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KAT6B Disorders

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Summary

Clinical characteristics

KAT6B disorders include genitopatellar syndrome (GPS) and Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome (SBBYSS) which are part of a broad phenotypic spectrum with variable expressivity; individuals presenting with a phenotype intermediate between GPS and SBBYSS have been reported. Both phenotypes are characterized by some degree of global developmental delay / intellectual disability; hypotonia; genital abnormalities; and skeletal abnormalities including patellar hypoplasia/agenesis, flexion contractures of the knees and/or hips, and anomalies of the digits, spine, and/or ribs. Congenital heart defects, small bowel malrotation, feeding difficulties, slow growth, cleft palate, hearing loss, and dental anomalies have been observed in individuals with either phenotype.

Diagnosis/testing

The diagnosis of a *KAT6B* disorder is established by the identification of a heterozygous pathogenic variant in *KAT6B* on molecular genetic testing.

Management

Treatment of manifestations: Medical problems associated with gastrointestinal, genitourinary, cardiac, palatal or dental anomalies; abnormal vision or lacrimal duct abnormality; hearing loss; or hypothyroidism associated with *KAT6B* disorders are treated or managed in the standard manner by the appropriate specialist. Referral to an early intervention program to access occupational, physical, speech, and feeding therapy beginning in infancy. Orthopedic intervention as needed for contractures and clubfoot; physical therapy to increase joint mobility.

Surveillance: Evaluations of developmental progress and educational needs, assessment for feeding issues, and monitoring for hearing loss, amblyopia, hypothyroidism, and contractures and/or scoliosis should occur annually. Evaluation and monitoring of cardiac malformation and/or renal function (if hydronephrosis or renal cysts are present) as needed.

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Genetic counseling

KAT6B disorders are inherited in an autosomal dominant manner. To date, most individuals with a *KAT6B* disorder have had a *de novo* pathogenic variant. Prenatal and preimplantation genetic testing are possible for families in which the pathogenic variant has been identified.

GeneReview Scope

KAT6B Disorders: Included Phenotypes [1]
• Genitopatellar syndrome (GPS) • Say-Barber-Biesecker variant of Ohdo syndrome (SBBYSS)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

KAT6B disorders include genitopatellar syndrome (GPS) and Say-Barber-Biesecker variant of Ohdo *s*yndrome (*S*ay-*B*arber-*B*iesecker-*Y*oung-*S*impson *s*yndrome; SBYSS).

Suggestive Findings

A *KAT6B* disorder **should be suspected** in individuals with findings of either GPS or SBBYSS.

Genitopatellar syndrome (GPS). While clinical diagnostic criteria have not been defined for genitopatellar syndrome, the authors propose that the following features (Table 1) should raise suspicion for this disorder. Individuals with two major features or one major feature and two minor features are likely to have a *KAT6B* disorder.

Table 1. Features Suggestive of GPS

Category	Features
Major features	• Genital anomalies (females: clitoromegaly &/or hypoplasia of the labia minora or majora; males: cryptorchidism & scrotal hypoplasia) • Patellar hypoplasia/agenesis • Flexion contractures at the hips & knees (incl clubfoot) • Agenesis of the corpus callosum w/microcephaly • Hydronephrosis &/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

Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome (SBBYSS). Clinical criteria for the diagnosis of SBBYSS [White et al 2003] have been expanded by the authors (Table 2) to prompt suspicion of SBBYSS. Individuals with two major features or one major feature and two minor features are likely to have a *KAT6B* disorder.

Table 2. Features Suggestive of Ohdo/SBBYS Syndrome (SBBYSS)

Category	Features
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 &/or delayed eruption of teeth) • Hearing loss • Thyroid anomalies • Cleft palate • Genital anomalies (males: cryptorchidism) • Hypotonia • Global developmental delay / intellectual disability

Establishing the Diagnosis

The diagnosis of a *KAT6B* disorder **is established** in a proband by identification of a heterozygous pathogenic variant in *KAT6B* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *KAT6B* disorders is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of a *KAT6B* disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of a *KAT6B* disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *KAT6B* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *KAT6B* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of a *KAT6B* disorder is not considered because an individual has atypical or nonspecific phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 3. Molecular Genetic Testing Used in *KAT6B* disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KAT6B	Sequence analysis [3]	>98% [4]
	Gene-targeted deletion/duplication analysis [5]	1 deletion reported [6, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gannon et al [2015], Radvanszky et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Preiksaitiene et al [2017] and Herriges et al [2019]) may not be detected by these methods.
6. A 5-Mb 10q22.1q22.3 deletion encompassing *KAT6B* has been described in an individual with a phenotype compatible with SBBYSS [Preiksaitiene et al 2017].
7. Interstitial 10q21.3q22.2 deletions encompassing *KAT6B* have been reported in eight individuals who presented with some features overlapping with *KAT6B* disorders, such as hypotonia, developmental delay, feeding difficulties, and craniofacial dysmorphisms [Herriges et al 2019].

Note: One individual had a "Noonan syndrome-like" phenotype resulting from a translocation interrupting intron 3 of *KAT6B* [Kraft et al 2011].

Clinical Characteristics

Clinical Description

Genitopatellar syndrome (GPS) and Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) are part of a broad phenotypic spectrum, and the variable expressivity of *KAT6B* disorders is being increasingly recognized. Individuals presenting with a phenotype intermediate between GPS and SBBYSS have been reported in the past years.

Genitopatellar Syndrome (GPS)

Skeletal features. Patellae are either absent or hypoplastic in the majority of individuals. In a minority, the patellae are dislocated but not hypoplastic. Note: In normal individuals, the patellae begin ossifying between ages 1.5 and four years in females and ages 2.5 and six years in males. Before that, they are cartilaginous and can be imaged by ultrasound.

Club feet and flexion contractures of the knees and/or hips are also present in nearly all individuals with GPS and constitute major features of this syndrome. This can significantly hinder mobility, especially since the knees in some cases cannot be extended beyond 90 degrees. Most of the musculoskeletal findings in GPS involve the lower extremities, but contractures of the wrists or elbows have also been observed in two affected individuals [Authors, personal observation].

Other skeletal anomalies are occasionally seen in affected individuals. Spinal anomalies resulting in thoracolumbar kyphoscoliosis have been observed in 11% of individuals reported in the literature. Some have thoracic anomalies such as narrow thorax, pectus excavatum, the presence of small cervical ribs, absence of a pair of ribs, and clavicular exostoses.

Pelvic anomalies include hip dislocations and hypoplasia of the iliac bone, ischia, and pubic rami.

Rare musculoskeletal findings include osteoporosis, radioulnar synostosis, radial head deformity, brachydactyly, camptodactyly, short stature, joint laxity, undertubulation of long bones, and coxa vara.

Neurologic features. Developmental delay and/or intellectual disability are noted in nearly all individuals diagnosed to date. The delay is global (motor and intellectual) and usually severe; some can communicate through vocalization, manipulate objects, and ambulate with walkers or tricycles. Behavioral and/or psychiatric issues (e.g., features suggestive of autism spectrum disorder, anxiety, aggressive behavior, and attention problems) have been noted.

Nearly all individuals with GPS have agenesis or hypoplasia of the corpus callosum. Seizures, cortical malformations, hydrocephaly, or ventriculomegaly have also been described in some affected individuals.

Some have hypotonia at birth, resulting in respiratory and feeding difficulties that can require invasive procedures (see Management). Laryngomalacia may exacerbate these difficulties. Both the feeding and respiratory difficulties often resolve in infancy; hypotonia of the extremities with hypertonia of the trunk has been described in older children.

Most have microcephaly, with occipitofrontal circumferences (OFCs) typically 2 SD (and occasionally 3 SD) below the mean.

Genital anomalies. Genitourinary anomalies are frequently present in individuals affected by GPS. In males, this can include cryptorchidism, retractile testis, scrotal hypoplasia, micropenis, unilateral testicular agenesis and hypospadias. Most females have clitoromegaly and/or hypoplasia of the labia (minora or majora). Delayed puberty with primary amenorrhea has also been reported [Okano et al 2018].

Renal anomalies. Many individuals affected by GPS have renal anomalies, especially hydronephrosis and multicystic kidneys. Renal anomalies resulting in renal failure and oligohydramnios sequence have been observed in three affected individuals who died in the neonatal period [Kim et al 2019; Authors, personal observation].

Anal anomalies. Anal atresia or stenosis and an anteriorly positioned anus are occasionally seen in GPS.

Facial features. Individuals with GPS can have bitemporal narrowing, prominent eyes (proptosis), and a nose with either a bulbous end or a broad or prominent base. Other features that can be common in both GPS and

SBBYSS include low-set and posteriorly rotated ears, prominent cheeks, downslanting palpebral fissures, flat broad nasal bridge, long philtrum, thin upper lip, thin lip vermilion, and micro/retrognathia. See Figure 1.

Cancer. Knight et al reported a child with GPS who developed a stage one neuroblastoma extending into the portal vein. While it was poorly differentiated, it had an overall favorable histopathology [Knight et al 2018].

Say-Barber-Biesecker-Young-SImpson Variant of Ohdo Syndrome (SBBYSS)

Neurologic features. Affected individuals generally have some degree of developmental delay and/or intellectual disability. Milder cases have recently been described, where the pathogenic variant was inherited from an affected parent [Kim et al 2017, Yates et al 2019]. A language disorder is present in many affected individuals. Behavioral and/or psychiatric issues such as features suggestive of autism spectrum disorder, anxiety, aggressive behavior, and attention problems have been noted. A few affected individuals have agenesis or hypoplasia of the corpus callosum or other cerebral anomalies. 36% of reported cases have microcephaly.

Some neonates have hypotonia, with feeding and respiratory difficulties requiring hospitalization.

Ocular anomalies. Visual deficits and a variety of ocular anomalies have been reported in a large number of affected individuals. Blepharophimosis is a major feature of SBBYSS and it can impact visual function. Lacrimal duct anomalies, mainly dacryostenosis, are found in many individuals with SBBYSS and with an intermediate phenotype. Cortical visual impairment, optic atrophy or hypoplasia has also been described. Myopia and amblyopia are common. Telecanthus, epicanthus inversus, and hypertelorism are also sometimes noted

Skeletal features. Most individuals have long thumbs and great toes. Other digital malformations have been observed, including preaxial or postaxial polydactyly, camptodactyly, clinodactyly, bradydactyly, and syndactyly of toes. Some have patellar anomalies similar to those seen in GPS (i.e., aplasia or hypoplasia). Club feet and flexion contractures of the knees and/or hips are occasionally observed in some individuals.

Genital anomalies. Genital anomalies including cryptorchidism, hypospadias, clitoromegaly, and/or hypoplasia of the labia minora or majora are observed in approximately 40% of reported affected individuals with the SBBYSS phenotype.

Facial features. Facial appearance is distinctive with a mask-like facies, blepharophimosis, and ptosis. Other features that can be common in both GPS and SBBYSS include prominent cheeks, low-set and posteriorly rotated ears, downslanting palpebral fissures, flat broad nasal bridge, tubular/bulbous nose, long philtrum, thin upper lip, thin lip vermilion, and micro-/retrognathia. See Figure 1.

Other Features Observed in Individuals with Either the GPS or SBBYSS Phenotype

More than 50% of individuals with *KAT6B* disorders have congenital heart defects. These include mainly atrial and/or ventricular septal defects, patent foramen ovale and patent ductus arteriosus.

Small bowel malrotation has been described in eight affected individuals [Campeau et al 2012a; Gannon et al 2015; Okano et al 2018; Authors, personal observation].

Most affected individuals present with feeding difficulties and pathologic gastroesophageal reflux.

Growth restriction, short stature, failure to thrive/poor weight gain and delayed bone age have been reported in 18% of affected individuals.

Cleft palate has been reported in one third of affected individuals [Clayton-Smith et al 2011]. Pierre Robin sequence (defined as microretrognathia, glossoptosis, and cleft palate) has previously been observed in five affected individuals [Lonardo et al 2019; Authors, personal observation].

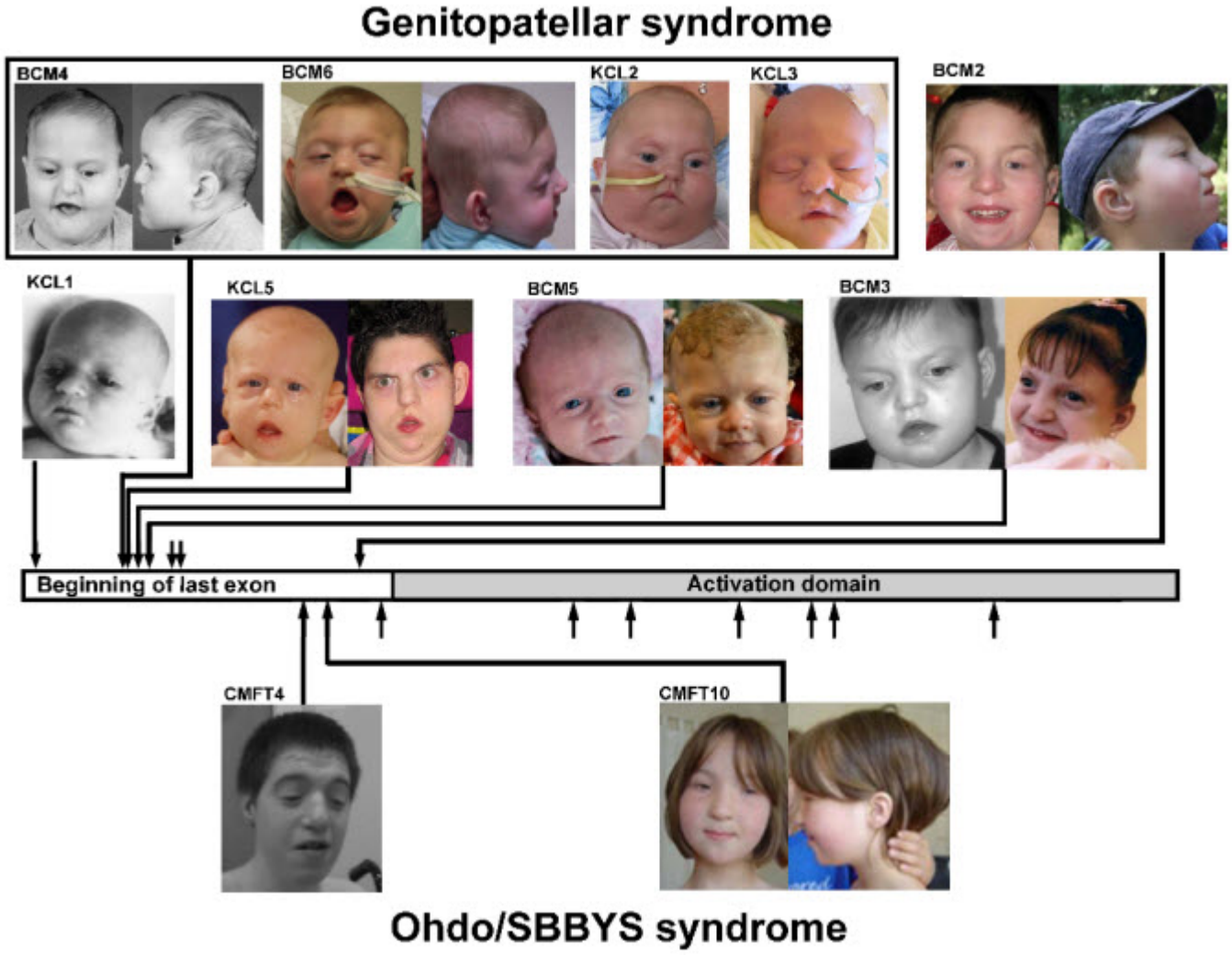

Figure 1. Photographs of 11 individuals with a *KAT6B* pathogenic variant

Arrows point to the relative location of an individual's pathogenic variant in the schematic of the last *KAT6B* exon (exon 18), the distal part of which encodes the activation domain. Photographs and arrows above the exon schematic are for GPS and those below are for SBBYSS. The four individuals with GPS included within the black box have the same pathogenic variant (Lys1258GlyfsTer13). Short arrows indicate pathogenic variants in individuals not pictured.

Note: Alphanumeric designations above each photograph identify the institution of the author who described the pathogenic variant and the author's order in the publication originally describing the pathogenic variant. These identifiers are also used in the *KAT6B* mutation database (www.LOVD.nl/*KAT6B*).

Reprinted from Campeau et al [2012b] with permission from the publisher

Bilateral hearing loss, both conductive and sensorineural, is often present.

Occasional dental anomalies including natal teeth, absent/hypoplastic teeth, retained primary dentition, and delayed eruption of teeth are mostly seen in in individuals with SBBYSS.

A minority of individuals have hypothyroidism – some of them having thyroid agenesis or hypoplasia.

Polyhydramnios can complicate the pregnancy of fetuses affected with *KAT6B* disorders. Increased nuchal translucency and/or cystic hygroma have also been observed in four affected individuals [Authors, personal observation].

Sagittal craniosynostosis was noted in two individuals with the intermediate phenotype [Bashir et al 2017]

Cutaneous manifestations are rarely observed in individuals with *KAT6B* disorders. Abnormal palmar creases, widely spaced nipples, hypoplastic nails, and café au lait macules have been reported in a few affected individuals.

Genotype-Phenotype Correlations

GPS. Most GPS-associated pathogenic variants cluster in *KAT6B* exon 18, the last exon, and are predicted to produce truncated proteins associated with a gain-of-function mechanism (see Molecular Genetics). Consistent with this hypothesis, pathogenic variants associated with more severe GPS phenotypes are located more proximally in exon 18 and are predicted to result in a more truncated protein.

SBBYSS. SBBYS-causing pathogenic variants also occur most frequently in exon 18, but more distally than the GPS-associated variants (Figure 1). Recently, predicted loss-of-function variants in exons 3, 7, 11, and 14-17 were reported to be associated with the SBBYSS phenotype.

Penetrance

Penetrance appears to be complete since all individuals reported to date who carry a *KAT6B* pathogenic variant present a phenotype compatible with *KAT6B* disorders.

Nomenclature

GPS. The term "genitopatellar syndrome" was coined by Valérie Cormier-Daire [Cormier-Daire et al 2000].

SBBYSS. Ohdo et al [1986] first described a family in which children had blepharophimosis, ptosis, congenital heart defects, intellectual disability, and hypoplastic teeth.

Subsequently, the Young-Simpson syndrome was described [Young & Simpson 1987]. Later the Young-Simpson syndrome was renamed the Say-Barber-Biesecker-Young-Simpson (SBBYS) variant of Ohdo syndrome (SBBYSS) [Say & Barber 1987, Biesecker 1991], which is discussed in this *GeneReview*.

Of note, the disorder described by Ohdo was distinct from the SBBYS variant of Ohdo syndrome because the facial features differed, proteinuria was present, and skeletal anomalies were absent; the mode of inheritance appeared to be autosomal recessive, autosomal dominant with reduced penetrance, or multifactorial.

Prevalence

The prevalence of *KAT6B* disorders is not known, but is estimated at fewer than one in a million individuals. To date, 89 individuals with molecularly confirmed *KAT6B* disorders have been reported in the literature, including 18 with GPS, 58 with SBBYSS, and 13 described as having an intermediate phenotype.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *KAT6B*.

Differential Diagnosis

Table 4. Genes of Interest in the Differential Diagnosis of *KAT6B* Disorders

Gene(s)	Differential Diagnosis Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*KAT6B* Disorders	Not Observed in *KAT6B* Disorders
CDC45 *CDC6* *CDT1* *GMNN* *ORC1* *ORC4* *ORC6*	Meier-Gorlin syndrome (OMIM PS224690)	AR (AD)	Patellar aplasia or hypoplasia; microcephaly; genital anomalies; contractures	Severe intrauterine & postnatal growth restriction; bilateral microtia
ERCC6 *ERCC8*	Cerebrooculofacioskeletal syndrome (severe fetal form of Cockayne syndrome)	AR	Arthrogryposis; microcephaly; severe ID	Progressive neurodegenerative disorder; congenital cataracts & facial dysmorphism
FBN2	Congenital contractural arachnodactyly	AD	Congenital contractures	Marfanoid habitus; aortic root dilatation; arachnodactyly; hypoplastic calf muscles
FOXL2	Blepharophimosis, ptosis, epicanthus inversus syndrome [1]	AD [2]	Blepharophimosis & ptosis	Epicanthus inversus (a fold of skin that runs from the lower lids inwards & upwards)
LMX1B	Nail-patella syndrome	AD	Absent patella; renal anomalies; flexion deformities of knees & hips, clubfoot	Proteinuria; open-angle glaucoma; nail changes
RECQL4	RAPADILINO syndrome (OMIM 266280)	AR	Patellar hypoplasia; hearing loss; cleft palate	Irregular pigmentation w/café au lait spots; normal intelligence; palate defects; radial ray defects; GI abnormalities
TBX4	Ischiocoxopodopatellar syndrome (OMIM 147891)	AD	Patellar aplasia or hypoplasia	Absent, delayed, or irregular ossification of the ischiopubic junctions or infraacetabular axe-cut notches
ZEB2	Mowat-Wilson syndrome	AD [3]	Agenesis of the corpus callosum; genital anomalies; ID; congenital heart disease; microcephaly	Seizures; Hirschsprung disease; short stature

AD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Blepharophimosis, ptosis, epicanthus inversus syndrome type II is isolated; type I is associated with premature ovarian insufficiency.

2. Blepharophimosis, ptosis, epicanthus inversus syndrome is usually inherited in an autosomal dominant manner; autosomal recessive inheritance has been reported in one consanguineous family.

3. Mowat-Wilson syndrome is typically the result of a *de novo* dominant pathogenic variant.

Other Disorders to Consider in the Differential Diagnosis

Dubowitz syndrome (OMIM 223370) is an autosomal recessive disorder of uncertain etiology consisting of blepharophimosis, ptosis, microcephaly, intellectual disability, growth restriction, and eczema (features variably present) [Tsukahara & Opitz 1996]. A Dubowitz-like syndrome was reported in a single family in association with biallelic pathogenic variants in *NSUN2* [Martinez et al 2012].

Fetal alcohol spectrum disorders (FASD) associated with in utero alcohol can include blepharophimosis with short palpebral fissures, flat midface, long and smooth philtrum, thin vermilion of the upper lip, microcephaly,

and intellectual disability. Various degrees and combinations of these features, along with a variety of birth defects, may be present in individuals with FASD. Affected individuals tend to have severe pre- and postnatal growth restriction, a finding more rarely observed in *KAT6B* disorders.

Toriello-Carey syndrome (agenesis of the corpus callosum with facial anomalies and Pierre Robin sequence) (OMIM 217980) shows multiple elements of overlap with *KAT6B* disorders: hypotonia, genital anomalies, microcephaly, agenesis of the corpus callosum, cleft palate, growth restriction, developmental delay and intellectual disability, ptosis, and congenital heart defects. Of note, Pierre Robin sequence is described as a cardinal manifestation of this disorder, whereas this sequence has been reported only in a small number of individuals with *KAT6B* disorders. However, Toriello-Carey syndrome is etiologically heterogeneous as different genetic alterations have been identified in individuals who are clinically suspected of having this disorder (various chromosomal deletions and pathogenic variants in *PGAP3*, *DDX3X*, and *UBE3B*). In one individual, a deleterious *KAT6B* variant has been identified [Dr John Carey, personal communication].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *KAT6B* disorders, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *KAT6B* Disorders

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	EEG if clinical suspicion of seizures	
	Assessment of corpus callosum anomalies & other cerebral malformations	Brain MRI
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in patients w/dysphagia &/or aspiration risk.
	Evaluate for anal anomalies.	
	If clinical suspicion of malrotation, perform appropriate imaging. [1]	
Cardiovascular	Eval by cardiologist for cardiovascular malformation	Include echocardiogram
Genitourinary	Evaluate for genital anomalies in both males & females.	
	Evaluate for hydronephrosis, cysts or other renal anomalies.	Renal ultrasound
Hearing	Assess for hearing loss.	Audiologic eval
Ocular	Assess lacrimal duct abnormalities, blepharophimosis, optic nerve anomalies, myopia, & amblyopia.	Ophthalmologic eval
Endocrine	Assess thyroid function.	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Eval of contractures or malposition of knees/ feet/ankles & upper limbs	Orthopedic eval if needed
	Eval of pelvic, spinal, or thoracic anomalies	X-rays could be considered to complement clinical exam.
Respiratory	Evaluate for laryngomalacia.	
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

1. Further evidence of utility is required prior to recommending screening of all individuals with *KAT6B* disorder for small bowel malrotation with a barium enema study.

Treatment of Manifestations

Medical problems associated with gastrointestinal, genitourinary, cardiac, palatal, or dental anomalies; abnormal vision or lacrimal duct abnormality; hearing loss; or hypothyroidism associated with *KAT6B* disorders are treated or managed in the standard manner by the appropriate specialist. Other recommended treatments are listed below.

Table 6. Treatment of Manifestations in Individuals with *KAT6B* Disorders

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding evaluation &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Contractures	Orthopedics / physical medicine & rehabilitation / PT / OT incl surgical release of contractures, stretching to increase joint mobility	Consider need for positioning & mobility devices, disability parking placard.
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

Developmental Disability / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or

cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-

generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder (ADHD), when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 7. Recommended Periodic Surveillance for Individuals with *KAT6B* Disorders

System/Concern	Evaluation [1]
Development	Monitor developmental progress & educational needs.
Neurologic	EEG if clinical suspicion of seizures
Gastrointestinal	Evaluation of feeding & symptoms suggestive of small bowel malrotation
Cardiovascular	Follow up w/cardiologist if cardiac malformation present
Genitourinary	Renal function (if hydronephrosis or multiple renal cysts are present)
Hearing	Monitor for hearing loss.
Ocular	Evaluate for amblyopia.
Endocrine	Thyroid function
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills
	Follow up for scoliosis if vertebral anomalies are present

OT = occupational therapy; PT = physical therapy
1. Annual or as needed

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

KAT6B disorders including genitopatellar syndrome (GPS) and Say-Barber-Biesecker variant of Ohdo syndrome (SBBYSS) are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with a *KAT6B* disorder have a *de novo* pathogenic variant.
- An individual diagnosed with a *KAT6B* disorder had an affected parent in at least three families.
  - Transmission of a *KAT6B* pathogenic variant in three generations of a family with SBBYSS has been reported [Kim et al 2017].
  - An inherited pathogenic variant has been found in individuals with mild SBBYSS phenotypes [Yates et al 2019; Authors, personal observation]
  - A woman with relatively mild SBBYSS had a child with classic SBBYSS [Mhanni et al 1998]; however, to the authors' knowledge molecular testing has not been performed in this family.
- If a *KAT6B* pathogenic variant has been identified in a proband, molecular genetic testing is recommended for the parents of the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *KAT6B* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with a *KAT6B* disorder has a 50% chance of inheriting the *KAT6B* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *KAT6B* pathogenic variant, members of the parent's family may also be heterozygous for the pathogenic variant.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence

of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to couples who have had a child with a *KAT6B* disorder and young adults who are more mildly affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *KAT6B* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for a *KAT6B* disorder are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Ohdo syndrome, Say-Barber-Biesecker-Young-Simpson variant
- **National Library of Medicine Genetics Home Reference**
  Genitopatellar syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. KAT6B Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KAT6B	10q22.2	Histone acetyltransferase KAT6B	KAT6B@LOVD Lee Lab(KAT6B)	KAT6B	KAT6B

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for KAT6B Disorders (View All in OMIM)

603736	OHDO SYNDROME, SBBYS VARIANT; SBBYSS
605880	LYSINE ACETYLTRANSFERASE 6B; KAT6B
606170	GENITOPATELLAR SYNDROME; GTPTS

Molecular Pathogenesis

KAT6B encodes the highly conserved histone acetyltransferase KAT6B, which functions in a multi-subunit complex with other proteins including KAT6A, BRPF1, and ING5 [Yang 2015]. KAT6B chromatin remodeling through histone acetylation regulates the expression of multiple genes [Doyon et al 2006, Kraft et al 2011].

Mechanism of disease causation. GPS and SBBYSS are hypothesized to occur through a gain-of-function and loss-of-function disease mechanism, respectively. Pathogenic variants, which include nonsense, missense, splice site, and predicted frameshift variants, are most often located in exon 18, the last exon of the gene.

- **GPS.** Most pathogenic variants causing GPS cluster in *KAT6B* exon 18, the last exon, and are predicted to escape nonsense-mediated decay, resulting in a truncated protein causing disease via a gain-of-function mechanism. Consistent with this hypothesis, pathogenic variants causing the more severe GPS phenotype are located proximally in exon 18 and are believed to lead to the expression of a truncated protein lacking less of the C-terminal domain. A gain-of-function effect was hypothesized to occur from altered binding affinity or dysregulated interactions of KAT6B with its natural binding partners. This has not yet been tested experimentally.
- **SBBYSS.** SBBYSS-causing pathogenic variants occur throughout the gene are hypothesized to be loss-of-function variants. SBBYSS-associated variants occur most frequently in exon 18, but more distally than the GPS-associated variants (Figure 1). In addition, more proximal disease-associated variants in exons 3, 7, 11, and 14-17 have also been reported. The SBBYSS phenotype is hypothesized to result from the loss of KAT6B functions. This has not yet been tested experimentally.

***KAT6B*-specific laboratory technical considerations.** *KAT6B* comprises 18 exons, the first two of which are untranslated. Three protein isoforms exist owing to alternative splice donor sites used for exon 8. NM_012330.3 represents the longest transcript and encodes the longest isoform.

Table 8. Notable *KAT6B* Pathogenic Variants

	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
Variants associated w/GPS	NM_012330.3 NP_036462.2	c.3769_3772delTCTA	p.Lys1258GlyfsTer13	Common pathogenic variant reported in 5 persons [Campeau et al 2012b, Simpson et al 2012, Gannon et al 2015]
Variants associated w/SBBYSS		c.5201_5210dup	p.Gln1737HisfsTer41	Common pathogenic variant reported in 2 persons w/SBBYSS [Clayton-Smith et al 2011] & in 1 individual w/an intermediate phenotype [Niida et al 2017]
		c.3147G>A	p.Pro1049=	Common pathogenic variant affecting splicing reported in 6 persons [Gannon et al 2015, Yilmaz et al 2015]
		c.2299C>T	p.His767Tyr	Pathogenic variant reported in 3 family members, transmitted by an affected parent [Kim et al 2017]
		c.4205_4206delCT	p.Ser1402CysfsTer5	Common pathogenic variant reported in 4 persons w/SBBYSS [Clayton-Smith et al 2011, Gannon et al 2015] & in 2 individuals w/an intermediate phenotype [Gannon et al 2015, Bashir et al 2017]

Table 8. continued from previous page.

	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
		c.5389C>T	p.Arg1797Ter	Common pathogenic variant reported in 6 persons [Clayton-Smith et al 2011, Szakszon et al 2013, Gannon et al 2015]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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Chapter Notes

Author Notes

Dr Brendan Lee's website

Dr Philippe Campeau's website

About the Authors' research. The spectrum of our research program extends from gene identification in human disease, to correlating mechanisms of disease with normal biologic processes, to measuring and manipulating these pathways for diagnosis and treatment in humans and in animal models.

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- 2 January 2020 (ha) Comprehensive update posted live
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