormalities were shown. *FMR1* length mutation for the fragile X syndrome was not detected *via* DNA fragment analysis. The clinical features of the monozygotic twins suggested Sotos syndrome. However, clinical manifestations associated with Sotos syndrome overlapped with other congenital overgrowth syndromes represented such as Beckwith-