A neonate with Say–Barber–Biesecker–Young–Simpson syndrome with a novel pathogenic mutation in KAT6B gene: A case report

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The Say–Barber–Biesecker–Young–Simpson variant of Ohdo syndrome (SBBYSS) (Online Mendelian Inheritance in Man #603736) is a rare autosomal dominant disorder and clinically features blepharophimosis with ptosis, a mask-like facial appearance, cryptorchidism, congenital heart defect, long thumbs/great toes, and thyroid dysfunction. The etiology of SBBYSS has been shown to be due to heterozygous KAT6B gene mutation. Here we report a case of a neonate with SBBYSS identified a novel mutation in KAT6B gene. The patient showed typical dysmorphic facies, cryptorchidism with micropenis, overriding fingers, and long thumbs and toes at birth. He had also hypothyroidism, large atrial septal defect, and sensorineural hearing loss. The next generation sequencing identified a heterozygous novel variant, c.5206C>T (p.Gln1736Ter) in KAT6B gene. At the 9 months of age, he underwent patch closure for atrial septal defect. Until the 12-month follow-up, he was under-developed.

Key words: Say–Barber–Biesecker–Young–Simpson syndrome, KAT6B protein.

Introduction

Say–Barber–Biesecker–Young–Simpson syndrome (SBBYSS; Online Mendelian Inheritance in Man [OMIM] #603736), which overlaps with the originally described Ohdo syndrome, is an autosomal dominant disorder clinically recognizable at birth. Clinical features are blepharophimosis with ptosis, mask-like facial appearance, long thumbs/great toes, cryptorchidism, congenital heart defect, and thyroid dysfunction [1]. The etiology of SBBYSS has been recognized as a heterozygous de novo mutation of the KAT6B gene. KAT6B encodes a highly conserved histone acetyltransferase and regulates the expression of multiple genes that are important for early development, including development of the skeleton and nervous system [2]. This is essential for proper growth and development, and its role in human genetic diseases is increasingly recognized KAT6B disorders include SBBYSS and genitopatellar syndrome (GPS; OMIM #606170). GPS is another phenotype of KAT6B disorders with characteristic features including patellar hypoplasia, flexion contractures of the limbs, renal and genital anomalies, microcephaly, agenesis...
of the corpus callosum, and intellectual disability [3]. Although
the prevalence of SBBYSS and GPS is still not accurately known,
some individuals with molecularly confirmed KAT6B disorders
have been reported in the literature, including 20% with GPS,
64% with SBBYSS, and 14% described as having an interme-
diate phenotype [4]. The pathogenic variant spectrum from
individuals includes 39% substitutions, 39% small intragenic
deletions, 18% small intragenic duplications and 3% small in-
tragenic deletions associated with an insertion [4], which results
in most of frameshift and nonsense mutations [1,5]. Here we
report a neonate diagnosed typical SBBYSS caused by a patho-
genic nonsense novel variant of KAT6B gene. This study was
approved by the Institutional Review Board (IRB) of Chungnam
National University Hospital (IRB no. CNUH 2021-11-009). The
written informed consent was waived by IRB.

Case

A male newborn was the first baby of healthy noncon-
sanguineous parents. Family history was unremarkable and
there were no antenatal problems. Amniocentesis with fetal
chromosomal analysis was normal. He was born via vaginal
delivery at 40+4 weeks’ gestation at the local obstetric clinic. He
was transferred to our institute for multiple anomalies at birth.
His weight, height, and head circumference were 2,720 g (3rd-
10th percentile), 47.5 cm (3rd–10th percentile) and 34 cm (10th–
50th percentile), respectively. He showed weak-cry and had
generalized low muscle tone. Apgar scores at 1- and 5-minute
were 7 and 9, respectively. Physical examination revealed hyper-
telorism, low set ear with underdeveloped antihelix, low nasal
bridge, upward nostril, micrognathia, small scrotum with micro-
penis, overriding fingers, and long thumbs and toes (Fig. 1A, C,
and D). The testes were not palpable in bilateral scrotums. Pelvic
sonography performed at admission showed intra-abdominal
testes. Simple cysts in both kidneys were seen in ultrasonogra-
phy. Echocardiography showed a large atrial septal defect (ASD).
There were unremarkable findings in brain sonography. Sensori-
near hearing loss in the left ear was suspicious by automated
auditory brainstem response test.

On the 7th and 14th day after birth, he experienced two
events of atrial flutter, and flecainide was administered. No addi-
tional attacks were developed until 4 month and medication
was stopped. Free thyroxine and thyroid-stimulating hormone
levels measured at the 14 days old were 0.58 ng/dL and 445.18
μIU/mL, respectively. Thyroid scans showed diffuse goiter with
significantly increased uptake in both lobes. Levothyroxine was
administrated after the diagnosis of congenital hypothyroid-
ism. His karyotyping was 46 XY and chromosomal microarray
revealed no deletions or duplications. For underlying causes
of the multiple abnormalities, we performed targeted exome

Fig. 1. Representative photographs showing the clinical features of the patient. Patient showed hypertelorism, shore and retro forehead, low
nasal bridge, upward nostril, micrognathia, low set ear with underdevelopment antihelix (A), small scrotum with micropenis, cryptorchidism (C),
overriding fingers and long thumbs/great toes (D) at admission. (B) Immobile mask-like face, a bulbous nasal tip, and severe blepharophimosis at
the age of 4 months.
sequencing by hereditary endocrine disorder panel (111 genes) and hereditary skeletal disorder panel (362 genes). A heterozygous nonsense mutation, c.5206C>T (p.Gln1736Ter), in exon 18 of KAT6B gene (NM_012330.3) was identified and confirmed Sanger sequencing (Fig. 2). The c.5206C>T is a mutation at an evolutionarily conserved position in eutherian mammals, which determined by comparative genomics with alignments from Ensembl Genome Browser (https://asia.ensembl.org). And this allelic mutation was not inherited from his parents, and was also not identified in control populations and was predicted as damaging by in-silico analysis (Sorting Intolerant from Tolerant and Polyphen-2). So, we concluded that this de novo mutation is a novel pathogenic variant according to American College of Medical Genetics classification [6].

He was discharged at the age of one month. Then, at the age of 4 months, he was confirmed unilateral sensorineural hearing loss in the auditory brain threshold test. Clinical findings revealed an immobile mask-like face, a bulbous nasal tip, and severe blepharophimosis (Fig. 1B). He underwent patch closure for ASD at the age of 9 months. At the same time, the Denver developmental screening test was 5.9 months, 5.6 months, 4.3 months, and 5.4 months for personal-social, fine motor-adaptive, language, and gross motor, respectively. In the follow-up 12 months later, his weight, height, and head circumference were all less than 3rd percentile. He was undergoing rehabilitation treatment because of developmental delay. He is scheduled for surgery of cryptorchidism.

**Discussion**

The KAT6B gene located in the 10q22.2 region of DNA encodes lysine acetyltransferase 6B. Exome sequencing has enabled identification of de novo heterozygous variants in KAT6B as etiology of both GPS and SBBYSS, a variant of Ohdo syndrome [4]. Ohdo syndrome was first described as a genetic condition characterized by intellectual disability in association with congenital heart disease and dysmorphisms [7]. Subsequently, Young and Simpson reported a more severe phenotype later referred to as the SBBYS variant of Ohdo syndrome, or SBBYSS [8–10]. GPS and SBBYSS have been described as distinct disorders with respect to clinical findings but with several overlapping features including global developmental delay/intellectual disability, hypotonia, genital abnormalities, congenital heart defects, hearing loss, and thyroid anomalies [11]. Lemire et al. [5] proposed that
the features listed in Table 1 should raise suspicion for KAT6B disorder. Individuals with two major features or one major feature and two minor features are likely to have a KAT6B disorder. The major features of SBBYSS are characterized by blepharophimosis, dacrystostenosis, ptosis, a mask-like facial appearance and long thumbs/great toes. GPS is characterized by patellar hypoplasia/agenesis, agenesis of the corpus callosum, flexion contractures of the hips and knees, and club feet [12]. Mendez et al. [13] reported a newborn with the facial dysmorphisms and long thumbs/halluces as the main findings clearly suggested the diagnosis of SBBYSS. But he also had a corpus callosum agenesis, a typical feature of GPS. Another reported a boy that had a KAT6B mutation previously reported in typical SBBYSS, but he also manifested severe developmental delay, as well as genital features and laryngomalacia requiring tracheostomy that confirmed to GPS [14]. Our patient had three major features like distinctive face, long thumbs/great toes, and blepharophimosis without structural brain defects or respiratory problems suggesting the SBBYSS. Furthermore, he had some minor features such as cryptorchidism, hypothyroidism, sensorineural hearing loss, and congenital heart defect.

Vlckova et al. [11] summarized genotype-phenotype correlations and classified 62 reported KAT6B mutations into four groups. Group 1 mutation (codons 1 to 1205) produces KAT6B lacking a significant part of the acidic (A) domain and the whole transcription activation (TA) domain and is associated with GPS. Group 3 (codons 1350 to 1520) is retaining a larger part of the A domain but lacking the TA domain, and most cases (5/7) with GPS/SBBYSS mixed phenotypes are included in this group. Group 4 (codons 1520 to 2073) is retaining the whole A domain but lacking the TA domain and cause almost exclusively SBBYSS. The genotype (p.Gln1736Ter) of our patient was included in KAT6B mutation group 4. It is a novel mutation in KAT6B gene that has not been reported yet (http://gnomad.broadinstitute.org). While KAT6B disorders are inherited in an autosomal dominant manner, most individuals with a KAT6B disorder have had a de novo pathogenic variant including ours. Kim et al. [16] reported the familial inherited mutation of the KAT6B variant (c.2292C>T, p.His767Tyr) causing relatively mild disease in three individuals with SBBYSS. In Korea, two cases have reported KAT6B mutation including GPS (NM_012330.3: c4543C>T, p.Gln1515Ter) and familial SBBYSS mentioned above [16,17].

In summary, SBBYSS is a rare disease characterized by multiple congenital anomalies and developmental delay and a few cases have been reported in worldwide. In patients with these phenotypes, sequencing can be performed to confirm the diagnosis. We identified a novel mutation in KAT6B gene by targeted exome sequencing and it is meaningful addition to the literature. After the diagnosis, follow-up is necessary because

| Major features                     | GPS               | SBBYSS          |
|------------------------------------|-------------------|-----------------|
| Genital anomalies                  | Long thumbs/great toes<sup>a</sup> |                  |
| Patellar hypoplasia/agenesis       | Immobile mask-like face<sup>a</sup> |                  |
| Contractures at the hips, knees and/or club foot | Blepharophimosis and/or ptosis<sup>a</sup> | Lacrimal duct anomalies |
| Agenesis of the corpus callosum    | Patellar hypoplasia/agenesis          |                  |
| Renal anomalies (hydronephrosis or multiple renal cysts) | Genital anomalies (cryptorchidism in male)<sup>a</sup> | Cleft palate |

| Minor features                     |                  |                 |
|------------------------------------|------------------|-----------------|
| Anal anomalies                     |                  |                 |
| Congenital heart defect<sup>a</sup> |                  |                 |
| Dental anomalies (delayed eruption of teeth) |                  |                 |
| Hearing loss<sup>a</sup>           |                  |                 |
| Thyroid anomalies<sup>a</sup>      |                  |                 |
| Hypotonia<sup>a</sup>              |                  |                 |
| Global developmental delay/intellectual disability<sup>a</sup> |                  |                 |

Diagnostic criteria: 2 majors or 1 major plus 2 minors [5].
<sup>a</sup>Presented in our patient.
GPS, genitopatellar syndrome; SBBYSS, Say–Barber–Biesecker–Young–Simpson syndrome.
Modified from the article of Lemire G et al. (GeneReviews® 1993-2021; https://www.ncbi.nlm.nih.gov/books/NBK114806/) [5].
developmental delay, hearing loss, and hypothyroidism may be accompanied.

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Author’s Contributions

Conception and design: HHL, JHS, MHG, MC. Acquisition of data: JHS, SYK. Analysis and interpretation of data: JHS, HHL, SY. Drafting the article: JHS, HHL, MC, SYK, MHG. Critical revision of the article: JHS, HHL, MC, MHG. Final approval of the version to be published: all authors.

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