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Delineation of a Phenotype Caused by a *KAT6B* Missense Variant Not Resembling Say-Barber-Biesecker-Young-Simpson and Genitopatellar Syndromes

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Established Facts

- Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) and genitopatellar syndrome (GPS) are characterized by developmental delay and multisystemic abnormalities caused by truncating variants of *KAT6B*.
- Causative variants in SBBYSS and GPS tend to occur in the terminal exons of *KAT6B* consisting of 18 exons.

Novel Insights

- We report a patient with global developmental delay, autistic behavior, muscular hypotonia, facial dysmorphism, and seizures not resembling SBBYSS and GPS caused by a novel missense variant in exon 7 of KAT6B.
- Our findings highlight the unique phenotype of KAT6B variants and suggest that complex mechanisms underlie the genotype-phenotype correlation in KAT6B-related disorders.

Keywords
Lysine acetyltransferase 6B · Say-Barber-Biesecker-Young-Simpson syndrome · Genitopatellar syndrome · Genotype-phenotype correlation · Whole-exome sequencing

Abstract
Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) and genitopatellar syndrome (GPS) are caused by variants of lysine acetyltransferase 6B (*KAT6B*). These variants tend to occur in the terminal exons of *KAT6B*. Here, we report a patient with global developmental delay, intellectual disability, autistic behavior, muscular hypotonia, facial dys-

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morphism, and seizures caused by a novel missense variant in exon 7 of *KAT6B*. The patient showed a phenotype differing from those of SBBYSS and GPS. We also report patients with missense variants in the proximal exons of *KAT6B* showing dysmorphic features and autistic behavior not resembling the characteristics of SBBYSS and GPS. Missense variants in the proximal exons of *KAT6B* may have a dominant negative effect or cause gain of function, leading to unique phenotypes not resembling those of SBBYSS and GPS.

Introduction

Heterozygous lysine acetyltransferase 6B (*KAT6B*) variants cause Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS, OMIM # 603736) and genitopatellar syndrome (GPS, OMIM # 606170) [Campeau et al., 2012]. Particularly, SBBYSS is characterized by an immobile mask-like face, blepharophimosis, lacrimal duct anomalies, patellar hypoplasia/agenesis, and long thumbs/great toes, whereas GPS is characterized by genital anomalies, patellar hypoplasia/agenesis, flexion contractures at the hips and knees, and renal anomalies. Clinical phenotypes, including developmental delay, intellectual disability, muscular hypotonia, congenital heart defects, and thyroid abnormalities, are common in both syndromes [Lemire et al., 2020]. *KAT6B*, which encodes a histone acetyltransferase involved in chromatin modification, consists of 18 exons. Causative variants of SBBYSS and GPS tend to occur in the terminal exons of *KAT6B*. Although causative variants of SBBYSS are located distally to exon 18 of *KAT6B*, those of GPS are located more proximally to exon 18 [Zhang et al., 2020]. Recently, several reports have shown that *KAT6B* variants in exons more proximal to exon 18 can cause unique SBBYSS and GPS phenotypes [Clayton-Smith et al., 2011; Kim et al., 2017; Marangi et al., 2018; Zhang et al., 2020]. Here, we present a patient with global developmental delay, intellectual disability, autistic behavior, muscular hypotonia, facial dysmorphism, and seizures, but with a phenotype different from that of SBBYSS and GPS caused by a de novo heterozygous missense variant in exon 7 of *KAT6B*. Our findings highlight the unique phenotype of *KAT6B* variants and suggest that complex mechanisms underlie the genotype-phenotype correlation in *KAT6B*-related disorders.

Case Report

The proposita was born at 40 weeks of gestation following an uneventful pregnancy. The weight, length, and occipitofrontal circumference of the newborn were 3,135 g (+0.3 standard deviation [SD]), 48.7 cm (−0.5 SD), and 33.5 cm (0 SD), respectively. Her parents were healthy and nonconsanguineous. During infancy, she developed epileptic seizures with episodes of desaturation that were successfully controlled by treatment with phenobarbital. She attained head control at 4 months. Her global developmental delay became apparent at 1 year of age, at which point she was referred to our hospital. Neurological assessment showed hypotonia and tremulousness of the limbs. However, no abnormal finding was detected by brain magnetic resonance imaging. At 7 years of age, she redeveloped monthly generalized tonic seizures and was subjected to sleep electroencephalography, which revealed frontal dominant generalized, high voltage, slow-wave burst activity. The occurrence of seizures decreased following treatment with valproate and lamotrigine. Echocardiogram, skeletal X-ray, and thyroid hormone levels were all normal. At 8 years of age, she was still unable to walk and speak meaningful words and had severe intellectual disability (intelligence quotient <20) and exhibited autistic behavior. Facial dysmorphisms included an arched and flared eyebrow, blepharophimosis, hypertelorism, bulbous nose, short palpebral fissure, strabismus, prominent cheeks, and an immobile mask-like face. Generalized hypopigmentation of the skin was noted (Fig. 1a).

The patient's clinical phenotype was initially suggestive of Angelman syndrome. Chromosome testing and methylation-specific polymerase chain reaction showed normal results. Genomic DNA was purified from the peripheral blood of the patient and her parents using standard protocols. We performed whole-exome sequencing of the patient. Purified DNA was enriched using a SureSelect Human All Exon V6 kit (Agilent Technologies, Santa Clara, CA, USA) and sequenced on a NovaSeq platform (Illumina, San Diego, CA, USA) using 151-bp paired-end reads. Exome data alignment, variant calling, and variant annotation were assessed as previously described [Murakami et al., 2020]. The candidate variant was confirmed by Sanger sequencing. Copy number variants were calculated by analyzing the log ratio of exon depth [Enomoto et al., 2020]. Targeted sequencing identified a de novo *KAT6B* heterozygous variant in exon 7, NM_012330.3:c.1013A>G, p.(Tyr338Cys). This variant has not been previously reported in the general population (The Genome Aggregation Database, https://gnomad.broadinstitute.org/ or Leiden Open Variation Database *KAT6B* variant database, https://databases.lovd.nl/shared/genes/KAT6B). The CADD score (28.2) indicated that the variant was deleterious, with Provean (deleterious), SIFT (damaging), and PolyPhen-2 (damaging) analyses predicting different types of pathogenicity. According to the guidelines of the American College of Medical Genetics and Genomics, the variant is likely pathogenic (PS2 + PM2 + PP3) [Richards et al., 2015].

Discussion and Conclusion

In this case report, we conducted whole-exome sequencing analysis and identified a novel missense variant in *KAT6B* (NM_012330.3:exon 7:c.1013A>G, p.(Tyr338Cys))

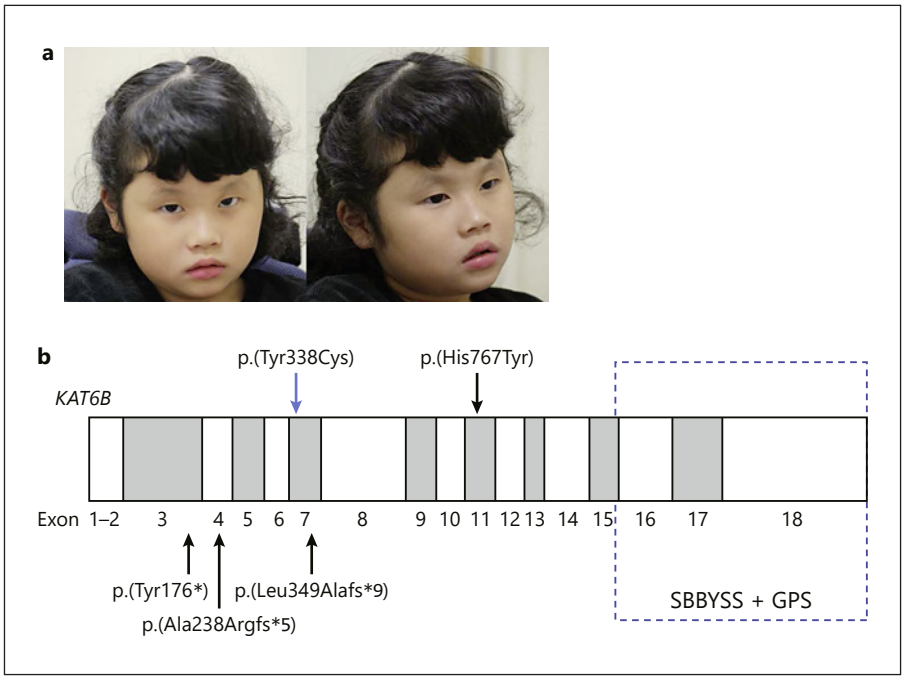

Fig. 1. Patient photograph and *KAT6B* variants reported in previous studies. **a** The patient at 7 years of age (published with permission from her parents). The patient had dysmorphic features, including an arched and flared eyebrow, blepharophimosis, hypertelorism, bulbous nose, short palpebral fissure, strabismus, prominent cheeks, and an immobile mask-like face. **b** Diagram of *KAT6B* exons and the variants identified in this study (blue arrow) and previous studies reporting 4 patients with unique SBBYSS and GPS phenotypes in the proximal exons (exons 3–11) of *KAT6B*. The locations of the 4 variants, including 1 missense variant (top), 1 nonsense variant, and 2 frameshift variants (bottom), are indicated by black arrows. Variants of SBBYSS and GPS tend to occur in the terminal exons of *KAT6B*. SBBYSS, Say-Barber-Biesecker-Young-Simpson syndrome; GPS, genitopatellar syndrome.

in a patient with an atypical phenotype exhibiting global developmental delay, severe intellectual disability, autism spectrum disorder, muscular hypotonia, facial dysmorphism, and seizures. In general, *KAT6B*-related disorders show a divergent phenotype, including developmental delay/intellectual disability (SBBYSS: 97% of cases; GPS: 73% of cases), muscular hypotonia (SBBYSS: 75%; GPS: 23%), and seizures (SBBYSS: 3%; GPS: 12%) [Zhang et al., 2020]. Neurological symptoms, such as tremulousness of the limbs, have not been described in patients with a *KAT6B* variant. The facial phenotypes of our patient, such as an immobile mask-like face, partially overlapped with those of SBBYSS. However, an immobile mask-like face is common among individuals with severe intellectual disability associated with autism spectrum disorders [Trevisan et al., 2018]. Thus, we concluded that the missense variant in *KAT6B* contributes to the clinical phenotype of our patient, which partially overlaps with, but is not consistent with, those associated with SBBYSS and GPS.

Both SBBYSS and GPS are caused by truncating variants in the terminal exons of *KAT6B* (exons 16–18). Most *KAT6B* variants in SBBYSS are located at the C-terminal end of exon 18. This region comprises a highly conserved serine- and methionine-rich domain. Notably, *KAT6B* variants in GPS tend to cluster more in the proximal region compared with those in SBBYSS [Gannon et al., 2015]. The hypothesized molecular mechanism of SBBYSS and GPS is haploinsufficiency or loss of function of the terminal exons of *KAT6B* [Campeau et al., 2012]. To date, 4 patients have been reported to exhibit phenotypes that are unique compared with those of SBBYSS and GPS (Table 1) [Clayton-Smith et al., 2011; Kim et al., 2017; Marangi et al., 2018; Zhang et al., 2020]. The facial phenotypes show overlap in patients with GPS and SBBYSS. All 4 patients exhibited various degrees of developmental delay. The *KAT6B* variants causing the unique phenotypes in these patients and our patient were in the part (exons 3–11) of the gene more proximal to exon 18 than those in typical SBBYSS and GPS (Fig. 1b). Patients with truncating variants in the proximal exon of *KAT6B* showed mild to severe intellectual disability. However, those with missense variants in the proximal exon of *KAT6B* showed severe autism. Together with the findings of previous reports, our results can be used to classify *KAT6B*-related disorders into 4 types according to a genotype-phenotype correlation of *KAT6B* variants: type 1: terminal exons of *KAT6B* associated with SBBYSS; type 2: proximal exons of terminal exons of *KAT6B* associated with GPS; type 3: proximal exons of *KAT6B* associated with intellectual disability and autism caused by haploinsufficiency; and type 4: proximal exons of *KAT6B* associated with severe autism caused by missense variants [Zhang et al., 2020]. These findings suggest that missense variants in *KAT6B* proximal exons have a dominant negative effect or cause a gain of function associated with unique SBBYSS and GPS phenotypes.

Table 1. Variants and clinical features of the proposita and other reported patients with *KAT6B*-related neurodevelopmental disorders involved in unique SBBYSS and *G*PS phenotypes

	Clayton-Smith et al., 2011	Zhang et al., 2020	Marangi et al., 2018	Kim et al., 2017	Present patient
Sex	Male	Male	Female	Female	Female
Exon	Exon 3	Exon 4	Exon 7	Exon 11	Exon 7
c-Notation	c.527dupA	c.708_709delTT	c.1045_1049delTTAAA	c.2292C>T	c.1013A>G
p-Notation	p.(Tyr176*)	p.(Ala238Argfs*5)	p.(Leu349Alafs*9)	p.(His767Tyr)	p.(Tyr338Cys)
Origin	Not tested	de novo	de novo	Inherited	de novo
Developmental delay	+	+	+	+	+
Intellectual disability	+	+	+	+	+
Autism	–	NA	–	+	+
Neurological symptoms	Hypotonia	Seizures	Hypotonia	–	Hypotonia Tremulousness of the limbs Seizures
Lacrimal duct anomalies	–	+	–	–	–
Ophthalmological anomalies	–	Hyperopia	Myopia Astigmatism	Strabismus	–
Hearing problems	–	–	–	–	NA
Patellar hypoplasia/agenesis	–	–	NA	–	–
Flexion contractures at the hips and knees	NA	–	+	–	–
Thyroid abnormalities	–	–	+	–	–
Heart defect	–	–	–	–	–
Renal anomalies	NA	–	–	–	–
Genital anomalies	+	–	–	–	–
Dysmorphism					
Immobile mask-like face	–	NA	+	+	+
Blepharophimosis	–	+	+	+	+
Bulbous nose	–	+	+	+	–
Long thumbs/great toes	–	+	+	+	–
Radiological investigations	NA	NA	NA	–	–
Other findings		Gastroesophageal reflux	Narrow chest Exophytic spine lesions		EEG abnormality Sleep disturbance Constipation

NA, not available; EEG, electroencephalography.

Our study has some limitations. First, the number of patients in this case report is small. Further investigations are required to clarify the phenotypes resulting from *KAT6B* missense variants in proximal exons. Second, an unidentified pathogenic variant may be involved. Specifically, we identified 151 heterozygous, 42 compound heterozygous, and 7 homozygous variants as candidate variants from single whole-exome sequencing of a patient. Clinically, she was suspected with Angelman syndrome based on several clinical manifestations. However, no variants in the genes that are known to cause neurodevelopmental disorders, including *UBE3A*, were identified. From the candidate genes, *KAT6B* was selected as the only gene that could explain the patient's phenotype. Improvements in genetic testing can resolve this question. Third, our study does not provide evidence of epigenetic regulation of genes through DNA methylation of *KAT6B*. Gene-specific DNA methylation signatures were previously validated and can identify epigenetic mechanisms that molecularly link genes [Butcher et al., 2017]. Analysis of a *KAT6B*-specific DNA methylation signature may reveal the underlying epigenetic etiology of this disorder.

Individuals with missense variants in the proximal exons of *KAT6B* show phenotypes that differ from those of SBBYSS and GPS, with haploinsufficiency in the terminal exons. Our study provides evidence that *KAT6B* variants in proximal exons cause various neurodevelopmental disorders, including unique SBBYSS and GPS phenotypes.

Acknowledgement

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Statement of Ethics

This study was approved by the Review Board and Ethics Committee of the Kanagawa Children's Medical Center (approval No. 121-3). Written informed consent, which included consent for the pictures appearing in the manuscript, was obtained from the patient's parents.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.N. and K.K. provided clinical and molecular genetics data and wrote the manuscript. Y.E. contributed to sequence analysis. T.K., H.M., A.I., and T.G. provided clinical data. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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