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KBG Syndrome

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Summary

Clinical characteristics

KBG syndrome is typically characterized by macrodontia (especially of the upper central incisors), characteristic facial features (triangular face, brachycephaly, synophrys, widely spaced eyes, broad or bushy eyebrows, prominent ears, prominent nasal bridge, bulbous nose, anteverted nares, long philtrum, and thin vermilion of the upper lip), short stature, developmental delay / intellectual disability, and behavioral issues. Affected individuals may have feeding difficulties (particularly in infancy), skeletal anomalies (brachydactyly, large anterior fontanelle with delayed closure, scoliosis), hearing loss (conductive, mixed, and sensorineural), seizure disorder, and brain malformations. There is significant variability in the clinical findings, even between affected members of the same family.

Diagnosis/testing

The diagnosis of KBG syndrome is confirmed in a proband by detection of either a heterozygous pathogenic variant in *ANKRD11* or deletion of 16q24.3 that includes *ANKRD11*.

Management

Treatment of manifestations: Surgical corrections and/or speech therapy for palatal anomalies; nasogastric tube feeding in infants; pharmacologic treatment for gastroesophageal reflux disease; pressure-equalizing tubes and/or tonsillectomy/adenoidectomy for chronic otitis media; consideration of amplification for hearing loss; consideration of growth hormone therapy for short stature and medication to arrest puberty for premature pubertal development; standard treatment of seizure disorder, undescended testis in males, congenital heart defects, strabismus / refractive errors, and developmental disabilities.

Surveillance: Routine monitoring of hearing, vision, growth, pubertal status (in prepubertal individuals), and cognitive development.

Agents/circumstances to avoid: Ototoxic drugs should be avoided because of the risk for hearing loss.

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Pregnancy management: Pregnancy management should be tailored to the specific features in the affected woman. For example, involvement of a cardiologist and maternal fetal medicine physician for a pregnant woman with a history of a congenital heart defect; control of seizures during pregnancy for those with a seizure disorder.

Genetic counseling

Recurrence risk for sibs of a proband with KBG syndrome depends on the genetic alteration:

- Deletion of 16q24.3 (~75% of reported pathogenic variants are *de novo* and the remainder are inherited in an autosomal dominant manner.)
- *ANKRD11* sequence variants (~66% of reported pathogenic variants are *de novo* and the remainder are inherited in an autosomal dominant manner.)

Prenatal testing and preimplantation genetic testing are possible if the causative genetic alteration has been identified in an affected family member.

Diagnosis

While no consensus clinical diagnostic criteria for KBG syndrome have been published, several authors have suggested diagnostic criteria [Brancati et al 2006, Skjei et al 2007, Low et al 2016].

Suggestive Findings

KBG syndrome **should be suspected** in a proband with developmental delay / cognitive impairment or significant behavioral issues who has [Brancati et al 2006, Skjei et al 2007, Goldenberg et al 2016, Low et al 2016]:

- At least two of the findings highlighted by an asterisk (*); OR
- One finding highlighted by an asterisk and at least two additional findings.

Craniofacial features

- * Macrodontia (mesiodistal width of permanent central incisors ≥10 mm in males, ≥9.7 mm in females) (see Figure1), especially of the upper central incisors
- * Characteristic facial appearance (See Figure 2.)
- Conductive hearing loss and/or chronic/recurrent otitis media
- Palatal abnormalities
- Hair anomalies (e.g., low hairline, coarse hair)

Skeletal features

- Costovertebral anomalies
- * Postnatal short stature (length and/or height <10th centile)
- Delayed bone age (>2SD below mean)
- Brachydactyly
- Large anterior fontanelle with delayed closure
- Scoliosis

Neurologic features

- Learning difficulties of variable severity
- EEG abnormalities with or without seizures

Family history

- * A first-degree relative with KBG syndrome

- Note: Absence of a family history of KBG syndrome does not preclude the diagnosis.

Other

- Feeding difficulties
- Cryptorchidism in males

Establishing the Diagnosis

The diagnosis of KBG syndrome **is established** in a proband by detection of either a heterozygous pathogenic (or likely pathogenic) variant in *ANKRD11* or deletion of 16q24.3 that includes *ANKRD11* (see Table 1). However, some individuals with clinical findings highly suggestive of KBG syndrome do not have a detectable pathogenic *ANKRD11* variant or 16q24.3 deletion [Sirmaci et al 2011].

Note: 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 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.

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Persons with the distinctive features described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom a specific diagnosis has been elusive are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of KBG syndrome, genetic testing approaches can include EITHER:

- **Single-gene testing** or use of a **multigene panel**; OR
- **Chromosomal microarray analysis**.

Single-gene testing. Sequence analysis of *ANKRD11* is performed first. If no pathogenic variant is found, gene-targeted deletion/duplication analysis could be considered (see Table 1 for information on deletion/duplication analysis).

A multigene intellectual disability panel that includes *ANKRD11* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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 condition, 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.

Chromosomal microarray analysis (CMA) using oligonucleotide arrays or single nucleotide polymorphism (SNP) arrays in current clinical use target the 16q24.3 region.

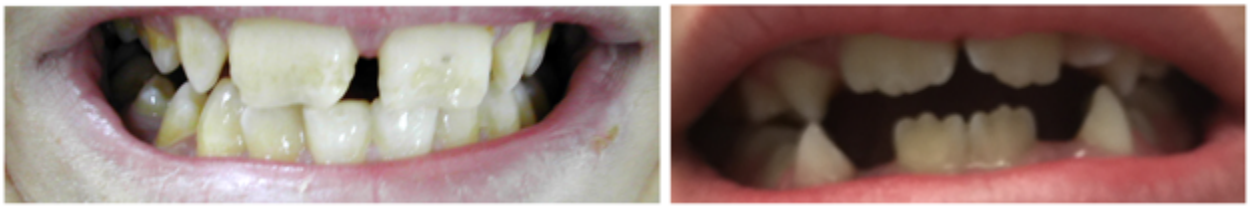

Figure 1. Macrodontia of permanent upper central incisors, dental pits, and prominent mamelons

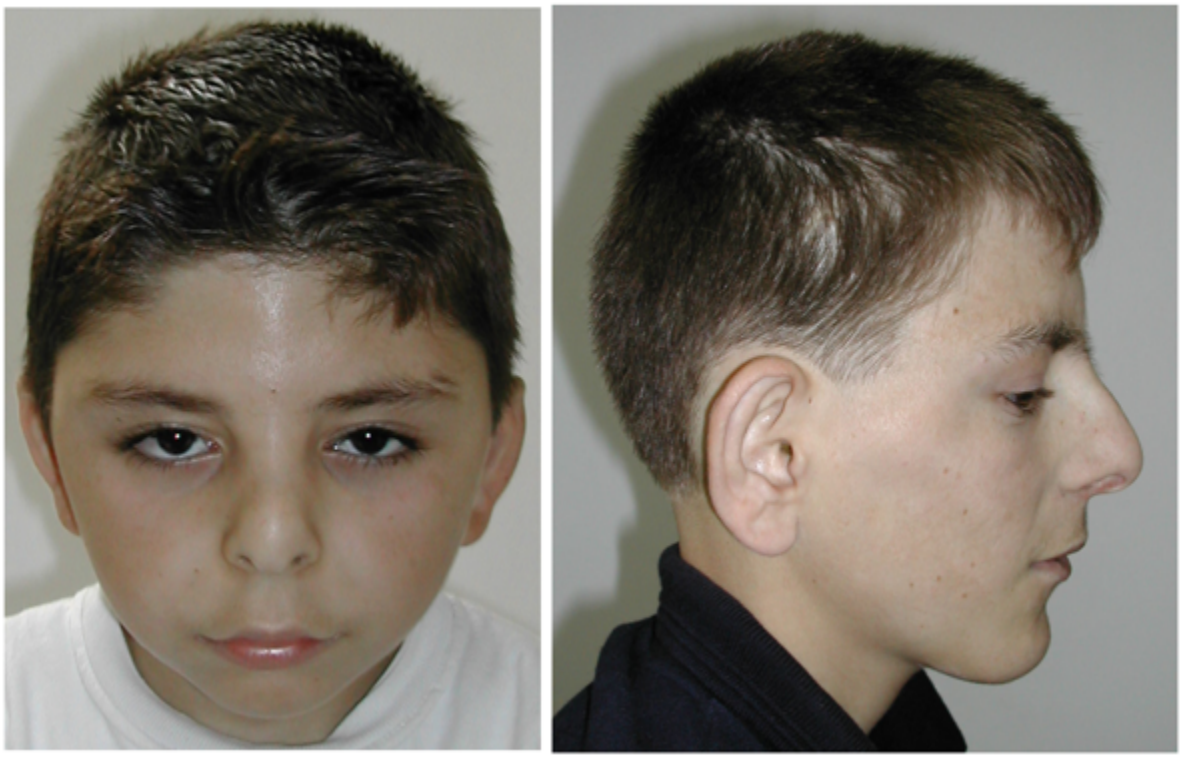

Figure 2. Triangular face, synophrys, prominent nasal bridge, anteverted nares, long philtrum, and thin vermilion of the upper lip in two affected males

Option 2

When the diagnosis of KBG syndrome has not been considered, **comprehensive genomic testing** (when clinically available) including exome sequencing and genome sequencing is likely to be the diagnostic modality selected.

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 KBG Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ANKRD11	Sequence analysis [3]	69% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	14% [4]
	CMA [7]	17% [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. The percentage represents the proportion of affected individuals who were detected to have a causative *ANKRD11* variant using each method [Low et al 2016, Goldenberg et al 2016]. The proportion of individuals who have suggestive clinical findings of KBG syndrome but do not have a detectable *ANKRD11* variant has not been clearly established.
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.
6. Gene-targeted deletion/duplication testing will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods. Note that one intragenic duplication variant that included *ANKRD11* exons 3-9 was reported [Crippa et al 2015].
7. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 16q24.3 region. Note: The 16q24.3 deletion may not have been detectable by older oligonucleotide or bacterial artificial chromosome (BAC) platforms.

Clinical Characteristics

Clinical Description

KBG syndrome was first described in 1975. The name KBG is derived from the initials of the first three families in which the condition was characterized [Herrmann et al 1975]. More than 100 affected individuals have been reported in the literature – the majority of whom are simplex (meaning the first individual in the family to be affected by the condition); although familial cases have been described. There is variable expressivity among and within families. More males than females with KBG syndrome have been reported. In some families a mildly affected mother is diagnosed only after a typically affected son is recognized [Brancati et al 2006].

Macrodontia of the permanent upper incisors is a main finding, making diagnosis prior to the eruption of these teeth more difficult. It is likely this syndrome is underdiagnosed, since many of the features are nonspecific [Sirmaci et al 2011].

Dental

Macrodontia of permanent upper central incisors is reported in 85%-95% of affected individuals [Skjei et al 2007, Ockeloen et al 2015, Low et al 2016]. In addition to macrodontia (see Suggestive Findings), cleft teeth, shovel-shaped incisors, enamel hypoplasia, hypo/oligodontia, dental pits, talon cusps, dental crowding, large dental pulps, and supernumerary mamelons can be seen [Kumar et al 2009, Ockeloen et al 2015].

Craniofacial

Craniofacial findings have been reported in 62%-80% of affected individuals. The characteristic facial appearance (see Figure 1) includes a triangular face, brachycephaly, synophrys with full eyebrows, and widely spaced eyes. A prominent nasal bridge, bulbous nose, anteverted nares, broad or bushy eyebrows, prominent

ears, long philtrum, and thin vermilion of the upper lip are also common [Brancati et al 2006, Goldenberg et al 2016, Low et al 2016]. Less commonly, cleft of the soft palate or submucous cleft, bifid uvula, and velopharyngeal insufficiency have been reported [Brancati et al 2006, Goldenberg et al 2016, Low et al 2016]. The craniofacial findings may not always be apparent, so lack of these features does not preclude the diagnosis.

Feeding

Feeding issues, especially during infancy, are reported in 20% of affected individuals and include vomiting, constipation, and gastroesophageal reflux disease [Low et al 2016].

Growth

Short stature (below the 3rd centile) has been observed in 40%-77% of affected individuals [Reynaert et al 2015, Goldenberg et al 2016]. Birth weight, length, and head circumference are usually normal. Delayed bone age is an additional finding [Brancati et al 2006]. Endocrinologic evaluations for short stature typically are normal. Preliminary evidence suggests that growth hormone therapy may increase the height potential of affected individuals [Reynaert et al 2015].

Skeletal

Variable skeletal anomalies have been reported in 75% of affected individuals [Skjei et al 2007, Low et al 2016]. The most frequent findings are costovertebral anomalies, such as cervical ribs, abnormal vertebral shape, end plate abnormalities, posterior fusion defects, or spina bifida occulta [Skjei et al 2007]. A large anterior fontanelle with delayed closure can also be seen [Ockeloen et al 2015, Low et al 2016]. Other abnormalities include a short and webbed neck, abnormal ribs, brachydactyly, clinodactyly, syndactyly of toes 2-3, kyphosis, scoliosis, hip dysplasia or Perthes disease, sternum abnormalities, and wormian bones in the skull [Brancati et al 2006]. Clavicular pseudoarthrosis and osteopenia have also been reported [Murray et al 2017].

Neurologic

Intellectual abilities – childhood. Cognitive skills can be quite variable among affected individuals. More than 90% will have some degree of developmental delay, especially in speech [Lo-Castro et al 2013, Goldenberg et al 2016]. The voice character may be hoarse. No developmental regression has been reported. Average age for walking is 21 months [Brancati et al 2006, Low et al 2016]. Average age for first words is 36 months [Brancati et al 2006]. Some affected children attend mainstream classes with minimal additional aid while others require special education [Low et al 2016].

Intellectual abilities – adulthood. Intelligence ranges from moderate intellectual disability to normal intelligence, with most individuals having mild intellectual disability [Lo-Castro et al 2013, van Dongen et al 2017]. It is not uncommon for verbal IQ to surpass performance IQ. Completing a regular high school without support appears to be rare; however, some reported adults have completed trade school. More than half of affected adults had jobs and were self-sufficient. Some were able to live completely independently, while others required some assistance with tasks at home, such as finances. Some affected women have had children and raised them with help from a spouse or other family members [Goldenberg et al 2016, Low et al 2016].

Seizures. EEG abnormalities, with or without seizures, have been reported in about 50% of affected individuals [Skjei et al 2007]. Age of onset can range from infancy to the teenage years [Low et al 2016]. The type of epilepsy is variable. Although tonic-clonic seizures are most common, no one specific type of epilepsy has been associated with the syndrome. Treatment with anti-seizure medication has proven effective in the majority of affected individuals. Many have remission of symptoms after adolescence [Lo-Castro et al 2013]. A few affected individuals have reportedly had severe seizures at a young age (described as infantile spasms / epileptic encephalopathy), in some cases drug resistant [C Ockeloen, personal communication; Samanta & Willis 2015].

Brain malformations. Various brain abnormalities have been reported, including cerebellar vermis hypoplasia [Zollino et al 1994], enlarged cysterna magna, chiari I malformation, periventricular nodular heterotopia, pineal cyst, dysgenesis of the corpus callosum, colpocephaly, posterior fossa arachnoid cyst, and optic nerve hypoplasia [Oegema et al 2010, Willemsen et al 2010, Ockeloen et al 2015]. Meningomyelocele has also been reported [Maegawa et al 2004, Brancati et al 2006]. The frequency of brain malformations is not known because brain MRI has not been performed in large cohorts of affected individuals. In a cohort of 13 affected children, two had mild periventricular leukomalacia with normal ventricles and an isolated dilated left ventricle, and the other two showed moderate enlargement of the cisterna magna with normal ventricles [Low et al 2016]. In another cohort five out of six affected individuals who had neuroimaging had significant brain changes including widespread calcification, agenesis of corpus callosum, and small optic nerves [Murray et al 2017].

Behavior. Behavioral issues are reported in at least half of affected persons with KBG syndrome. Milder issues include poor concentration and restless movement. More severe issues include obsessions and deteriorating behavior when routines are changed. Anxiety and shyness are common, as are reports of difficulty in understanding social situations.

- Attention deficit hyperactivity disorder is diagnosed in 10%-15% of affected individuals [Goldenberg et al 2016, Low et al 2016].
- While behavior issues are common among affected individuals, reports regarding the extent of association between autism spectrum disorder (ASD) and KBG syndrome are conflicting:
    - Previous studies reported an association between ASD and the 16q24.3 deletion [Willemsen et al 2010, Handrigan et al 2013].
    - ASD has not been commonly seen in affected individuals with intragenic *ANKRD11* pathogenic variants: Goldenberg et al [2016] reported one affected individual with ASD in a cohort of 35 affected people; in a study by Murray et al [2017] one of 18 affected individuals met DSM-V criteria for ASD; Ockeloen et al [2015] reported ASD in eight of 20 affected individuals (40%); Low et al [2016] reported eight children with ASD out of 32 (25%) who had intragenic *ANKRD11* pathogenic variants. Ascertainment bias may have played a role in this discrepancy.

Hearing

Hearing issues are seen in 25%-31% of affected individuals. Recurrent otitis media has been shown to cause hearing loss in some individuals with KBG syndrome. All types of hearing loss (conductive, mixed, and sensorineural) have been reported in association with the condition, with conductive loss being the most common.

Less Common Findings

Undescended testicles have been reported in 25%-35% of males [Brancati et al 2004, Low et al 2016].

Cardiac defects, including ASD and VSD, have been reported [Goldenberg et al 2016] in 10%-26% of affected individuals.

Various ocular findings, including strabismus, congenital bilateral cataract, high myopia, and megalocornea [Brancati et al 2006], have also been reported.

Advanced puberty, sometimes requiring treatment, has been reported in some individuals.

Skin and hair abnormalities, such as hyperpigmentation, ichthyosis, hypertrichosis, abnormal hair whorls, and dystrophic nails, have been reported [Low et al 2016].

Prenatal

There is one report of prenatal diagnosis of KBG syndrome [Hodgetts Morton et al 2017]. A 1.86-Mb microdeletion encompassing *ANKRD11* and 25 other genes was identified in a male fetus showing multiple external congenital anomalies including a triangular-shaped face, mildly low-set ears, and a right retained testis. Internal congenital anomalies included incomplete lobation of the left lung, lobulated spleen, cervical ribs, irregularity of vertebral body C1-4, and calcification of the liver associated with the portal tracts.

Genotype-Phenotype Correlations

The vast majority of pathogenic variants are loss-of-function variants. No specific genotype/phenotype correlations have been reported, with the exception of those who have a larger 16q24.3 deletion.

16q24.3 deletions. Individuals with a 16q24.3 deletion have the findings of KBG syndrome listed previously in addition to intellectual disability and autism spectrum disorder (although the increased frequency of autism spectrum diagnoses in this cohort may be a result of ascertainment bias) [Willemsen et al 2010, Sacharow et al 2012, Khalifa et al 2013, Miyatake et al 2013].

- Deletions in the 16q24.3 region are not recurrent; each affected individual or family appears to have a novel deletion. It is likely that other genes deleted in this region have an effect on the phenotype [Sacharow et al 2012, Lim et al 2014].
- Individuals with a 16q24.3 deletion that includes *ANKRD11* and surrounding genes have a more severe phenotype, with brain anomalies detected in 28%, congenital heart defects in 33%, severe astigmatism in 28%, and thrombocytopenia in 22% [Novara et al 2017].

Prevalence

KBG syndrome was initially thought to be quite rare; however, it is likely underdiagnosed because of mild and nonspecific features in some affected individuals especially before eruption of the permanent dentition [Sirmaci et al 2011]. To date, more than 100 individuals have been reported in the literature.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ANKRD11*.

Individuals with larger deletions of the 16q24.3 region that include *ANKRD11* have findings of KBG syndrome in addition to other features (see Genotype-Phenotype Correlations). This disorder is occasionally referred to as "16q24.3 microdeletion syndrome" [Novara et al 2017], although deletions of this region are non-recurrent.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of KBG Syndrome

DiffDx Disorder	Gene(s)	MOI	Clinical Features of the DiffDx Disorder	
			Overlapping w/KBG syndrome	Distinguishing from KBG syndrome
Cornelia de Lange syndrome	*NIPBL* *SMC1A* *HDAC8* *SMC3* *RAD21*	AD XL	• Facial features • DD • Growth restriction • Hearing loss • Cryptorchidism	Typically: • Head circumference small • ID more severe

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of the DiffDx Disorder	
			Overlapping w/KBG syndrome	Distinguishing from KBG syndrome
Silver-Russell syndrome	See footnote 1.	See footnote 1.	• Facial features • DD • Growth restriction • Cryptorchidism	• IUGR • Limb/facial asymmetry
Aarskog-Scott syndrome (OMIM 305400)	*FGD1*	XL	• Short stature • Distinctive facial features • Macrodontia • Brachydactyly • Vertebral anomalies • Cryptorchidism	• Cognitive ability normal in most • Shawl scrotum in males
Cohen syndrome	*VPS13B*	AR	• Prominent central incisors • DD	• Microcephaly • Obesity • Myopia • Choreoretinal dystrophy

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

1. Silver-Russell syndrome has multiple etiologies including: epigenetic changes that modify expression of genes in the imprinted region of chromosome 11p15.5, maternal UPD7, and (infrequently) autosomal dominant or autosomal recessive inheritance.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with KBG syndrome, the evaluations summarized in Table 3 (if they have not already been completed) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis of KBG Syndrome

System/Concern	Evaluation	Comment
Oropharynx	Dental eval for anomalies incl macrodontia, oligodontia, enamel hypoplasia [Kumar et al 2009]	
	Assessment for cleft palate, bifid uvula, velopharyngeal insufficiency	Refer to cleft/craniofacial team if palatal anomalies are present or suspected.
Neurologic	EEG if seizures are suspected	Consider head MRI to evaluate for brain malformations if seizures are present.
Genitourinary	Assessment for undescended testes in males	Refer to urologist as needed.
Hearing	Audiologic eval	
Cardiovascular	Echocardiogram to assess for congenital heart disease	Refer to cardiologist as needed.
Eyes	Ophthalmologic eval	
Miscellaneous/ Other	Developmental assessment	Consider psychiatric eval for severe behavioral issues.
	Consultation w/clinical geneticist &/or genetic counselor	

Table 4. Evaluations To Consider Following Initial Diagnosis of KBG Syndrome

System/Concern	Evaluation	Comment
Gastrointestinal	Feeding & nutrition eval [Goldenberg et al 2016, Low et al 2016]	Consider nasogastric or gastrostomy tube placement if clinically indicated.
Musculoskeletal	Skeletal survey to assess for costovertebral anomalies, scoliosis, kyphosis	Consider referral to orthopedist if indicated.
Endocrine	Assess for short stature.	Consider bone age assessment.
	Assess for advanced or premature puberty.	Refer to endocrinologist as needed.

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with KBG Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Palatal anomalies	Surgical correction &/or speech therapy may be required.	
Feeding issues	Nasogastric tube during infancy or medication for GERD may be required.	Refer to nutritionist or dietician as needed [Goldenberg et al 2016, Low et al 2016].
Seizures	Treatment per neurologist based on type of seizure present [Lo-Castro et al 2013]	
Undescended testes	Standard treatment per urologist	
Chronic otitis media	Referral to otolaryngologist for consideration of pressure-equalizing tubes &/or tonsillectomy/adenoidectomy	
Hearing loss	Consider amplification.	See Hereditary Hearing Loss and Deafness Overview.
Cardiovascular anomalies	Standard treatment per cardiologist	
Vision issues / strabismus	Standard treatment per ophthalmologist	
Short stature	Consider growth hormone therapy.	
Premature puberty	Consider medication to arrest puberty, as per endocrinologist.	

GERD = gastroesophageal reflux disease

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. In the US, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.

- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a 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., scoliosis, hip dislocation).
- Consider use of durable medical equipment 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 (e.g., feeding, grooming, dressing, writing).

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding as a result of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

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 when necessary.

Surveillance

Routine monitoring for the following should be considered:

- Hearing, to assess for hearing loss
- Vision, if ophthalmologic issues are present
- Growth and pubertal status, to assess for short stature, growth velocity, and advanced or premature puberty [Goldenberg et al 2016, Low et al 2016]

- Regular developmental assessments to evaluate cognition and learning

Agents/Circumstances to Avoid

Because of the risk of hearing loss, ototoxic drugs should be avoided.

Evaluation of Relatives at Risk

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

Pregnancy Management

There are no universal pregnancy issues in women with KBG syndrome. Pregnancy management should be tailored to the specific features present in the affected woman. For those who have congenital heart defects, management by a cardiologist and maternal fetal medicine physician during pregnancy should be considered. For those who have a seizure disorder that requires medical therapy, management by a neurologist during pregnancy should be considered.

In general, women with epilepsy or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication during pregnancy reduces this risk. However, exposure to anti-seizure medication may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from anti-seizure medication exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of anti-seizure medication to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given anti-seizure drug during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

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

KBG syndrome, caused by a non-recurrent deletion of 16q24.3 that includes *ANKRD11* or by a pathogenic variant within *ANKRD11*, is inherited in an autosomal dominant manner.

Risk to Family Members

Non-Recurrent Deletion of 16q24.3 Including *ANKRD11*

Parents of a proband

- 25% of probands with KBG syndrome caused by deletion of 16q24.3 have a parent who is mildly affected and/or harbors the deletion in a mosaic fashion.
- 75% of probands with KBG syndrome caused by deletion 16q24.3 have a *de novo* deletion.
- Evaluation of the parents by genomic testing that will detect the deletion identified in the proband is recommended.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband's parents.
- If the 16q24.3 deletion found in the proband is not identified in one of the parents, the risk to sibs is low (<1%) but greater than that of the general population because of the possibility of parental germline mosaicism [Khalifa et al 2013].
- If one of the parents has the deletion identified in the proband, the risk to each sib of inheriting the deletion is 50%. However, it is not possible to reliably predict clinical severity in sibs who inherit the deletion.

Offspring of a proband. Each child of an individual with deletion 16q24.3 has a 50% chance of inheriting the 16q24.3 deletion; however, it is not possible to reliably predict clinical severity in offspring who inherit the deletion.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the 16q24.3 deletion, the parent's family members may be at risk.

Pathogenic Variant Within *ANKRD11*

Parents of a proband

- Approximately 34% of individuals with KBG syndrome caused by a pathogenic variant within *ANKRD11* have an affected parent.
- Approximately 66% of individuals with KBG syndrome caused by a pathogenic variant within *ANKRD11* have a *de novo* variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *ANKRD11* pathogenic variant to determine if the variant was inherited or is *de novo* in the proband.
- If the *ANKRD11* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo ANKRD11* pathogenic variant in the proband or, theoretically, germline mosaicism in a parent.
    - If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected [Crippa et al 2015].
    - No cases of mosaicism for the *ANKRD11* pathogenic variant limited to only the germline have been reported.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband's parents:
    - If a parent of the proband has the *ANKRD11* pathogenic variant, the risk to sibs of inheriting the variant is 50%. Intrafamilial clinical variability has been reported.
    - If the *ANKRD11* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism.
- If the parents have not been tested for the *ANKRD11* pathogenic variant but are clinically unaffected, sibs are still at increased risk for KBG syndrome because of the possibility of parental somatic mosaicism leading to a very mild phenotype [Crippa et al 2015] or the theoretic possibility of parental germline mosaicism.

Offspring of a proband have a 50% chance of inheriting the *ANKRD11* sequence variant; however, it is not possible to reliably predict clinical severity in offspring who inherit the 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 *ANKRD11* pathogenic variant, the parent's family members may be at risk.

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 genetic alteration identified in the proband or clinical evidence of the disorder, the genetic alteration is likely *de novo;* however, gonadal mosaicism cannot be excluded. Further 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 young adults who are affected or at risk of having a child with KBG syndrome.

Prenatal Testing and Preimplantation Genetic Testing

Once an intragenic *ANKRD11* pathogenic variant or deletion of 16q24.3 has been identified in an affected family member, prenatal and preimplantation genetic testing 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.

- **KBG Foundation**
  8539 South Redwood Road
  West Jordan UT 84088
  Phone: 801-566-5949
  Fax: 801-566-5949
  Email: contact@KBGFoundation.com
  www.kbgfoundation.com
- **MedlinePlus**
  KBG syndrome
- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **FACES: National Craniofacial Association**

Phone: 800-332-2373; 423-266-1632
Email: info@faces-cranio.org
www.faces-cranio.org

- **World Craniofacial Foundation**
  7777 Forest Lane
  Suite C-616
  Dallas TX 75230
  Phone: 800-533-3315
  Fax: 972-566-3850
  Email: info@worldcf.org
  www.worldcf.org

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. KBG Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ANKRD11	16q24.3	Ankyrin repeat domain-containing protein 11	ANKRD11 @ LOVD Iran Variation Database - ANKRD11	ANKRD11	ANKRD11

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 KBG Syndrome (View All in OMIM)

148050	KBG SYNDROME; KBGS
611192	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 11; ANKRD11

Molecular Pathogenesis

Gene structure. The *ANKRD11* transcript NM_013275.5 has 13 exons, of which exons 1 and 2 are noncoding.

Pathogenic variants. The great majority of pathogenic variants are frameshift and nonsense. Most are clustered within exon 9, although this is likely because this exon represents more than 80% of the coding region; missense variants should be interpreted with caution, as many have been reported among the general population [Goldenberg et al 2016]. The vast majority of reported pathogenic variants are private to individual families. The pathogenic c.1903_1907delAAACA variant has been reported in multiple affected individuals from different backgrounds [Low et al 2016]. Pathogenic deletion can involve all of *ANKRD11* or only a portion of the gene [Goldenberg et al 2016]. One intragenic multiexon duplication has been reported [Crippa et al 2015].

Table 6. *ANKRD11* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1903_1907delAAACA	p.Lys635GlnfsTer26	NM_013275.5 NP_037407.4

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.

Normal gene product. *ANKRD11* encodes the ankryn repeat domain-containing protein 11 (ANKRD11). The protein typically regulates transcription by binding chromatin modifying enzymes, such as histone deacetylases. This is important for nervous system development and function. The gene contains two transcriptional repression domains at the N and C terminals. There is also an activation domain that can stimulate transcription. ANKRD11 is known to interact with TP53 and there is an indirect association with CDKN1A, both of which are proteins known to be important in cell cycle progression. It is proposed that ANKRD11 functions as a transcriptional co-regulator for histone acetylation, thereby affecting the developing nervous system [Gallagher et al 2015, Walz et al 2015, Sirmaci et al 2011]. Recent findings suggest that ANKRD11 plays a role in epigenetic modification of genes involved in neuron differentiation during brain development [Ka & Kim 2018].

Abnormal gene product. The mechanism of pathogenicity for ANKRD11 has not yet been fully elucidated; however, there are two proposed mechanisms. It is possible that ANKRD11 is involved in synaptogenesis. Another likely possibility is that the protein is involved in early nervous system development, and abnormal localization causes a damaged template for the circuitry of the nervous system to be built, thereby causing abnormal cognitive function [Sirmaci et al 2011, Walz et al 2015, Gallagher et al 2015]. It appears that haploinsufficiency results in the KBG syndrome phenotype [Sirmaci et al 2011]; however, since the vast majority of detected pathogenic variants affect the ANKRD11 C terminal region, and the N terminal region contains a dimerization motif, a dominant-negative effect of the pathogenic allele has not been excluded [Walz et al 2015].

Chapter Notes

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