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Phenotypic Characterization of Seven Pediatric Patients Diagnosed With *KAT6B*-Related Disorders: Case Series and Review of the Literature

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ABSTRACT

Genitopatellar syndrome (GPS) and Say-Barber-Biesecker-Young-Simpson Syndrome (SBBYSS) are clinically distinct neurodevelopmental disorders caused by monoallelic pathogenic variants in *KAT6B*. In some cases, GPS and SBBYSS features can overlap, determining an intermediate phenotype. In the present study, we describe seven patients, four with a clinical diagnosis of SBBYSS and three presenting with an intermediate phenotype. All patients carried *de novo* pathogenic variants in *KAT6B* that were identified by exome sequencing. Five variants were novel. We provide both molecular and clinical findings, highlighting the previously undescribed association with two additional features: partial penoscrotal transposition and hypopigmented macules. We performed a review of the literature, listing the clinical features of 152 patients described in 33 papers, with a molecularly confirmed diagnosis of *KAT6B*-related disorders, reporting the frequency of each clinical feature detected in patients diagnosed with SBBYSS and GPS. The present work provides new insights into the phenotype associated with "*KAT6B*-related disorders", expanding the spectrum of features that can lead to a clinical suspicion of these conditions, also guiding the molecular investigations.

1 | Introduction

Monoallelic pathogenic variants in the *KAT6B* gene (lysine acetyltransferase 6B; MIM *605880) are associated with two allelic neurodevelopmental disorders with an autosomal dominant trait of inheritance: genitopatellar syndrome (GPS, OMIM # 606170) and Say-Barber-Biesecker-Young-Simpson Syndrome (SBBYSS, OMIM # 603736), a variant of Ohdo syndrome. Despite the fact that GPS and SBBYSS have been historically classified as two distinct diseases, due to an increasingly described phenotypic

Abbreviations: ACMG, American College of Medical Genetics and Genomics; ASD, atrial septal defects; CC, Corpus Callosum; CHD, congenital heart defects; DD, developmental delay; DSH, hereditary symmetric dyschromatosis; EEG, electroencephalography; GPS, Genitopatellar syndrome; ID, intellectual disability; IUGR, intrauterine growth restriction; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; PFO, patent foramen ovale; SBBYSS, Say-Barber-Biesecker-Young-Simpson Syndrome; u, unknown; VSD, ventricular septal defect; VUS, variant of uncertain significance.

overlap, they are now considered a continuum clinically referred to as "*KAT6B* disorders" (Radvanszky et al. 2017; Lemire et al. 2012).

Say-Barber-Biesecker-Young-Simpson Syndrome is a rare genetic condition, characterized by a mask-like facial appearance, blepharophimosis, ptosis, long thumbs or great toes, patellar hypoplasia or agenesis, and lacrimal duct anomalies. The condition is generally associated with intellectual disability, delayed motor milestones, and significantly impaired speech. Instead, GPS is connoted by brain defects (agenesis or hypoplasia of corpus callosum), microcephaly, severe psychomotor retardation, genital anomalies, patellar hypoplasia or agenesis, renal anomalies, and contractures.

Besides the cognitive deficits, clinical features described in both diseases include congenital heart defects, dental anomalies (hypoplastic teeth and/or delayed eruption of teeth), hearing loss, thyroid anomalies, palate anomalies, and hypotonia. Both disorders are ultra-rare diseases. The estimated prevalence of SBBYSS is lower than one in a million individuals (Lemire et al. 2012).

With the aim of expanding the clinical spectrum and molecular diversity associated with *KAT6B* variations, here we report both clinical and molecular features of seven patients diagnosed with *KAT6B*-related disorders. Furthermore, we compared the clinical features of these seven individuals with those who have a molecularly confirmed diagnosis of a *KAT6B*-related disorder reported in the literature.

2 | Material and Methods

This study included seven subjects with a clinical and molecular diagnosis of *KAT6B*-related disorders. The patients came from two different centers: one (Patient 1, P1) from the Policlinico Umberto I, Rome, and six (Patients 2–7, P2-P7) from the Bambino Gesù Children Hospital, Rome. All individuals exhibited clinical features suggestive of a KAT6B-related disorder and underwent clinical exome sequencing. Genetic testing was performed after genetic counseling and the signing of informed consent. The molecular analyses were performed at the Laboratory of Medical Genetics of the Bambino Gesù Children's Hospital. For each patient, both clinical and molecular features were reported. Clinical data were collected from medical records. For each individual in this cohort, the presence of major and minor features indicative of GPS or SBBYSS was assessed.

2.1 | Features Suggestive of SBBYSS

Major features: Long thumbs/great toes, immobile mask-like face, blepharophimosis/ptosis, lacrimal duct anomalies, patellar hypoplasia/agenesis.

Minor features: Congenital heart defect, dental anomalies (hypoplastic teeth and/or delayed eruption of teeth), hearing loss, thyroid anomalies, cleft palate, genital anomalies (males: cryptorchidism), hypotonia, global developmental delay/intellectual disability (Lemire et al. 2012).

2.2 | Features Suggestive of GPS

Major features: Genital anomalies (females: clitoromegaly and/or hypoplasia of the labia minora or majora; males: cryptorchidism and scrotal hypoplasia), patellar hypoplasia or agenesis, flexion contractures at the hips and knees (including clubfoot), agenesis of the corpus callosum with microcephaly, hydronephrosis and/or multiple renal cysts.

Minor features: Congenital heart defect, dental anomalies (delayed eruption of teeth), hearing loss, thyroid anomalies, anal anomalies, hypotonia, global developmental delay/intellectual disability (Lemire et al. 2012).

2.3 | The Patients Were Subdivided Into the Following Three Different Clinical Phenotypes

SBBYSS: Individuals with two major features or one major feature and two minor features suggestive of SBBYSS.

GPS: Individuals with two major features or one major feature and two minor features suggestive of GPS.

Intermediate: Individuals with two major features or one major feature and two minor features suggestive of both (GPS and SBBYSS).

Additionally, the frequency of clinical manifestations in the present cohort was compared to 152 previously described individuals with molecularly confirmed *KAT6B*-related phenotypes. Articles containing details of these patients were searched on PubMed using the keywords: "*KAT6B*, SBBYSS, GPS, *KAT6B* variant". For each patient, the clinical and genotypic characteristics were retrieved from the various articles and reported in Table S1. The same criteria mentioned above were used to classify individuals from the literature as GPS, SBBYSS, or an intermediate phenotype. Specifically, patients 30, 31, and 32 from Zhang et al. (2020), as well as patients 19 and 20 from Yabumoto et al. (2021), were originally reported with a "not otherwise specified" phenotype, making their classification into either the SBBYSS or GPS phenotype challenging. In our review, these individuals were categorized as having an intermediate phenotype (Zhang et al. 2020; Yabumoto et al. 2021).

3 | Results

We report the clinical features and pathogenic variants of 7 individuals with *KAT6B*-related disorders, including four diagnosed with SBBYSS (P2, P3, P5, P6) and three with an intermediate phenotype (P1, P4, P7) (Table 1). Six patients are unpublished, while Patient 3 had already been described by Zhang et al. in 2020 (Patient 15) and has continued to be in care at our institution. In these patients, five novel variants (P2, P4, P5, P6, P7) and two previously described variants (P1, P3) were detected. Additionally, in the literature we identified 152 cases (Radvanszky et al. 2017; Lemire et al. 2012; Zhang et al. 2020; Li et al. 2017; Campeau et al. 2012; Davarnia et al. 2024; Brea-Fernández et al. 2019; Klaniewska et al. 2023; Niida et al. 2017; Lonardo et al. 2019; Turkyilmaz

and Ozden 2021; Bashir et al. 2017; Clayton-Smith et al. 2011; Ferrando Meseguer et al. 2020; Gannon et al. 2015; Kim et al. 2019; Kim et al. 2017; Knight et al. 2018; Lundsgaard et al. 2017; Marangi et al. 2018; Mendez et al. 2020; Nishimura et al. 2022; Okano et al. 2018; Preiksaitiene et al. 2017; Simpson et al. 2012; Szakszon et al. 2013; Vlckova et al. 2015; Yabumoto et al. 2021; Yang et al. 2022; Yates et al. 2019; Yilmaz et al. 2015; Yu et al. 2014; Zhu et al. 2020; Miller et al. 2023) with molecularly confirmed *KAT6B*-related phenotypes, and their clinical features are summarized in Table S1. The percentage frequency of 21 key clinical manifestations was calculated for both SBBYSS and GPS patients (Table 1). The prevalence of clinical manifestations in this case series was largely consistent with data reported in the literature, particularly in the prevalence of contractures, facial anomalies, and developmental delay. Of note, penoscrotal transposition and hypopigmented macules were identified as new clinical manifestations that had not previously been reported. The clinical manifestations are analyzed in detail below.

3.1 | Neurological Features

Developmental delay/intellectual disability (DD/ID): All patients in our cohort but P1, who could not be assessed due to young age (5 months old), exhibited DD/ID, a common clinical manifestation in disorders associated with *KAT6B* variants. In particular, the degree of ID and language delay was mild in one patient (P2), while it was severe in subjects P3, P4, and P7, who also exhibited severe language impairment. Additionally, subject P3, previously reported by Zhang in 2020 (patient 15), exhibited behavioral issues including hetero-aggressive behavior, attention disorder, anxiety disorder, and sleep problems, which were unmentioned in the original report (Zhang et al. 2020). These latter issues were not reported in the other patients of our cohort. From the data collected in the medical records, no information was available regarding the severity of intellectual and language delay in subjects P5 and P6.

Corpus callosum (CC) abnormalities: Only Patient 7, who exhibits clinical features consistent with an intermediate phenotype, presented with CC hypoplasia (CC < 3° centile). This finding aligns with the observation that this clinical manifestation is unusual in patients with SBBYSS (10%), while it represents a common feature in GPS (94%) (Table 1).

Hypotonia: Axial and appendicular hypotonia, a feature that occurs in 78% of patients with SBBYSS and 36% of patients with GPS, was observed in 3/7 (42%) individuals from this cohort (P1, P3, P5). On the contrary, only one patient (14%) had hypertonia, an infrequently reported though previously described manifestation (Zhang et al. 2020).

Microcephaly: A clinical feature more frequently observed in patients with GPS (73%) compared to those with SBBYSS (32%). In our cohort, it was observed in only 2/7 (28%) of individuals.

Seizure: Seizures are an uncommon clinical manifestation in both SBBYSS (8%) and GPS (21%). In the present cohort, P1 did not develop seizures, but electroencephalography (EEG) showed fairly active focal anomalies prevalent in the frontal regions while brain magnetic resonance imaging (MRI) performed at 2 months of age was normal.

3.2 | Congenital Heart Defects (CHD)

Cardiac malformations were described in 86 of the 152 (56%) reported patients with a *KAT6B* pathogenic variant, including atrial septal defects (ASD) in 25 patients, ventricular septal defect (VSD) in 18, patent ductus arteriosus (PDA) in 16 (Table S1). In this cohort, only two individuals (28%) had CHD: they showed PDA (P3) and mitral valve dysplasia associated with ASD (P4).

3.3 | Craniofacial Features

Mask-like facies/blepharophimosis/ptosis: The main facial features of SBBYSS are mask-like facies, blepharophimosis, and ptosis. Additional features that are often observed in both GPS and SBBYSS include prominent cheeks, low-set and posteriorly rotated ears, down-slanted palpebral fissures, a flat and broad nasal bridge, a tubular or bulbous nose, a long philtrum, a thin upper lip, reduced lip vermilion, and micrognathia or retrognathia. (Lemire et al. 2012) Mask-like facies and blepharophimosis/ptosis were observed respectively in 85% and 100% of individuals of this cohort, consistent with the hallmark facial features of SBBYSS. Figure 1 shows the distinctive facial dysmorphisms of SBBYSS characterizing P3 at the age of 4 years and 11 months and at her current age of 13 years and 8 months.

Dental Anomalies: Anomalies were observed in three subjects. One subject (P2) showed dental diastemas, while two patients (P4 and P6) had prominent upper central incisors with dental diastemas.

Palate anomalies (cleft lip and palate and high-arched palate): Palate anomalies are observed fairly equally in patients with GPS (24%) and SBBYSS (30%). Cleft of the soft palate was observed only in 1/7 (14%) of individuals from this cohort.

Lacrimal duct anomalies: In our cohort, only Patient 5 (P5) had lacrimal duct anomalies (14%) aligns with the reported prevalence in SBBYSS (19%).

Other craniofacial features: P1 and P7 had auricular pits. Auricular pits were previously reported in two patients by Gannon et al. (Patient n. 53) and Zhang et al. (Patient n. 26) (Zhang et al. 2020; Gannon et al. 2015).

3.4 | Musculoskeletal Features

Patellar anomalies and contractures: Patellar anomalies and contractures are key characteristics of GPS. Four subjects (57%) including one with the SBBYSS (P3) and three with an intermediate phenotype (P1, P4, P7), exhibited contractures of the knees (P3, P4, P7) or hips (P1). Patients P4 and P7 also exhibited patellar hypoplasia. In P1, the presence of patellar hypoplasia could not be evaluated, because patellar ossification begins between 17 months and 6 years in males (Lemire et al. 2012).

TABLE 1 | In the second and third columns are reported frequencies of clinical features in 86 subjects with SBBYSS and 33 subjects with GPS, while in the subsequent columns are listed clinical features of our seven patients.

				P1 (M) (5 months)	P2 (M) (15 years, 4 months)	P3 (F) (13 years, 8 months)	P4 (F) (18 years, 8 months)	P5 (M) (3 years, 9 months)	P6 (F) (25 years)	P7 (7 years, 7 months)
				Intermediate	SBBYSS	SBBYSS	Intermediate	SBBYSS	SBBYSS	Intermediate
				KAT6B (NM_012330.4)						
				exon 17	exon 18	exon 16	exon 18	exon 18	exon 18	exon 17
				c.3401del, p.Gly1134ValfsTer11	c.4993A>G, p.Ser1665Gly	c.3202_3203 delAG p.Ser1068GlnfsX2	c.3998dup p.Ser1334LysfsTer8	c.5876T>A p.Leu1959*	c.4721_4722insCTACACC p.Arg1577fs*24.	c.3664+1G>A
Clinical features		**SBBYSS**	**GPS**	**P**	**LP**	**LP**	**P**	**LP**	**LP**	**P**
Neurological features	DD/ID	84/86 (96%)	23/33 (70%)	u	+	+	+	+	+	+
	Absent or thin CC	9/86 (10%)	31/33 (94%)	−	−	−	−	−	−	+
	Hypotonia	67/86 (78%)	12/33 (36%)	+	u	+	−	+	u	−
	Microcephaly	28/86 (32%)	24/33 (73%)	−	−	u	+	−	+	u
	Seizures	6/86 (8%)	7/33 (21%)	+/−	−	−	−	−	u	−
Congenital heart defect		39/86 (45%)	24/33 (73%)	−	u	+	+	−	u	−
Craniofacial features	Mask-like facies	71/86 (82%)	5/33 (15%)	+	−	+	+	+	+	+
	Blepharophimosis/ ptosis	83/86 (96%)	7/33 (21%)	+	+	+	+	+	+	+
	Dental anomalies	35/86 (40%)	6/33 (18%)	−	+	u	+	u	+	u
	Palate anomalies	26/86 (30%)	8/33 (24%)	−	−	+	−	u	u	−
	Lacrymal duct anomalies	17/86 (19%)	0	u	u	u	u	+	u	u

(Continues)

TABLE 1 | (Continued)

				P1 (M) (5 months)	P2 (M) (15 years, 4 months)	P3 (F) (13 years, 8 months)	P4 (F) (18 years, 8 months)	P5 (M) (3 years, 9 months)	P6 (F) (25 years)	P7 (7 years, 7 months)
				Intermediate	SBBYSS	SBBYSS	Intermediate	SBBYSS	SBBYSS	Intermediate
				KAT6B (NM_012330.4)						
				exon 17	exon 18	exon 16	exon 18	exon 18	exon 18	exon 17
				c.3401del, p.Gly1134ValfsTer11	c.4993A>G, p.Ser1665Gly	c.3202_3203 delAG p.Ser1068GlnfsX2	c.3998dup p.Ser1334LysfsTer8	c.5876T>A p.Leu1959*	c.4721_4722insCTACACC p.Arg1577fs*24.	c.3664 + 1G>A
Clinical features		**SBBYSS**	**GPS**	**P**	**LP**	**LP**	**P**	**LP**	**LP**	**P**
Musculoskeletal Features	Contractures (hips/knee, club feet)	26/86 (30%)	31/33 (94%)	+	u	+	+	−	−	+
	Patellar anomalies	17/86 (19%)	26/33 (79%)	u	u	−	+	u	u	+
	Long thumbs or long great toes	59/86 (68%)	11/33 (33%)	+	−	+	+	−	+	u
Genital anomalies		37/86 (43%)	31/33 (94%)	+	−	−	u	+	u	+
GI and feeding issues	Feeding difficulties	63/86 (73%)	12/33 (36%)	+	−	+	+	−	u	+
	Anal anomalies	3/86 (3%)	9/33 (27%)	−	+	−	u	u	u	u
Tracheomalacia laryngomalacia respiratory distress		15/86 (17%)	10/33 (30%)	−	u	u	u	u	u	u
Thyroid anomalies		30/86 (34%)	7/33 (21%)	u	−	+	u	+	u	+
Renal and urinary tract anomalies		7/86 (8%)	28/33 (85%)	−	u	−	u	−	u	u
Hearing impairment and EAC malformations		20/86 (24%)	3/33 (9%)	−	−	−	u	u	−	−
Optic atrophy or hypoplasia or cortical visual impairment		5/86 (6%)	9/33 (27%)	−	−	−	−	+	−	−

Note: References of the table: Radvanszky et al. (2017), Lemire et al. (2012), Zhang et al. (2020), Li et al. (2017), Campeau et al. (2012), Davarnia et al. (2024), Brea-Fernández et al. (2019), Klaniewska et al. (2023), Niida et al. (2017), Lonardo et al. (2019), Turkyilmaz and Ozden (2021), Bashir et al. (2017), Clayton-Smith et al. (2011), Ferrando Meseguer et al. (2020), Gannon et al. (2015), Kim et al. (2019), Kim et al. (2017), Knight et al. (2018), Lundsgaard et al. (2017), Marangi et al. (2018), Mendez et al. (2020), Nishimura et al. (2022), Okano et al. (2018), Preiksaitiene et al. (2017), Simpson et al. (2012), Szakszon et al. (2013), Vlckova et al. (2015), Yabumoto et al. (2021), Yang et al. (2022), Yates et al. (2019), Yilmaz et al. (2015), Yu et al. (2014), Zhu et al. (2020), and Miller et al. (2023).

Abbreviations: CC: corpus callosum; DD/ID: developmental delay/intellectual disability; EAC: external auditory canal; F: female; GI: gastrointestinal; GPS: genitopatellar syndrome; LP: likely pathogenic; M: male; P: pathogenic; SBBYSS: Say-Barber-Biesecker-Young-Simpson syndrome; u: unknown.

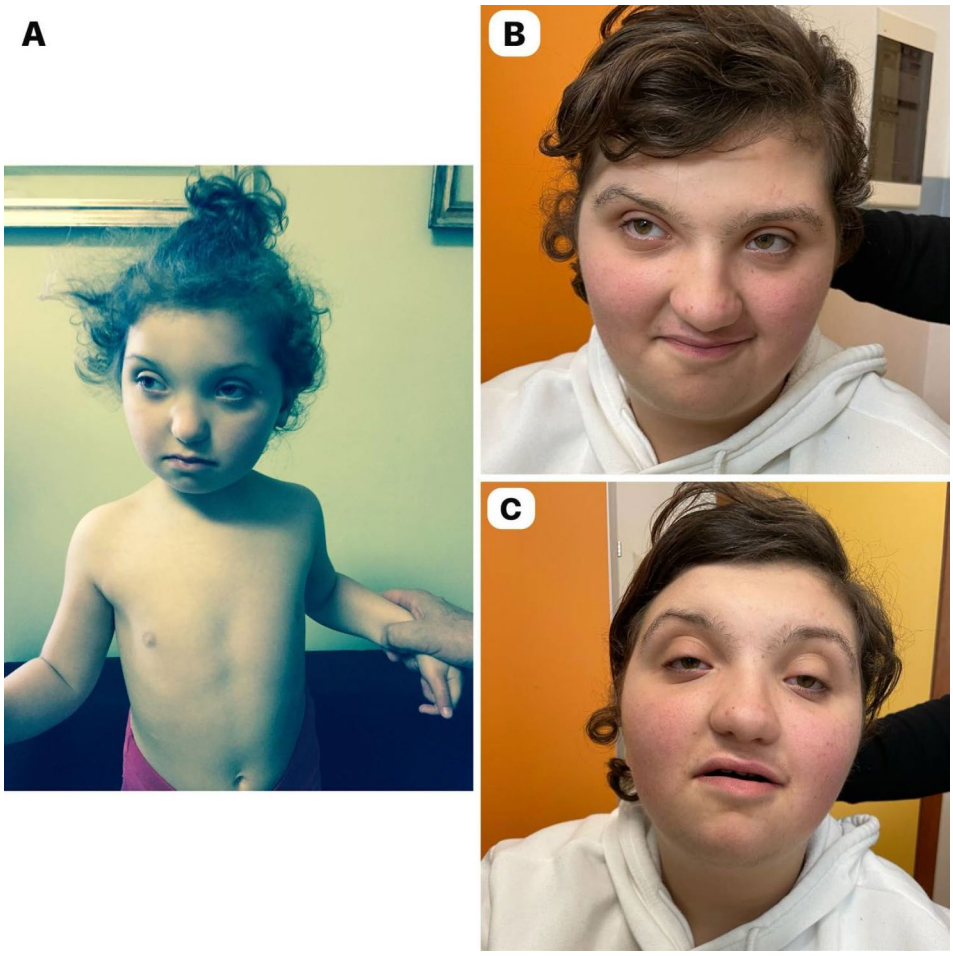

FIGURE 1 | Dysmorphic features of Patient 3 (referred to as Patient 15 by Zhang et al. 2020). In image A, she is shown at the age of 4 years and 11 months. In images B and C, the same patient is depicted at her current age of 13 years and 8 months. The subject exhibits mask-like facies, laterally sparse eyebrows, ptosis, hypertelorism, blepharophimosis, prominent cheeks, low-set ears, a flat and broad nasal bridge, a bulbous nose, a thinner upper lip, and a thin lip vermilion.

Other musculoskeletal features: P4 had inwardly rotated feet, hands with interdigital folds, a narrow carpus, radial deviation of the first finger of the left hand, and camptodactyly. Skeletal anomalies such as thoracolumbar scoliosis, an asymmetrical shield-shaped chest, and knee valgus with patellar hypoplasia and dislocation were present. Scoliosis was present even in P7.

3.5 | Genital Anomalies

In this cohort, 3/7 (42%) of individuals exhibited genital anomalies: Patient 1 had cryptorchidism, Patient 5 had bilateral cryptorchidism, micropenis, and distal hypospadias, while Patient 7 presented with hypogonadism (bilateral cryptorchidism, micropenis, hypospadias, penoscrotal transposition). To our knowledge, this is the first time that penoscrotal transposition has been reported in a patient with a *KAT6B* pathogenic variant.

Endocrinological features: Delayed puberty was observed in one patient (P2), while thyroid involvement with congenital hypothyroidism in P5 and subclinical hypothyroidism with positivity for anti-thyroperoxidase antibodies in P7 were reported in two subjects.

3.6 | Gastrointestinal and Feeding Issues

Feeding difficulties: Feeding difficulties were documented in 4/7 (57%) of individuals in this cohort (P1, P3, P4, P7).

Anal anomalies: Anal anomalies were notable in Patient 2 who underwent anoplasty for imperforate anus, aligning with the low reported prevalence in SBBYSS (3%).

3.7 | Other Features

None exhibited tracheomalacia, laryngomalacia, respiratory distress, renal or urinary tract anomalies, deafness, ear canal malformations, optic atrophy or hypoplasia, or cortical visual impairment.

Ocular anomalies: P3 had astigmatism, P5 had nystagmus, P6 had severe myopia, while P7 had myopia and astigmatism.

Cutaneous anomalies: Patient 3 had three hypopigmented macules: one on the chest and two on the back. Patient 7 exhibited one achromic and one hypopigmented macule spot in the right iliac fossa. Cutaneous anomalies are not very common in

KAT6B-related Disorders. To the best of our knowledge, these are the only two patients in whom hypopigmented macules have been reported.

Prenatal findings: P5 and P7 showed intrauterine growth restriction (IUGR). Additionally, P7 exhibited an increased nuchal translucency measurement.

3.8 | Analysis of the *KAT6B* Pathogenic Variants Identified

We identified five novel variants along with two previously reported variants (c.3401del in Patient 1 and c.3202_3203 delAG in Patient 3) in *KAT6B* (NM_012330.4). (Zhang et al. 2020) The identified variants included one small intragenic deletion (c.3202_3203delAG), one small intragenic duplication (c.3998dup), one intragenic insertion (c.4721_4722insCTACACC), and four single nucleotide variants (c.3401del; c.4993A>G; c.5876T>A; c.3664+1G>A). At the protein level, these variants consisted of four frameshift variants (p.Arg1577fs*24; p.Gly1134ValfsTer11; p.S1068QfsX2; p.Ser1334LysfsTer8) one nonsense variant (p.Leu1959*), one missense variant (p.Ser1665Gly), and one variant predicted to affect splicing (Figure 2). Four of the variants were located in exon 18, two in exon 17, and one in exon 16. All variants were confirmed to be *de novo* and were classified as likely pathogenic/pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria (Richards et al. 2015). The classification result of each *KAT6B* variant in the individuals of our cohort is included in Table 1.

4 | Discussion

The *KAT6B* gene is located on the long arm of chromosome 10 (10q22.2) and encodes for KAT6B (Lysine Acetyltransferase 6B), a component of a multi-subunit complex involved in transcription regulation through histone acetylation (Zu et al. 2022). KAT6B is essential for proper human tissue growth and development and plays a pivotal role in neurogenesis and skeletogenesis (Li et al. 2017).

To date, 152 patients with molecularly confirmed *KAT6B*-related disorders have been described, including 86 with SBBYSS, 33 with GPS, and 33 with an intermediate phenotype (Radvanszky et al. 2017; Lemire et al. 2012; Zhang et al. 2020; Li et al. 2017; Campeau et al. 2012; Davarnia et al. 2024; Brea-Fernández et al. 2019; Klaniewska et al. 2023; Niida et al. 2017; Lonardo et al. 2019; Turkyilmaz and Ozden 2021; Bashir et al. 2017; Clayton-Smith et al. 2011; Ferrando Meseguer et al. 2020; Gannon et al. 2015; Kim et al. 2019; Kim et al. 2017; Knight et al. 2018; Lundsgaard et al. 2017; Marangi et al. 2018; Mendez et al. 2020; Nishimura et al. 2022; Okano et al. 2018; Preiksaitiene et al. 2017; Simpson et al. 2012; Szakszon et al. 2013; Vlckova et al. 2015; Yabumoto et al. 2021; Yang et al. 2022; Yates et al. 2019; Yilmaz et al. 2015; Yu et al. 2014; Zhu et al. 2020; Miller et al. 2023).

Interesting genotype–phenotype correlations have been reported in cases with *KAT6B*-related disorders. In particular, a large number of causative variants in exon 18 are evident (Clayton-Smith et al. 2011). Several molecular-based classifications have been proposed in the literature, defining associations between the localization of the pathogenic variant, the impact on the protein product, and the related phenotypic picture.

In order to highlight the clinical characteristics of these diseases and their genotype–phenotype correlations, a comparison was made between the clinical features of our 7 patients and the 152 patients previously described in 33 papers, with a molecularly confirmed diagnosis (Table 1).

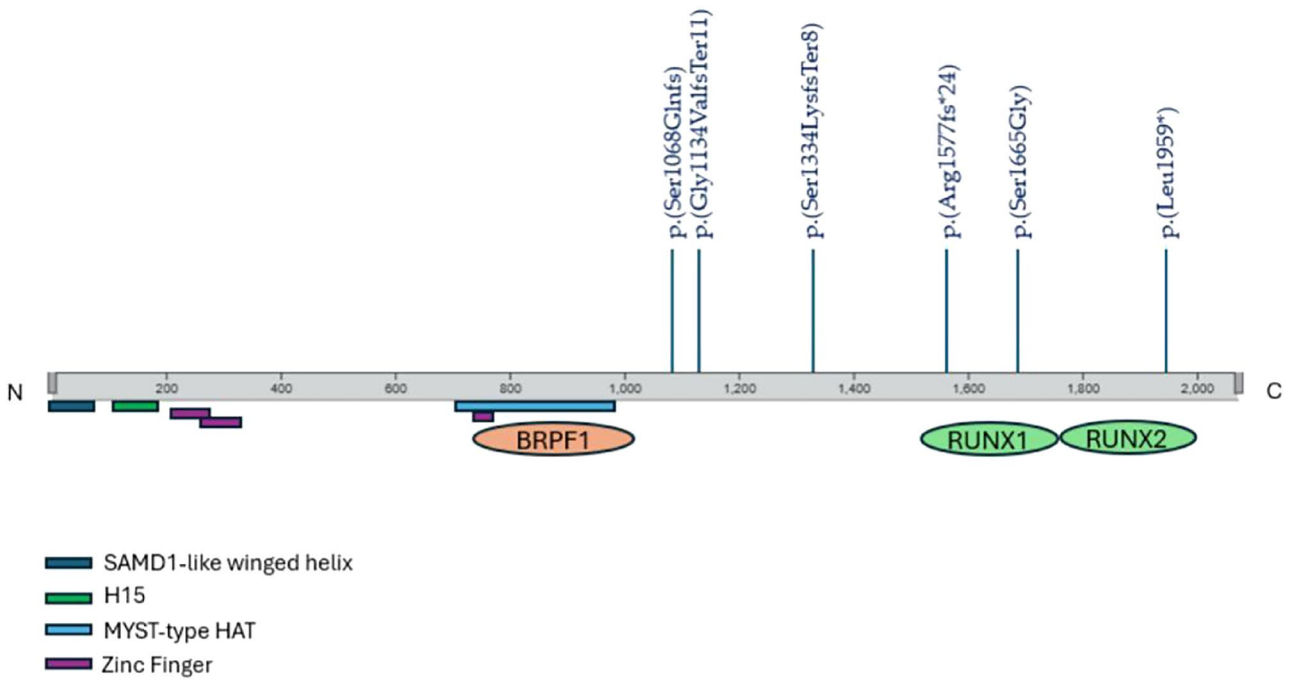

FIGURE 2 | Distribution of pathogenic variants in KAT6B reported in the seven patients of our cohort.

The majority of *KAT6B* pathogenic variants are sporadic, but some cases with familial inheritance have been described (Zhang et al. 2020; Kim et al. 2017; Yates et al. 2019). All seven of our patients had *de novo* variants.

Interestingly, although lacrimal duct abnormalities and patellar hypoplasia/agenesis are considered two SBBYSS main features, they were present in only 19% of the 86 patients with SBBYSS phenotype (Table 1). Moreover, in the 33 previously reported patients diagnosed with GPS, hearing impairment and external auditory canal (EAC) malformations were present in just 3 patients, while lacrimal duct abnormalities were not reported (Table 1).

In this work, we reported the clinical features of seven new patients, four of whom exhibited phenotypic characteristics consistent with SBBYSS (P2, P3, P5, P6), and three patients with an intermediate phenotype (P1, P4, P7).

The prevalence of clinical features of this cohort was largely comparable to that of individuals previously reported in the literature. The typical SBBYSS facies was present in all patients. Intellectual disability and developmental delay were common features. Corpus callosum anomalies were reported only in the P7, with an intermediate phenotype. Hypotonia affected three patients, one with an intermediate phenotype and two with SBBYSS. Contractures were present in one patient with SBBYSS and two with an intermediate phenotype. No patients exhibited renal anomalies, auditory anomalies, or EAC abnormalities. Additionally, we reported clinical features that, to our knowledge, have never been described before in these conditions: penoscrotal transposition and hypopigmented macules.

Genital anomalies are observed in 43% of individuals with SBBYSS and 94% of those with GPS. Specifically, in males, features such as cryptorchidism, retractile testis, scrotal hypoplasia, micropenis, unilateral testicular agenesis, and hypospadias have been described, while in females, clitoromegaly and hypoplasia of the labia minora/majora have been reported, along with a single case of bicornuate uterus (Zhang et al. 2020). P7, showing an intermediate phenotype, was diagnosed with bilateral cryptorchidism, micropenis, hypospadias, and partial penoscrotal transposition, which was addressed with reconstructive surgery at the age of 18 months. Penoscrotal transposition (PST) is a rare congenital anomaly of the genitalia in which the scrotum is positioned superior and anterior to the penis. In complete transposition, the scrotum envelops the penis, which protrudes from the perineum. In the more common incomplete transposition, the penis is positioned centrally within the scrotum (Sexton et al. 2015). It can be accompanied by craniofacial, cardiac, gastrointestinal, urological, central nervous system malformations, and other genital abnormalities (cryptorchidism, hypospadias, penile curvature) (Sexton et al. 2015) This phenotype has been documented in association with several conditions, including Neurocardiofaciodigital syndrome (OMIM # 619869), Silver-Russell syndrome (OMIM # 616489), Simpson-Golabi-Behmel syndrome, Type 1 (OMIM # 312870) and Klinefelter syndrome (Kawakami et al. 2023). This is the first time that penoscrotal transposition has been associated with *KAT6B*-related disorder, suggesting that it may be a rare manifestation of this syndrome.

Cutaneous anomalies are not very common in *KAT6B*-related disorders. Abnormal palmar creases, widely spaced nipples, hypoplastic nails, and café au lait macules have been documented in a small number of affected individuals (Lemire et al. 2012). In our cohort, a single individual had three hypopigmented macules (P3) while another subject presented both hypopigmented and hyperpigmented macules (P7). To the best of our knowledge, these are the first two patients with *KAT6B*-related disorders in whom hypopigmented macules have been described. In this regard, interestingly, in P7, the presence of the c.911G>A variant in heterozygous condition was identified in the *ADAR* gene, which at the protein level results in the amino acid change p.Cys304Tyr. The c.911G>A variant, which arose *de novo*, is not present in the general population frequency database (gnomAD), is not described in the scientific literature, and can be classified according to the ACMG guidelines as a variant of uncertain significance (Richards et al. 2015). Pathogenic variants in the *ADAR* gene are associated with hereditary symmetric dyschromatosis (DSH, OMIM: #127400) in the dominant form. Hereditary symmetric dyschromatosis is characterized by a combination of hypopigmented and hyperpigmented macules, approximately 5 mm in diameter, located on the dorsa of the hands and feet, along with freckle-like macules on the face. Around 70% of affected individuals develop these lesions by the age of 7 (Kono et al. 2016). In our case, the spots were located in the right iliac fossa and therefore were not typical of DSH. However, at present, it cannot be ruled out that this variant may have played a role in the development of these skin dyschromias. Moreover, this finding should be reassessed in our patient, as dyschromias in hereditary symmetric dyschromatosis may appear over time.

In our cohort, five novel variants and two previously reported variants (c.3401del in Patient 1 and c.3202_3203 delAG in Patient 3) were observed.

The c.3401del; p.(Gly1134ValfsTer11) variant in the *KAT6B* gene was absent in GnomAD, and it was noted in ClinVar (ID: 422790). It can be classified as a pathogenic variant according to the ACMG criteria (Richards et al. 2015) and it has been previously reported as a causative variant by Zhang et al. in 2020 in a single patient (subject 19) (Zhang et al. 2020). The clinical features of the two patients were compared in Table S2.

P1 showed hip contractures and genital anomalies, both major diagnostic criteria for GPS, whereas these features were absent in the patient described by Zhang et al. (2020). Despite sharing the same variant, our patient displayed an intermediate phenotype, while Patient 19 presented with a classic SBBYSS phenotype. This observation highlights the *KAT6B*-related Disorders phenotypic variability.

Pathogenic variants in *KAT6B* have been described primarily in exon 18, but have also been reported in exons 3, 4, 7, 11, 14, 15, 16, 17, and in introns 3 and 5 (Zhang et al. 2020; Gannon et al. 2015; Kim et al. 2017; Nishimura et al. 2022; Yates et al. 2019; Yu et al. 2014). The variants were four in exon 18,

two in exon 17, and one in exon 16. In recent years, the *KAT6B* genotype–phenotype correlations have been carefully studied (Radvanszky et al. 2017; Zhang et al. 2020; Vlckova et al. 2015). It has been hypothesized that the SBBYSS and GPS phenotypes result from two different mechanisms. In fact, most pathogenic variants associated with GPS are located proximally in exon 18 and are predicted to escape nonsense-mediated decay, leading to the production of truncated proteins through a gain-of-function mechanism. In contrast, pathogenic variants associated with SBBYSS are more frequently found in the distal regions of exon 18, as well as in exons 3, 7, 11, and 14–17. It has been suggested that these variants determine the phenotype through a haploinsufficiency mechanism (Lemire et al. 2012). In this regard, some authors proposed to subdivide the pathogenic variants into subgroups depending on their position and the related phenotype (Radvanszky et al. 2017; Vlckova et al. 2015).

Of note, Vlckova and colleagues proposed that variants between codons 1 to 1205 were associated with SBBYSS or a milder phenotype (Vlckova et al. 2015). In our case series, two patients had a variant within those codons: P1 (codon 1134) with an intermediate phenotype and P3 (codon 1068) with an SBBYSS phenotype. Furthermore, according to the same authors, intermediate variants (codons 1205–1350) caused a GPS phenotype, whereas Radvanszky and colleagues suggested that GPS variants are concentrated in the region between codons 1208–1321 (end of exon 17 and beginning of exon 18) (Radvanszky et al. 2017; Vlckova et al. 2015). In the present study, P4 carried the variant p.Ser1334LysfsTer8 (codon 1334) and presented with an intermediate phenotype between GPS and SBBYSS. Finally, the group of distal variants located between codons 1520 and 2073 was predominantly associated with SBBYSS. In our specific case, all three patients (P2, P5, P6) with a variant in this interval exhibited an SBBYSS phenotype.

Recently, an episignature was identified in individuals with *KAT6B*-related disorders. The identification of DNA methylation episignatures opens new possibilities for: improving the diagnosis of patients with suspected *KAT6B* variants, providing a supplementary test when genetic analyses are inconclusive, such as in cases involving variants of uncertain significance (VUS), and gaining a better understanding of the epigenetic mechanisms underlying these conditions. This approach could therefore be integrated into clinical protocols to enhance the recognition and management of *KAT6B*-related disorders (Vos et al. 2023).

5 | Conclusion

Here we reported five novel *KAT6B* pathogenic variants and their associated clinical phenotypes. Our findings suggest that hypopigmented macules and partial penoscrotal transposition might represent two new clinical manifestations of the phenotype associated with pathogenic variants in this gene.

The data collected from the analysis of our case series reveal that *KAT6B* variants can often cause an intermediate phenotype between these two clinical entities. The phenotypic spectrum related to causative variants in *KAT6B* is broad, heterogeneous, and some characteristics are partially overlapping, resulting in a challenge during genetic counseling.

Additionally, we compared our findings with the data available in the literature, calculating the frequency of clinical characteristics reported in SBBYSS and GPS. This data may be useful for clinical geneticists in establishing diagnosis, prognosis, and improving clinical management of affected patients, and it can assist in providing accurate genetic counseling. Functional studies are needed to explore the proposed molecular mechanisms underlying KAT6B disorders.

Author Contributions

Vittorio Maglione and Viviana Cardilli contributed to the clinical data collection and elaborated the text. Eleonora Cresta and Gioia Mastromoro contributed to the collection of clinical data. Viviana Cardilli, Paola Favata, Maria Lisa Dentici, Rossella Capolino, Lorenzo Sinibaldi: clinical follow-up. Antonio Novelli and Marco Tartaglia: genetic analyses. Antonio Pizzuti, Gianluca Terrin, Marco Tartaglia, and Maria Cristina Digilio contributed to the final revision and editing of the manuscript. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

Ethics Statement

The parents gave written informed consent, approved by the Ethical Committee of Sapienza University of Rome and Bambino Gesù Children Hospital.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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