

Say-Barber-Biesecker Syndrome

<https://www.ncbi.nlm.nih.gov/books/NBK114806/>

SummaryClinical 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.**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.

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GeneReview ScopeView in own windowKAT6B Disorders: Included

Phenotypes 1Genitopatellar 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.

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DiagnosisKAT6B disorders include genitopatellar syndrome (GPS) and Say-Barber-Biesecker variant of Ohdo syndrome (Say-Barber-Biesecker-Young-Simpson syndrome; SBYSS).Suggestive

FindingsA 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.

Category	Features
Major features	Genital anomalies (females: clitoromegaly &/or hypoplasia of the labia minora or majora; males: cryptorchidism & scrotal hypoplasia)Patellar hypoplasia/agenesisFlexion contractures at the hips & knees (incl clubfoot)Agenesis of the corpus callosum w/microcephalyHydronephrosis &/or multiple renal cysts
Minor features	Congenital heart defectDental anomalies (delayed eruption of teeth)Hearing lossThyroid anomaliesAnal anomaliesHypotoniaGlobal developmental delay / intellectual disability

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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.

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Syndrome (SBBYSS)

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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 View in own

window

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

KAT6B

Sequence analysis

deletion reported

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].

Suggestive FindingsA 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**
View in own window

CategoryFeatures

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 defectDental anomalies (delayed eruption of teeth)Hearing lossThyroid

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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

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Table 2. Features Suggestive of Ohdo/SBBYS

Syndrome (SBBYSS)View in own windowCategoryFeatures

Major features

Long thumbs / great toesImmobile mask-like faceBlepharophimosis/ptosisLacrimal duct

anomaliesPatellar hypoplasia/agenesis

Minor features

Congenital heart defectDental anomalies (hypoplastic teeth &/or delayed eruption of teeth)Hearing

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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

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KAT6B

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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].

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KAT6B		
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Sequence analysis	>98%	Gene-targeted deletion/duplication analysis
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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

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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. 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 (more...) 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, brachydactyly, 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]. 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 individuals with SBBYSS. A minority of individuals

have hypothyroidism [11]; 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.

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. 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 (more...) 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

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[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.

PrevalenceThe 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) DisordersNo phenotypes other than those discussed in this GeneReview are known to be associated with mutation of KAT6B.

Differential DiagnosisTable 4. Genes of Interest in the Differential Diagnosis of KAT6B DisordersView in own windowGene(s)Differential Diagnosis DisorderMOIClinical Features of Differential Diagnosis DisorderOverlapping w/KAT6B DisordersNot 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; contracturesSevere intrauterine & postnatal growth restriction; bilateral microtia

ERCC6

ERCC8

Cerebrooculofacioskeletal syndrome (severe fetal form of Cockayne syndrome)ARArthrogryposis; microcephaly; severe IDProgressive neurodegenerative disorder; congenital cataracts & facial dysmorphism

FBN2

Congenital contractural arachnodactyly

ADCongenital contracturesMarfanoid habitus; aortic root dilatation; arachnodactyly; hypoplastic calf muscles

FOXL2

Blepharophimosis, ptosis, epicanthus inversus syndrome 1AD 2Blepharophimosis & ptosisEpicanthus 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 ax-cut notches

ZEB2

Mowat-Wilson syndrome

AD 1603 Agnesis 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].

Table 4. Genes of Interest in the Differential Diagnosis of KAT6B DisordersView in own windowGene(s)Differential Diagnosis DisorderMOIClinical Features of Differential Diagnosis DisorderOverlapping w/KAT6B DisordersNot Observed in KAT6B Disorders

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RAPADILINO syndrome (OMIM 266280)ARPatellar hypoplasia; hearing loss; cleft palateIrregular pigmentation w/café au lait spots; normal intelligence; palate defects; radial ray defects; GI

abnormalities

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Mowat-Wilson syndrome

AD 3Agenesis of the corpus callosum; genital anomalies; ID; congenital heart disease; microcephalySeizures; Hirschsprung disease; short statureAD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked1. 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.

Genes of Interest in the Differential Diagnosis of KAT6B Disorders

Gene(s)	Differential Diagnosis Disorder	MOI	Clinical Features of Differential Diagnosis
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Disorder	Overlapping w/KAT6B Disorders	Not Observed in KAT6B Disorders
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Blepharophimosis, ptosis, epicanthus inversus syndrome is usually inherited in an autosomal dominant manner; autosomal recessive inheritance has been reported in one consanguineous family.

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 View in own window
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.

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 View in own window 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 ConcernsChildren 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 View in own window System/ConcernEvaluation 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.

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

View in own window

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.

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.

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.

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

Disorders View in own window 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

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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 counselorTo incl genetic counseling1. 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.

Recommended Evaluations Following Initial Diagnosis in Individuals with KAT6B Disorders

System/Concern	Evaluation	Comment
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Development

Developmental assessment	To incl motor, adaptive, cognitive, & speech-language eval	Eval for early intervention / special education
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Neurologic

EEG if clinical suspicion of seizures	Assessment of corpus callosum anomalies & other cerebral malformations	Brain MRI
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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.
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Eval by cardiologist for cardiovascular malformation	Include echocardiogram
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Genitourinary

Evaluate for genital anomalies in both males & females.	Evaluate for hydronephrosis, cysts or other renal anomalies.	Renal ultrasound
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Hearing

Assess for hearing loss.	Audiologic eval
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Assess lacrimal duct abnormalities, blepharophimosis, optic nerve anomalies, myopia, & amblyopia. Ophthalmologic eval

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Evaluate for laryngomalacia.

Miscellaneous/

Other

Consultation w/clinical geneticist &/or genetic counselor To incl genetic counseling

To incl motor, adaptive, cognitive, & speech-language eval

Eval for early intervention / special education

To incl eval of aspiration risk & nutritional status

Consider eval for gastrostomy tube placement in patients w/dysphagia &/or aspiration risk.

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.

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Treatment of ManifestationsMedical 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

View in own window	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
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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.

Table 6. Treatment of Manifestations in Individuals with KAT6B Disorders

View in own window

Manifestation/Concern	Treatment	Considerations/Other
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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

Treatment of Manifestations in Individuals with KAT6B Disorders

Manifestation/Concern Treatment Considerations/Other

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See Developmental Delay / Intellectual Disability Management Issues.

Poor weight

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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.

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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,

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Surveillance Table 7. Recommended Periodic Surveillance for Individuals with KAT6B Disorders View in own window 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

Table 7. Recommended Periodic Surveillance for Individuals with KAT6B Disorders
View in own window
System/Concern
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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.

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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

National Library of Medicine Genetics Home Reference

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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 DatabasesView in own windowGeneChromosome

LocusProteinLocus-Specific DatabasesHGMDClinVar

KAT6B

10q22​.2

Histone acetyltransferase KAT6B

KAT6B@LOVDLee 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) View in own window

603736OHDO SYNDROME, SBBYS VARIANT; SBBYSS

605880LYSINE ACETYLTRANSFERASE 6B; KAT6B

606170GENITOPATELLAR SYNDROME; GTPTSMolecular PathogenesisKAT6B 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 VariantsView in own windowReference SequencesDNA NucleotideChangePredicted ProteinChangeComment [Reference]

Variants associated w/GPS

NM_012330​.3

NP_036462​.2

c.3769_3772delTCTAp.Lys1258GlyfsTer13Common pathogenic variant reported in 5 persons

[Campeau et al 2012b, Simpson et al 2012, Gannon et al 2015]

Variants associated w/SBBYSS

c.5201_5210dupp.Gln1737HisfsTer41Common 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>Ap.Pro1049=Common pathogenic variant affecting splicing reported in 6 persons

[Gannon et al 2015, Yilmaz et al 2015]c.2299C>Tp.His767TyrPathogenic variant reported in 3 family

members, transmitted by an affected parent [Kim et al

2017]c.4205_4206delCTp.Ser1402CysfsTer5Common 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]c.5389C>Tp.Arg1797TerCommon 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.

Table A.KAT6B Disorders: Genes and DatabasesView in own windowGeneChromosome

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Variants associated w/SBBYSS

c.5201_5210dupp.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>Ap.Pro1049= Common pathogenic variant affecting splicing reported in 6 persons [Gannon et al 2015, Yilmaz et al 2015] c.2299C>Tp.His767Tyr Pathogenic variant reported in 3 family members, transmitted by an affected parent [Kim et al 2017] c.4205_4206delCTp.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] c.5389C>Tp.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.

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.

Table 8. Notable KAT6B Pathogenic Variants			
	View in own window	Reference Sequences	DNA
Nucleotide	Change	Predicted Protein	Change
Comment [Reference]			
Variants associated w/GPS			
NM_012330​.3			
NP_036462​.2			
c.3769_3772delTCTAp.Lys1258GlyfsTer13Common pathogenic variant reported in 5 persons [Campeau et al 2012b, Simpson et al 2012, Gannon et al 2015]			
Variants associated w/SBBYSS			
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c.3147G>Ap.Pro1049=Common pathogenic variant affecting splicing reported in 6 persons			

[Gannon et al 2015, Yilmaz et al 2015]c.2299C>Tp.His767TyrPathogenic variant reported in 3 family members, transmitted by an affected parent [Kim et al 2017]c.4205_4206delCTp.Ser1402CysfsTer5Common 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]c.5389C>Tp.Arg1797TerCommon 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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ReferencesLiterature CitedBashir RA, Dixit A, Goedhart C, Parboosingh JS, Innes AM, Ferreira P, Au PB. Lin-Gettig syndrome: Craniosynostosis expands the spectrum of the KAT6B related disorders. Am J Med Genet A. 2017;173:2596–604. [PubMed: 28696035]Biesecker LG. The Ohdo blepharophimosis syndrome: a third case. J Med Genet. 1991;28:131–4. [PMC free article: PMC1016784] [PubMed: 2002485]Campeau PM, Kim JC, Lu JT, Schwartzentruber JA, Abdul-Rahman OA, Schlaubitz S, Murdock DM, Jiang MM, Lammer EJ, Enns GM, Rhead WJ,

Rowland J, Robertson SP, Cormier-Daire V, Bainbridge MN, Yang XJ, Gingras MC, Gibbs RA, Rosenblatt DS, Majewski J, Lee BH. Mutations in KAT6B, encoding a histone acetyltransferase, cause genitopatellar syndrome. *Am J Hum Genet.* 2012a;90:282-291. [PMC free article: PMC3276659] [PubMed: 22265014]

Campeau PM, Lu JT, Dawson BC, Fokkema IF, Robertson SP, Gibbs RA, Lee BH. The KAT6B-related disorders Genitopatellar syndrome and Ohdo/SBBYS syndrome have distinct clinical features reflecting distinct molecular mechanisms. *Hum Mutat.* 2012b;33:1520-1528. [PMC free article: PMC3696352] [PubMed: 22715153]

Clayton-Smith J, O'Sullivan J, Daly S, Bhaskar S, Day R, Anderson B, Voss AK, Thomas T, Biesecker LG, Smith P, Fryer A, Chandler KE, Kerr B, Tassabehji M, Lynch SA, Krajewska-Walasek M, McKee S, Smith J, Sweeney E, Mansour S, Mohammed S, Donnai D, Black G. Whole-exome-sequencing identifies mutations in histone acetyltransferase gene KAT6B in individuals with the Say-Barber-Biesecker variant of Ohdo syndrome. *Am J Hum Genet.* 2011;89:675-681. [PMC free article: PMC3213399] [PubMed: 22077973]

Cormier-Daire V, Chauvet ML, Lyonnet S, Briard ML, Munnich A, Le Merrer M. Genitopatellar syndrome: a new condition comprising absent patellae, scrotal hypoplasia, renal anomalies, facial dysmorphism, and mental retardation. *J Med Genet.* 2000;37:520-524. [PMC free article: PMC1734629] [PubMed: 10882755]

Doyon Y, Cayrou C, Ullah M, Landry AJ, Cormier-Daire V, Selleck W, Lane WS, Tan S, Yang XJ, Clayton-Smith J. ING tumor suppressor proteins are critical regulators of chromatin acetylation required for genome expression and perpetuation. *Mol Cell.* 2006;21:51-64. [PubMed: 16387653]

Gannon T, Perveen R, Schlecht H, Ramsden S, Anderson B, Kerr B, Clayton-Smith J. Further delineation of the KAT6B molecular and phenotypic spectrum. *Eur J Hum Genet.* 2015;23:1165-1170. [PMC free article: PMC4351891] [PubMed: 25424711]

Herriges JC, Dugan SL, Lamb AN. Clinical and molecular cytogenetic characterization of a novel 10q interstitial deletion: a case report and review of the literature. *Mol Cytogenet.* 2019;12:20. [PMC free article: PMC6525357] [PubMed: 31131026]

Kim BR, Han JH, Shin JE, Park MS, Park KI, Namgung R, Lee HJ, Lee JS, Eun HS. Genitopatellar syndrome secondary to de novo KAT6B mutation: the first genetically confirmed case in South Korea. *Yonsei Med J.* 2019;60:395-401. [PMC free article: PMC6433568] [PubMed: 31131026]

30900427]Kim YR, Park JB, Lee YJ, Hong MJ, Kim HT, Kim HJ. Identifying the KAT6B mutation via diagnostic exome sequencing to diagnose Say-Barber-Biesecker-Young-Simpson syndrome in three generations of a family. *Ann Rehabil Med*. 2017;41:505–10. [PMC free article: PMC5532359] [PubMed: 28758091]Knight S, VanHouwelingen L, Cervi D, Clay MR, Corkins M, Hines-Dowell S, Murphy AJ. Genitopatellar syndrome and neuroblastoma: The multidisciplinary management of a previously unreported association. *Pediatr Blood Cancer*. 2018;65:e27373. [PubMed: 30084242]Kraft M, Cirstea IC, Voss AK, Thomas T, Goehring I, Sheikh BN, Gordon L, Scott H, Smyth GK, Ahmadian MR, Trautmann U, Zenker M, Tartaglia M, Ekici A, Reis A, Durr HG, Rauch A, Thiel CT. Disruption of the histone acetyltransferase MYST4 leads to a Noonan syndrome-like phenotype and hyperactivated MAPK signaling in humans and mice. *J Clin Invest*. 2011;121:3479–91. [PMC free article: PMC3163944] [PubMed: 21804188]Lonardo F, Lonardo MS, Acquaviva F, Della Monica M, Scarano F, Scarano G.

Say-Barber-Biesecker-Young-Simpson syndrome and genitopatellar syndrome: lumping or splitting? *Clin Genet*. 2019;95:253–61. [PubMed: 28857140]Martinez FJ, Lee JH, Lee JE, Blanco S, Nickerson E, Gabriel S, Frye M, Al-Gazali L, Gleeson JG. Whole exome sequencing identifies a splicing mutation in NSUN2 as a cause of a Dubowitz-like syndrome. *J Med Genet*. 2012;49:380–5. [PMC free article: PMC4771841] [PubMed: 22577224]Mhanni AA, Dawson AJ, Chudley AE. Vertical transmission of the Ohdo blepharophimosis syndrome. *Am J Med Genet*. 1998;77:144–8. [PubMed: 9605288]Niida Y, Mitani Y, Kuroda M, Yokoi A, Nakagawa H, Kato A. A Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome with a KAT6B 10-base pair palindromic duplication: A recurrent mutation causing a severe phenotype mixed with genitopatellar syndrome. *Congenit Anom (Kyoto)*. 2017;57:86–8. [PubMed: 27696664]Ohdo S, Madokoro H, Sonoda T, Hayakawa K. Mental retardation associated with congenital heart disease, blepharophimosis, blepharoptosis, and hypoplastic teeth. *J Med Genet*. 1986;23:242–4. [PMC free article: PMC1049635] [PubMed: 3723552]Okano S, Miyamoto A, Fukuda I, Tanaka H, Hata K, Kaname T, Makita Y. Genitopatellar syndrome: the first reported case in Japan. *Hum Genome Var*. 2018;5:8. [PMC free article: PMC5972145] [PubMed: 29899993]Preiksaitiene E,

Tumiene B, Maldziene Z, Pranckeviciene E, Morkuniene A, Utkus A, Kucinskas V. Features of KAT6B-related disorders in a patient with 10q22.1q22.3 deletion. *Ophthalmic Genet.* 2017;38:383–389. [PubMed: 27880066]

Radvanszky J, Hyblova M, Durovcikova D, Hikkelova M, Fiedler E, Kadasi L, Szemes T. Complex phenotypes blur conventional borders between Say-Barber-Biesecker-Young-Simpson syndrome and genitopatellar syndrome. *Clin Genet.* 2017;91:339–343. [PubMed: 27452416]

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. *Nat Genet.* 2016;48:126–133. [PMC free article: PMC4731925] [PubMed: 26656846]

Say B, Barber N. Mental retardation with blepharophimosis. *J Med Genet.* 1987;24:511. [PMC free article: PMC1050218] [PubMed: 3656379]

Simpson MA, Deshpande C, Dafou D, Vissers LE, Woollard WJ, Holder SE, Gillissen-Kaesbach G, Derks R, White SM, Cohen-Shuiff R, Kant SG, Hoefsloot LH, Reardon W, Brunner HG, Bongers EM, Trembath RC. De novo mutations of the gene encoding the histone acetyltransferase KAT6B cause Genitopatellar syndrome. *Am J Hum Genet.* 2012;90:290–294. [PMC free article: PMC3276665] [PubMed: 22265017]

Szakszon K, Salpietro C, Kakar N, Knecht AC, Olah E, Dallapiccola B, Borck G. De novo mutations of the gene encoding the histone acetyltransferase KAT6B in two patients with Say-Barber/Biesecker/Young-Simpson syndrome. *Am J Med Genet A.* 2013;161A:884–888. [PubMed: 23436491]

Tsukahara M, Opitz JM. Dubowitz syndrome: review of 141 cases including 36 previously unreported patients. *Am J Med Genet.* 1996;63:277–289. [PubMed: 8723121]

White SM, Adams LC, Amor D, Liebelt J, Bankier A, Baker E, Wilson M, Savarirayan R. Two further cases of Ohdo syndrome delineate the phenotypic variability of the condition. *Clin Dysmorphol.* 2003;12:109–113. [PubMed: 12868473]

Yang XJ. MOZ and MORF acetyltransferases: Molecular interaction, animal development and human disease. *Biochim Biophys Acta.* 2015;1853:1818–1826. [PubMed: 25920810]

Yates TM, Langley CLM, Grozeva D, Raymond FL, Johnson DS. Novel KAT6B proximal familial variant expands genotypic and phenotypic spectrum. *Clin Genet.* 2019;95:334–339. [PubMed: 30353918]

Yilmaz R, Beleza-Meireles A, Price S, Oliveira R, Kubisch C, Clayton-Smith J, Borck G. A

recurrent synonymous KAT6B mutation causes Say-Barber-Biesecker/Young-Simpson syndrome by inducing aberrant splicing. *Am J Med Genet A*. 2015;167A:3006–10. [PubMed: 26334766]Young ID, Simpson K. Unknown syndrome: abnormal facies, congenital heart defects, hypothyroidism, and severe retardation. *J Med Genet*. 1987;24:715–6. [PMC free article: PMC1050356] [PubMed: 3430551]

Literature CitedBashir RA, Dixit A, Goedhart C, Parboosingh JS, Innes AM, Ferreira P, Au PB. Lin-Gettig syndrome: Craniosynostosis expands the spectrum of the KAT6B related disorders. *Am J Med Genet A*. 2017;173:2596–604. [PubMed: 28696035]Biesecker LG. The Ohdo blepharophimosis syndrome: a third case. *J Med Genet*. 1991;28:131–4. [PMC free article: PMC1016784] [PubMed: 2002485]Campeau PM, Kim JC, Lu JT, Schwartzentruber JA, Abdul-Rahman OA, Schlaubitz S, Murdock DM, Jiang MM, Lammer EJ, Enns GM, Rhead WJ, Rowland J, Robertson SP, Cormier-Daire V, Bainbridge MN, Yang XJ, Gingras MC, Gibbs RA, Rosenblatt DS, Majewski J, Lee BH. Mutations in KAT6B, encoding a histone acetyltransferase, cause genitopatellar syndrome. *Am J Hum Genet*. 2012a;90:282–9. [PMC free article: PMC3276659] [PubMed: 22265014]Campeau PM, Lu JT, Dawson BC, Fokkema IF, Robertson SP, Gibbs RA, Lee BH. The KAT6B-related disorders Genitopatellar syndrome and Ohdo/SBBYS syndrome have distinct clinical features reflecting distinct molecular mechanisms. *Hum Mutat*. 2012b;33:1520–5. [PMC free article: PMC3696352] [PubMed: 22715153]Clayton-Smith J, O'Sullivan J, Daly S, Bhaskar S, Day R, Anderson B, Voss AK, Thomas T, Biesecker LG, Smith P, Fryer A, Chandler KE, Kerr B, Tassabehji M, Lynch SA, Krajewska-Walasek M, McKee S, Smith J, Sweeney E, Mansour S, Mohammed S, Donnai D, Black G. Whole-exome-sequencing identifies mutations in histone acetyltransferase gene KAT6B in individuals with the Say-Barber-Biesecker variant of Ohdo syndrome. *Am J Hum Genet*. 2011;89:675–81. [PMC free article: PMC3213399] [PubMed: 22077973]Cormier-Daire V, Chauvet ML, Lyonnet S, Briard ML, Munnich A, Le Merrer M. Genitopatellar syndrome: a new condition comprising absent patellae, scrotal hypoplasia, renal anomalies, facial dysmorphism, and mental retardation. *J Med Genet*.

2000;37:520-524. [PMC free article: PMC1734629] [PubMed: 10882755] Doyon Y, Cayrou C, Ullah M, Landry AJ, Côté V, Selleck W, Lane WS, Tan S, Yang XJ, Côté J. ING tumor suppressor proteins are critical regulators of chromatin acetylation required for genome expression and perpetuation. *Mol Cell*. 2006;21:51-64. [PubMed: 16387653] Gannon T, Perveen R, Schlecht H, Ramsden S, Anderson B, Kerr B, Clayton-Smith J. Further delineation of the KAT6B molecular and phenotypic spectrum. *Eur J Hum Genet*. 2015;23:1165-70. [PMC free article: PMC4351891] [PubMed: 25424711] Herriges JC, Dugan SL, Lamb AN. Clinical and molecular cytogenetic characterization of a novel 10q interstitial deletion: a case report and review of the literature. *Mol Cytogenet*. 2019;12:20. [PMC free article: PMC6525357] [PubMed: 31131026] Kim BR, Han JH, Shin JE, Park MS, Park KI, Namgung R, Lee HJ, Lee JS, Eun HS. Genitopatellar syndrome secondary to de novo KAT6B mutation: the first genetically confirmed case in South Korea. *Yonsei Med J*. 2019;60:395-8. [PMC free article: PMC6433568] [PubMed: 30900427] Kim YR, Park JB, Lee YJ, Hong MJ, Kim HT, Kim HJ. Identifying the KAT6B mutation via diagnostic exome sequencing to diagnose Say-Barber-Biesecker-Young-Simpson syndrome in three generations of a family. *Ann Rehabil Med*. 2017;41:505-10. [PMC free article: PMC5532359] [PubMed: 28758091] Knight S, VanHouwelingen L, Cervi D, Clay MR, Corkins M, Hines-Dowell S, Murphy AJ. Genitopatellar syndrome and neuroblastoma: The multidisciplinary management of a previously unreported association. *Pediatr Blood Cancer*. 2018;65:e27373. [PubMed: 30084242] Kraft M, Cirstea IC, Voss AK, Thomas T, Goehring I, Sheikh BN, Gordon L, Scott H, Smyth GK, Ahmadian MR, Trautmann U, Zenker M, Tartaglia M, Ekici A, Reis A, Durr HG, Rauch A, Thiel CT. Disruption of the histone acetyltransferase MYST4 leads to a Noonan syndrome-like phenotype and hyperactivated MAPK signaling in humans and mice. *J Clin Invest*. 2011;121:3479-91. [PMC free article: PMC3163944] [PubMed: 21804188] Lonardo F, Lonardo MS, Acquaviva F, Della Monica M, Scarano F, Scarano G. Say-Barber-Biesecker-Young-Simpson syndrome and genitopatellar syndrome: lumping or splitting? *Clin Genet*. 2019;95:253-61. [PubMed: 28857140] Martinez FJ, Lee JH, Lee JE, Blanco S, Nickerson E, Gabriel S, Frye M, Al-Gazali L, Gleeson JG. Whole exome sequencing identifies a

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Olah E, Dallapiccola B, Borck G. De novo mutations of the gene encoding the histone acetyltransferase KAT6B in two patients with Say-Barber/Biesecker/Young-Simpson syndrome. *Am J Med Genet A*. 2013;161A:884–8. [PubMed: 23436491]Tsukahara M, Opitz JM. Dubowitz syndrome: review of 141 cases including 36 previously unreported patients. *Am J Med Genet*. 1996;63:277–89. [PubMed: 8723121]White SM, Adès LC, Amor D, Liebelt J, Bankier A, Baker E, Wilson M, Savarirayan R. Two further cases of Ohdo syndrome delineate the phenotypic variability of the condition. *Clin Dysmorphol*. 2003;12:109–13. [PubMed: 12868473]Yang XJ. MOZ and MORF acetyltransferases: Molecular interaction, animal development and human disease. *Biochim Biophys Acta*. 2015;1853:1818–26. [PubMed: 25920810]Yates TM, Langley CLM, Grozeva D, Raymond FL, Johnson DS. Novel KAT6B proximal familial variant expands genotypic and phenotypic spectrum. *Clin Genet*. 2019;95:334–5. [PubMed: 30353918]Yilmaz R, Beleza-Meireles A, Price S, Oliveira R, Kubisch C, Clayton-Smith J, Borck G. A recurrent synonymous KAT6B mutation causes Say-Barber-Biesecker/Young-Simpson syndrome by inducing aberrant splicing. *Am J Med Genet A*. 2015;167A:3006–10. [PubMed: 26334766]Young ID, Simpson K. Unknown syndrome: abnormal facies, congenital heart defects, hypothyroidism, and severe retardation. *J Med Genet*. 1987;24:715–6. [PMC free article: PMC1050356] [PubMed: 3430551]

Bashir RA, Dixit A, Goedhart C, Parboosingh JS, Innes AM, Ferreira P, Au PB. Lin-Gettig syndrome: Craniosynostosis expands the spectrum of the KAT6B related disorders. *Am J Med Genet A*. 2017;173:2596–604. [PubMed: 28696035]

Biesecker LG. The Ohdo blepharophimosis syndrome: a third case. *J Med Genet*. 1991;28:131–4. [PMC free article: PMC1016784] [PubMed: 2002485]

Campeau PM, Kim JC, Lu JT, Schwartzentruber JA, Abdul-Rahman OA, Schlaubitz S, Murdock DM, Jiang MM, Lammer EJ, Enns GM, Rhead WJ, Rowland J, Robertson SP, Cormier-Daire V,

Bainbridge MN, Yang XJ, Gingras MC, Gibbs RA, Rosenblatt DS, Majewski J, Lee BH. Mutations in KAT6B, encoding a histone acetyltransferase, cause genitopatellar syndrome. *Am J Hum Genet.* 2012a;90:282-291. [PMC free article: PMC3276659] [PubMed: 22265014]

Campeau PM, Lu JT, Dawson BC, Fokkema IF, Robertson SP, Gibbs RA, Lee BH. The KAT6B-related disorders Genitopatellar syndrome and Ohdo/SBBYS syndrome have distinct clinical features reflecting distinct molecular mechanisms. *Hum Mutat.* 2012b;33:1520-1529. [PMC free article: PMC3696352] [PubMed: 22715153]

Clayton-Smith J, O'Sullivan J, Daly S, Bhaskar S, Day R, Anderson B, Voss AK, Thomas T, Biesecker LG, Smith P, Fryer A, Chandler KE, Kerr B, Tassabehji M, Lynch SA, Krajewska-Walasek M, McKee S, Smith J, Sweeney E, Mansour S, Mohammed S, Donnai D, Black G. Whole-exome-sequencing identifies mutations in histone acetyltransferase gene KAT6B in individuals with the Say-Barber-Biesecker variant of Ohdo syndrome. *Am J Hum Genet.* 2011;89:675-681. [PMC free article: PMC3213399] [PubMed: 22077973]

Cormier-Daire V, Chauvet ML, Lyonnet S, Briard ML, Munnich A, Le Merrer M. Genitopatellar syndrome: a new condition comprising absent patellae, scrotal hypoplasia, renal anomalies, facial dysmorphism, and mental retardation. *J Med Genet.* 2000;37:520-524. [PMC free article: PMC1734629] [PubMed: 10882755]

Doyon Y, Cayrou C, Ullah M, Landry AJ, Cockerill V, Selleck W, Lane WS, Tan S, Yang XJ, Cockerill J. ING tumor suppressor proteins are critical regulators of chromatin acetylation required for genome expression and perpetuation. *Mol Cell.* 2006;21:51-64. [PubMed: 16387653]

Gannon T, Perveen R, Schlecht H, Ramsden S, Anderson B, Kerr B, Clayton-Smith J. Further

delineation of the KAT6B molecular and phenotypic spectrum. *Eur J Hum Genet.*

2015;23:1165–70. [PMC free article: PMC4351891] [PubMed: 25424711]

Herriges JC, Dugan SL, Lamb AN. Clinical and molecular cytogenetic characterization of a novel 10q interstitial deletion: a case report and review of the literature. *Mol Cytogenet.* 2019;12:20. [PMC free article: PMC6525357] [PubMed: 31131026]

Kim BR, Han JH, Shin JE, Park MS, Park KI, Namgung R, Lee HJ, Lee JS, Eun HS. Genitopatellar syndrome secondary to de novo KAT6B mutation: the first genetically confirmed case in South Korea. *Yonsei Med J.* 2019;60:395–8. [PMC free article: PMC6433568] [PubMed: 30900427]

Kim YR, Park JB, Lee YJ, Hong MJ, Kim HT, Kim HJ. Identifying the KAT6B mutation via diagnostic exome sequencing to diagnose Say-Barber-Biesecker-Young-Simpson syndrome in three generations of a family. *Ann Rehabil Med.* 2017;41:505–10. [PMC free article: PMC5532359] [PubMed: 28758091]

Knight S, VanHouwelingen L, Cervi D, Clay MR, Corkins M, Hines-Dowell S, Murphy AJ. Genitopatellar syndrome and neuroblastoma: The multidisciplinary management of a previously unreported association. *Pediatr Blood Cancer.* 2018;65:e27373. [PubMed: 30084242]

Kraft M, Cirstea IC, Voss AK, Thomas T, Goehring I, Sheikh BN, Gordon L, Scott H, Smyth GK, Ahmadian MR, Trautmann U, Zenker M, Tartaglia M, Ekici A, Reis A, Dörr HG, Rauch A, Thiel CT. Disruption of the histone acetyltransferase MYST4 leads to a Noonan syndrome-like phenotype and hyperactivated MAPK signaling in humans and mice. *J Clin Invest.* 2011;121:3479–91. [PMC free article: PMC3163944] [PubMed: 21804188]

Lonardo F, Lonardo MS, Acquaviva F, Della Monica M, Scarano F, Scarano G.

Say-Barber-Biesecker-Young-Simpson syndrome and genitopatellar syndrome: lumping or splitting? Clin Genet. 2019;95:253–61. [PubMed: 28857140]

Martinez FJ, Lee JH, Lee JE, Blanco S, Nickerson E, Gabriel S, Frye M, Al-Gazali L, Gleeson JG. Whole exome sequencing identifies a splicing mutation in NSUN2 as a cause of a Dubowitz-like syndrome. J Med Genet. 2012;49:380–5. [PMC free article: PMC4771841] [PubMed: 22577224]

Mhanni AA, Dawson AJ, Chudley AE. Vertical transmission of the Ohdo blepharophimosis syndrome. Am J Med Genet. 1998;77:144–8. [PubMed: 9605288]

Niida Y, Mitani Y, Kuroda M, Yokoi A, Nakagawa H, Kato A. A Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome with a KAT6B 10-base pair palindromic duplication: A recurrent mutation causing a severe phenotype mixed with genitopatellar syndrome. Congenit Anom (Kyoto). 2017;57:86–8. [PubMed: 27696664]

Ohdo S, Madokoro H, Sonoda T, Hayakawa K. Mental retardation associated with congenital heart disease, blepharophimosis, blepharoptosis, and hypoplastic teeth. J Med Genet. 1986;23:242–4. [PMC free article: PMC1049635] [PubMed: 3723552]

Okano S, Miyamoto A, Fukuda I, Tanaka H, Hata K, Kaname T, Makita Y. Genitopatellar syndrome: the first reported case in Japan. Hum Genome Var. 2018;5:8. [PMC free article: PMC5972145] [PubMed: 29899993]

Preiksaitiene E, Tumiene B, Maldziene Z, Pranckeviciene E, Morkuniene A, Utkus A, Kucinskas V. Features of KAT6B-related disorders in a patient with 10q22.1q22.3 deletion. Ophthalmic Genet. 2017;38:383–6. [PubMed: 27880066]

Radvanszky J, Hyblova M, Durovcikova D, Hikkelova M, Fiedler E, Kadasi L, Szemes T. Complex phenotypes blur conventional borders between Say-Barber-Biesecker-Young-Simpson syndrome and genitopatellar syndrome. *Clin Genet*. 2017;91:339–43. [PubMed: 27452416]

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. *Nat Genet*. 2016;48:126–33. [PMC free article: PMC4731925] [PubMed: 26656846]

Say B, Barber N. Mental retardation with blepharophimosis. *J Med Genet*. 1987;24:511. [PMC free article: PMC1050218] [PubMed: 3656379]

Simpson MA, Deshpande C, Dafou D, Vissers LE, Woollard WJ, Holder SE, Gillesen-Kaesbach G, Derks R, White SM, Cohen-Snuijf R, Kant SG, Hoefsloot LH, Reardon W, Brunner HG, Bongers EM, Trembath RC. De novo mutations of the gene encoding the histone acetyltransferase KAT6B cause Genitopatellar syndrome. *Am J Hum Genet*. 2012;90:290–4. [PMC free article: PMC3276665] [PubMed: 22265017]

Szakszon K, Salpietro C, Kakar N, Knecht AC, Olah E, Dallapiccola B, Borck G. De novo mutations of the gene encoding the histone acetyltransferase KAT6B in two patients with Say-Barber/Biesecker/Young-Simpson syndrome. *Am J Med Genet A*. 2013;161A:884–8. [PubMed: 23436491]

Tsukahara M, Opitz JM. Dubowitz syndrome: review of 141 cases including 36 previously unreported patients. *Am J Med Genet*. 1996;63:277–89. [PubMed: 8723121]

White SM, Adès LC, Amor D, Liebelt J, Bankier A, Baker E, Wilson M, Savarirayan R. Two further cases of Ohdo syndrome delineate the phenotypic variability of the condition. Clin Dysmorphol. 2003;12:109–13. [PubMed: 12868473]

Yang XJ. MOZ and MORF acetyltransferases: Molecular interaction, animal development and human disease. Biochim Biophys Acta. 2015;1853:1818–26. [PubMed: 25920810]

Yates TM, Langley CLM, Grozeva D, Raymond FL, Johnson DS. Novel KAT6B proximal familial variant expands genotypic and phenotypic spectrum. Clin Genet. 2019;95:334–5. [PubMed: 30353918]

Yilmaz R, Beleza-Meireles A, Price S, Oliveira R, Kubisch C, Clayton-Smith J, Borck G. A recurrent synonymous KAT6B mutation causes Say-Barber-Biesecker/Young-Simpson syndrome by inducing aberrant splicing. Am J Med Genet A. 2015;167A:3006–10. [PubMed: 26334766]

Young ID, Simpson K. Unknown syndrome: abnormal facies, congenital heart defects, hypothyroidism, and severe retardation. J Med Genet. 1987;24:715–6. [PMC free article: PMC1050356] [PubMed: 3430551]

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.
Revision History
2 January 2020 (ha) Comprehensive update posted live
10 January 2013 (cd) Revision: sequence analysis and prenatal diagnosis available clinically
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