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Kaufman Oculocerebrofacial Syndrome

Synonym: Blepharophimosis-Ptosis-Intellectual Disability (BPID) Syndrome

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Summary

Clinical characteristics

Kaufman oculocerebrofacial syndrome (KOS) is characterized by developmental delay, severe intellectual disability, and distinctive craniofacial features. Most affected children have prenatal-onset microcephaly, hypotonia, and growth deficiency. Feeding issues, ocular abnormalities, hearing impairment, and respiratory tract abnormalities are common. Ocular abnormalities can include structural abnormalities (microcornea or microphthalmia, coloboma, optic nerve hypoplasia), refractive errors (myopia ± astigmatism, hyperopia), strabismus, and entropion. Both conductive and sensorineural hearing loss have been reported as well as mixed conductive-sensorineural hearing loss of variable severity. Breathing problems can lead to prolonged hospitalization after birth in more than half of individuals. Less common findings include ectodermal abnormalities, cardiac manifestations, urogenital abnormalities, seizures, and skeletal abnormalities.

Diagnosis/testing

The diagnosis of KOS is established in a proband with developmental delay/intellectual disability and biallelic *UBE3B* pathogenic variants.

Management

Treatment of manifestations: Educational intervention and speech therapy beginning in infancy; standard treatment with anti-seizure medication in those with seizures; early intervention as needed for feeding problems and respiratory problems; routine management of ophthalmologic issues, hearing impairment, congenital heart defects, urogenital abnormalities, and skeletal abnormalities.

Surveillance: At least annual assessment of developmental progress, growth, vision, and hearing. Assess for seizures and respiratory issues at each visit. At least annual examination for contractures and scoliosis.

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Genetic counseling

KOS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *UBE3B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *UBE3B* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Kaufman oculocerebrofacial syndrome (KOS) have been published.

Suggestive Findings

KOS **should be suspected** in individuals with the following clinical and supportive laboratory findings.

Clinical findings

- Microcephaly
- Developmental delay and severe intellectual disability
- Growth deficiency (poor weight gain and/or short stature)
- Ocular anomalies (microcornea, microphthalmia, coloboma, optic nerve hypoplasia, refractive errors, strabismus, entropion)
- A typical and recognizable pattern of craniofacial features* (see Figure 1):
  - Eyebrows: highly arched, laterally broad with flaring (medial or lateral)
  - Telecanthus, blepharophimosis with epicanthal folds, ptosis, upslanted palpebral fissures
  - Ears: often apparently low set with overfolded helices and small lobes; variably seen: cupped ears, underdeveloped crus helix, preauricular tags
  - Narrow nasal bridge, wide nasal base, anteverted nares
  - Flat zygomata
  - Long, flat philtrum
  - Narrow mouth, thin vermilion of the upper lip with absent Cupid's bow
  - Micrognathia

  *With age, the face becomes more elongated, the zygomata become flatter and the palpebral fissures more upslanted, and the alae nasi thicken [Basel-Vanagaite et al 2014]. Micrognathia also becomes less prominent with age. (See Figure 1.) Note: Rarely, individuals with biallelic *UBE3B* pathogenic variants do not have (or have only mild) characteristic facial features [Basel-Vanagaite et al 2014].

Supportive laboratory findings include low serum concentration of cholesterol (performed as part of routine laboratory testing) in some individuals.

Establishing the Diagnosis

The diagnosis of KOS **is established** in a proband with developmental delay / intellectual disability and biallelic pathogenic (or likely pathogenic) variants in *UBE3B* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both

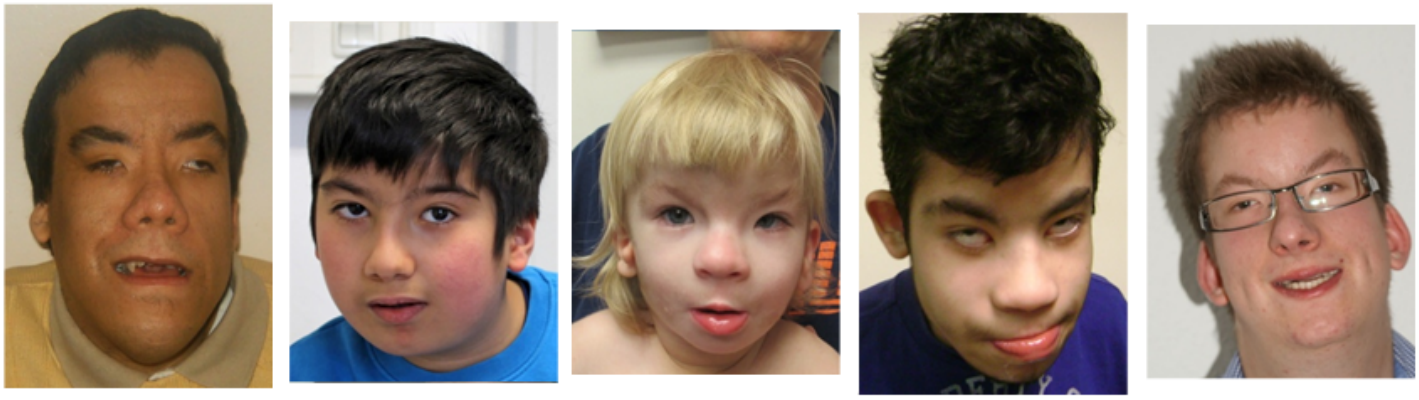

Figure 1. Facial dysmorphism associated with KOS caused by biallelic *UBE3B* pathogenic variants. See text for a detailed description of dysmorphic features. Affected individuals pictured are individuals 1, 2, 3, 4, and 6 in Basel-Vanagaite et al [2014].

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can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *UBE3B* variants of uncertain significance (or identification of one known *UBE3B* pathogenic variant and one *UBE3B* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, 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. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with microcephaly, poor growth, and/or developmental delay are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *UBE3B* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Although gene-targeted deletion/duplication analysis could be considered if only one pathogenic variant is found, no *UBE3B* deletions have been reported to date in individuals with suspected KOS [G Borck, personal observation].

A multigene panel that includes *UBE3B* and other genes of interest (see Differential Diagnosis) may also be considered 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in Kaufman Oculocerebrofacial Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
UBE3B	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

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. Pedurupillay et al [2015] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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 gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Kaufman oculocerebrofacial syndrome (KOS) is characterized by prenatal-onset microcephaly, growth deficiency, developmental delay, severe intellectual disability, and distinct facial features. To date, 36 individuals have been identified with biallelic pathogenic variants in *UBE3B* [Basel-Vanagaite et al 2012, Flex et al 2013, Basel-Vanagaite et al 2014, Pedurupillay et al 2015, Kariminejad et al 2017, Yilmaz et al 2018, Galarreta et al 2019, Zaki et al 2020, Ürel-Demir et al 2021]. Six additional individuals with characteristic clinical features that did not have molecular confirmation have been described [Kaufman et al 1971, Jurenka & Evans 1979, Figuera et al 1993]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Kaufman Oculocerebrofacial Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Developmental delay / intellectual disability	100%	Usually severe to profound
Hypotonia	>95%	
Microcephaly	~90%	Typically, prenatal onset (>60% present at birth)
Brain malformation	70%-75%	Brain imaging was not performed in all individuals.
Growth deficiency	80%-90%	40%-50% are small for gestational age.
Feeding difficulties	~90%	
Distinct facial features	80%-90%	~90% have blepharophimosis/ptosis.

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Ocular abnormalities	80%-90%	
Hearing impairment	60%	
Respiratory difficulties	~50%-60%	
Ectodermal anomalies	35%-45%	Sparse hair 20%-45%; nail dysplasia ~15%
Cardiac involvement	~30%	Congenital malformations & obstructive hypertrophy
Skeletal abnormalities	~20%	
Low serum cholesterol	~50%	Total, HDL, &/or LDL

Neurologic abnormalities/cognitive development

- Postnatal microcephaly is frequently present and more than 60% of affected children have prenatal microcephaly or a small occipitofrontal circumference (OFC) at birth (<10th centile), which in most individuals persists postnatally [Basel-Vanagaite et al 2014, Galarreta et al 2019]. Microcephaly is often moderate with OFC -2 to -3 SD; it is not currently known to worsen with age. The OFC of the oldest individual with biallelic *UBE3B* pathogenic variants was at the 75th centile at age 33 years; his father also had a large OFC.
- Hypotonia and delayed motor milestones are universal findings.
- The onset of independent ambulation varies; in most it is achieved by age four to five years. Gait is frequently described as unsteady.
- Intellectual disability is severe to profound in the individuals reported to date; rare, affected individuals develop limited speech.
- Seizures are reported in approximately 20% of individuals and are usually fever related.
- Abnormal brain MRI was reported in 19/26 individuals. Anomalies included corpus callosum hypoplasia or agenesis (13 individuals), dilated ventricles (3 individuals), Chiari 1 malformation (2), small pituitary (2), ectopic pituitary gland and hypoplastic vermis (1) [Galarreta et al 2019].
- Significant behavior problems do not appear to be prominent; six individuals were described as having a cheerful disposition [Galarreta et al 2019]. Autistic features were described in 4/9 individuals [Zaki et al 2020].

Growth

- Growth deficiency is common during infancy and most affected children have poor weight gain and short stature [Basel-Vanagaite et al 2014]. Growth may improve with age [Galarreta et al 2019].
- Stature is usually below the 10th centile or -2 to -3 SD; however, the number of reported individuals is limited.

Gastrointestinal tract abnormalities

- Feeding difficulties are a main complication and manifest as poor weight gain, generalized hypotonia, poor suck, poor swallowing, small oral cavity, palate defects, gastroesophageal reflux, and poor dietary intake. Feeding by nasogastric tube or gastrostomy is needed in some individuals.
- Constipation has been reported in several individuals.
- Three individuals had intestinal malrotation.

Distinct facial features. With age, the face becomes more elongated, the zygomata become flatter and the palpebral fissures more upslanted, and the alae nasi thicken [Basel-Vanagaite et al 2014]. Micrognathia also becomes less prominent with age. (See Figure 1.)

- Eyebrows: highly arched, laterally broad with flaring (medial or lateral)
- Telecanthus, blepharophimosis with epicanthal folds, ptosis, upslanted palpebral fissures
- Ears: often apparently low set with overfolded helices and small lobes; variably seen: cupped ears, underdeveloped crus helix, preauricular tags
- Narrow nasal bridge, wide nasal base, anteverted nares
- Flat zygomata
- Long, flat philtrum
- Narrow mouth, thin vermilion of the upper lip with absent Cupid's bow
- Micrognathia
- Prominent cheeks

Ocular abnormalities can include:

- Structural abnormalities (microcornea or microphthalmia, coloboma, optic nerve hypoplasia, spherophakia);
- Refractive errors (myopia with or without astigmatism, hyperopia);
- Abnormal alignment of the eyes (strabismus);
- Entropion (inward turning of the lower eyelid);
- Epibulbar dermoid in one individual [Ürel-Demir et al 2021].

Hearing impairment

- Hearing impairment is common. Both conductive and sensorineural hearing loss have been reported as well as mixed conductive-sensorineural hearing loss of variable severity.
- Ear anomalies include stenotic auditory canals, dysplastic ears, and cupped ears; ear tags are present in about 30%-40% of individuals.
- Two affected individuals had cholesteatoma [Basel-Vanagaite et al 2014].

Respiratory tract abnormalities

- Breathing problems are quite common leading to a complicated course with prolonged hospitalization after birth in more than half of individuals. Breathing problems include a spectrum of abnormalities including laryngomalacia, micrognathia, stridor or noisy breathing at the mild end to subglottic stenosis, tracheomalacia, and tracheostomy with or without mechanical ventilation at the severe end.
- A severe respiratory course was described in at least seven individuals including mechanical ventilation (in 2 individuals), tracheostomy placements (in 4 individuals), laryngeal reconstruction (in 3), and mandibular advancement (in 3) [Basel-Vanagaite et al 2012, Basel-Vanagaite et al 2014, Yilmaz et al 2018, Galarreta et al 2019, Ürel-Demir et al 2021].
- Obstructive sleep apnea is noted in some individuals.

Ectodermal abnormalities

- Sparse scalp hair, thin skin, dry skin, and hyperkeratosis are noted in some infants. The appearance of the scalp hair improves with age.
- Small teeth and nail dysplasia or hypoplasia have also been described [Basel-Vanagaite et al 2014, Ürel-Demir et al 2021].

Cardiac manifestations include:

- Pulmonary artery stenosis;

- Atrial septal defect;
- Ventricular septal defect;
- Aortic coarctation, supravalvular or subvalvular aortic stenosis;
- Dysplastic mitral valve;
- Hypertrophic cardiomyopathy (may be obstructive, may involve the left ventricle or the septum only).

Urogenital abnormalities

- Genital abnormalities are more frequent in females than males and include hypoplastic labia majora and/or minora or clitoromegaly.
- Micropenis was described in some males.
- Renal abnormalities are not common and include vesicoureteral reflux (grade V reflux has been reported) and duplicated renal pelvis. Small kidneys with borderline function were reported in one individual.

Skeletal abnormalities

- Chest is abnormal in shape (bell-shaped thorax, pectus carinatum).
- Fingers and toes are long and slender, and fingers may be tapering. Other findings include bilateral postaxial polydactyly, fifth finger clinodactyly, and metatarsus adductus. Absent or hypoplastic distal phalanges of the fingers are probably rare but a valuable diagnostic clue.
- Congenital hip dysplasia or coxa valga has been observed in several affected individuals.
- Clubfoot was described in nine individuals [Yilmaz et al 2018, Zaki et al 2020, Ürel-Demir et al 2021]. Hand contractures and specifically camptodactyly were described in some.
- Scoliosis has also been described.

Endocrine abnormalities. Transiently elevated TSH, reduced thyroid gland volume, and low GH and ACTH were observed occasionally.

Other

- Cleft palate, reported in nine individuals. Small oral cavity, high arched palate, and bifid uvula have also been described.
- Brachycephaly
- Torticollis of a muscular origin in some individuals

Pregnancy and birth

- Congenital structural malformations or polyhydramnios may be detected on prenatal ultrasound examination.
- Intrauterine growth restriction is not a major feature, and most affected pregnancies have an uncomplicated course. However, about 40% of individuals have been small for gestational age [Galarreta et al 2019].
- Affected infants are usually born at term with borderline low or normal birth weight.
- Abnormal fetal lie has been described, probably reflecting hypotonia.

Genotype-Phenotype Correlations

It is not possible to draw conclusions regarding genotype-phenotype correlations until more individuals are reported.

Nomenclature

Prior to the identification of causative biallelic *UBE3B* pathogenic variants, the following phenotypes (now known to be KOS) were thought to be distinct disorders:

- Blepharophimosis-ptosis-intellectual disability (BPID) syndrome
- Phenotype seen in a subset of individuals clinically diagnosed with Toriello-Carey syndrome [Toriello et al 2003]
- Phenotype described by Buntinx & Majewski [1990]

Prevalence

The prevalence of KOS is unknown. To date, 36 individuals (from 25 families) with KOS and biallelic *UBE3B* pathogenic variants have been reported. There are six additional individuals reported with a similar phenotype in whom there is no molecular confirmation. While it may be underdiagnosed, KOS is estimated to be very rare.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *UBE3B*.

Differential Diagnosis

Kaufman oculocerebrofacial syndrome (KOS) has a relatively uniform, clinically recognizable phenotype mainly due to the characteristic dysmorphic features combined with severe intellectual disability [Basel-Vanagaite et al 2014]. Because of the co-occurrence of blepharophimosis and intellectual disability, the differential diagnosis mainly includes (besides small chromosomal deletions or duplications identified by chromosomal microarray analysis) other mendelian blepharophimosis-intellectual disability syndromes; see Table 3.

Table 3. Disorders of Interest in the Differential Diagnosis of Kaufman Oculocerebrofacial Syndrome (KOS)

Gene / Genetic Mechanism	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/KOS	Distinguishing from KOS
3pter-p25 deletion	Chromosome 3pter-p25 deletion syndrome (OMIM 613792)	AD	ID; blepharophimosis; growth restriction; postaxial polydactyly	Trigonocephaly
BRPF1	Intellectual developmental disorder w/dysmorphic facies & ptosis (OMIM 617333)	AD [1]	Blepharophimosis; ophthalmologic anomalies; ID/DD; callosal malformations; seizures; hypotonia; feeding difficulties; clubfoot	Characteristic facial features (flat facial profile, round face, broad nasal root, hypertelorism, down-slanting palpebral fissures, ptosis, blepharophimosis). Growth impairment & microcephaly are not major features.
DHCR7	Smith-Lemli-Opitz syndrome	AR	Growth restriction; microcephaly; moderate-to-severe ID; cleft palate; cardiac defects	Characteristic facial features (narrow forehead, epicanthal folds, ptosis, short nose w/anteverted nares, short mandible w/preservation of jaw width, nevus simplex over the nasal root that extends onto the glabella); underdeveloped external genitalia in males; 2-3 toe syndactyly
KAT6B	Say-Barber-Biesecker-Young-Simpson variant of Ohdo syndrome (See *KAT6B* Disorders.)	AD [1]	Heart defects; hearing loss; optic atrophy; cleft palate; dental anomalies incl small & pointed teeth	Distinctive facial features (mask-like facies, blepharophimosis, ptosis); joint limitations; hypothyroidism. Persons w/ this syndrome & the allelic disorder genitopatellar syndrome (OMIM 606170) have patellar hypoplasia.

Table 3. continued from previous page.

Gene / Genetic Mechanism	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/KOS	Distinguishing from KOS
MED12	Maat-Kievit-Brunner syndrome or X-linked Ohdo syndrome (See *MED12*-Related Disorders.)	XL	ID; constipation; hypotonia	Distinctive facial features (blepharophimosis, ptosis, sparse eyebrows, epicanthal folds, wide & low nasal bridge, broad nasal tip, small mouth, maxillary hypoplasia, micrognathia, triangular face)
SMARCA2	Blepharophimosis-impaired intellectual development syndrome (OMIM 619293)	AD [1]	ID; speech delay; seizures; microcephaly; phalangeal abnormalities; hearing loss; feeding difficulties [2]	Characteristic facial features (frontal bossing, hypertelorism, downturned nasal tip, hypoplastic alae nasi, pinched nose, tented upper lip vermillion, exaggerated Cupid's bow, open mouth w/U-shaped upper lip, widely spaced teeth); enamel defect [2]
TBC1D24	DOORS syndrome (See *TBC1D24*-Related Disorders.)	AR	Microcephaly; ID; hypotonia; seizures; hearing impairment; congenital heart & urinary malformation; hypoplastic phalanges & nails	↑ serum & urinary 2-oxoglutarate; optic atrophy & blindness

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Typically caused by a *de novo* pathogenic variant.

2. Cappuccio et al [2020]

Management

No clinical practice guidelines for Kaufman oculocerebrofacial syndrome (KOS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with KOS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Kaufman Oculocerebrofacial Syndrome

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Growth	Growth assessment	
Gastrointestinal/ Feeding	• Gastroenterology / nutrition / feeding team eval • Eval for GERD; bowel malrotation (if indicated); cleft palate incl submucosal type	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/dysphagia & aspiration risk.
Eyes	Ophthalmologic eval	To assess for microcornea, cataract, ptosis, coloboma, refractive errors, & strabismus
Hearing	Audiologic eval	To assess for conductive, sensorineural, & mixed hearing impairment

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Respiratory	• Referral for ENT • Referral to pulmonologist	• To evaluate for subglottic stenosis, laryngomalacia, tracheomalacia if respiratory issues or obstructive sleep apnea are present • Evaluate for recurrent respiratory infections.
Cardiac	Echocardiogram	To assess for congenital heart defects & obstructive hypertrophy
Genitourinary	• Eval for genital anomalies • Renal ultrasound exam for structural renal abnormalities & vesicoureteral reflux	
Musculoskeletal	• Hip ultrasound exam to evaluate for femoral head dislocation • Eval of torticollis, clubfoot, & hand malformations or contractures • Referral to orthopedist & PT	
Endocrine	• Eval of thyroid function • Eval of other hormone levels if clinically indicated	
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of KOS in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

GERD = gastroesophageal reflux disease; KOS = Kaufman oculocerebrofacial syndrome; MOI = mode of inheritance; PT = physical therapist

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Kaufman Oculocerebrofacial Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for KOS. • Education of parents/caregivers [1]
Feeding issues / poor weight gain	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Ophthalmologic involvement	Treatment per ophthalmologist	• Cataract & ptosis surgery if indicated • Treatment of refractive errors &/or strabismus
	Low vision services	• Children: through early intervention programs &/or school district • Adults: referral to low vision clinic &/or community vision services

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hearing impairment	Hearing aids or cochlear implant if needed	Community hearing services through early intervention or school district
Respiratory problems	Multidisciplinary team of pulmonologist, ENT specialist, infectious diseases specialist, & intensive care specialist	• Tracheostomy placement if needed, laryngeal reconstruction, mandibular advancement, mechanical ventilation support if needed, mechanical aids for obstructive sleep apnea. • Aggressive treatment of respiratory infections to prevent deterioration of respiratory function
Cardiac anomalies	Treatment per cardiologist	
Genital anomalies	Orchidopexy in males w/undescended testes	
Renal anomalies	Treatment of vesicoureteral reflux if indicated	
Skeletal	• Referral to orthopedist if joint dislocations, clubfoot, hand contractures or scoliosis is present • Early referral to PT	
Endocrine	Thyroid hormone replacement as needed	
Cleft palate	Surgical repair if present	

ASM = anti-seizure medication; KOS = Kaufman oculocerebrofacial syndrome; PT = physical therapy

Developmental Delay / 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.

    - Physical therapy, occupational therapy, 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).

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

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.

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.

Surveillance

Table 6. Recommended Surveillance for Individuals with Kaufman Oculocerebrofacial Syndrome

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, mvmt disorders.	
Gastrointestinal/ Feeding	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake. • Monitor for constipation.	
Eyes	Vision assessment	At least annually
Hearing	Audiologic eval	
Respiratory	Assess for noisy breathing, obstructive sleep apnea, & respiratory infections.	At each visit
Cardiac	Follow up per cardiologist	At least annually for those w/ hypertrophy
Musculoskeletal	Assess for torticollis, contractures, &/or scoliosis.	At least annually
Endocrine	Follow up per endocrinologist	

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

Kaufman oculocerebrofacial syndrome (KOS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *UBE3B* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *UBE3B* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the

proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *UBE3B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Some intrafamilial clinical variability has been observed between affected sibs; reported phenotypic differences involved seizures, respiratory issues, the severity and extent of hearing impairment, and congenital malformations [Galarreta at al 2019, Ürel-Demir et al 2021].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with KOS are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *UBE3B* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *UBE3B* pathogenic variants in the family.

Related Genetic Counseling Issues

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 young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *UBE3B* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for KOS are possible.

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

Resources

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

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**

Phone: 202-387-1968
Fax: 202-387-2193
www.aaidd.org

- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. Kaufman Oculocerebrofacial Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
UBE3B	12q24.11	Ubiquitin-protein ligase E3B	UBE3B

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 Kaufman Oculocerebrofacial Syndrome (View All in OMIM)

244450	KAUFMAN OCULOCEREBROFACIAL SYNDROME; KOS
608047	UBIQUITIN-PROTEIN LIGASE E3B; UBE3B

Molecular Pathogenesis

UBE3B encodes the protein ubiquitin-protein ligase E3B, a mitochondrion-associated protein, containing an N-terminal IQ domain and a C-terminal HECT domain. The HECT domain in the C terminus of the longer isoform of this protein is the likely catalytic site of ubiquitin transfer and forms a complex with E2 conjugating enzyme. Shorter isoforms of this protein lack the C-terminal HECT domain and, if produced, are unlikely to interact with E2 enzymes.

UBE3B is highly expressed in the central nervous system, digestive tract, and respiratory system as well as in multiple cell lineages of skin and other soft tissues. In the brain UBE3B associates with postsynaptic density fractions and regulates dendritic branching in a cell-autonomous manner [Ambrozkiewicz et al 2020].

UBE3B pathogenic variants identified in individuals with KOS are missense substitutions in highly conserved amino acid residues of the HECT domain, or frameshift and nonsense variants that are predicted to lead to nonsense-mediated mRNA decay and/or protein truncation. These variants presumably suppress all E3 ligase enzyme activity [Basel-Vanagaite et al 2012, Basel-Vanagaite et al 2014, Ambrozkiewicz et al 2020].

Mechanism of disease causation. Loss of function

***UBE3B*-specific laboratory technical considerations.** *UBE3B* has five transcript variants: two encode longer transcripts (NM_130466.3, NM_183415.2), which comprise 28 exons and encode an 1,068 amino acid protein

isoform (~123 kd); three encode shorter transcript variants (NM_001270449.1, NM_001270451.1, NM_001270450.1), which comprise nine exons and are predicted to encode a 244-amino acid protein.

Chapter Notes

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