ANKRD11 And KBG Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK487886/

SummaryClinical 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.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.

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DiagnosisWhile 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 FindingsKBG 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 (*); OROne 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 mediaPalatal abnormalitiesHair anomalies (e.g., low hairline, coarse hair)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

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

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Learning difficulties of variable severityEEG abnormalities with or without seizures

Family history

* A first-degree relative with KBG syndromeNote: Absence of a family history of KBG syndrome does not preclude the diagnosis.

Other

Feeding difficultiesCryptorchidism in malesEstablishing the DiagnosisThe 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 1When the phenotypic findings suggest the diagnosis of KBG syndrome, genetic testing approaches can include EITHER:Single-gene testing or use of a multigene panel; ORChromosomal 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.Option 2When 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 SyndromeView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable

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Suggestive FindingsKBG 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 (*); OROne finding highlighted by an asterisk and at least two additional findings.

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

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Clinical CharacteristicsClinical DescriptionKBG 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].DentalMacrodontia 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].CraniofacialCraniofacial 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.FeedingFeeding issues, especially during infancy, are reported in 20% of affected individuals and include vomiting, constipation, and gastroesophageal reflux disease [Low et al 2016].GrowthShort 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].SkeletalVariable 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].

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Genetically Related (Allelic) DisordersNo 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 DiagnosisTable 2. Disorders to Consider in the Differential Diagnosis of KBG SyndromeView in own windowDiffDx DisorderGene(s)MOIClinical Features of the DiffDx DisorderOverlapping w/KBG syndromeDistinguishing from KBG syndrome
Cornelia de Lange syndrome

NIPBL

SMC1A

HDAC8

SMC3

RAD21

ADXL

Facial featuresDDGrowth restrictionHearing lossCryptorchidism

Typically:

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Silver-Russell syndrome

See footnote 1.See footnote 1.

Facial featuresDDGrowth restrictionCryptorchidism

IUGRLimb/facial asymmetry

Aarskog-Scott syndrome(OMIM 305400)

FGD1

XL

Short statureDistinctive facial featuresMacrodontiaBrachydactylyVertebral anomaliesCryptorchidism

Cognitive ability normal in mostShawl scrotum in males

Cohen syndrome

VPS13B

AR

Prominent central incisorsDD

MicrocephalyObesityMyopiaChoreoretinal 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-linked1. 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.

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Cognitive ability normal in mostShawl scrotum in males

Cohen syndrome

VPS13B

AR

Prominent central incisorsDD

MicrocephalyObesityMyopiaChoreoretinal dystrophy

Facial features

DD

Growth restriction

Hearing loss

Cryptorchidism

Head circumference small

ID more severe

Facial features

DD

Growth restriction

Cryptorchidism

IUGR

Limb/facial asymmetry

Short stature

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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-linked1. 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.

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ManagementEvaluations Following Initial DiagnosisTo 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 SyndromeView in own windowSystem/ConcernEvaluationComment
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Neurologic
EEG if seizures are suspectedConsider head MRI to evaluate for brain malformations if seizures are present.

Genitourinary

Assessment for undescended testes in malesRefer to urologist as needed.

Hearing

Audiologic eval

Cardiovascular

Echocardiogram to assess for congenital heart diseaseRefer to cardiologist as needed.

Eyes

Ophthalmologic eval

Miscellaneous/

Other

Developmental assessmentConsider psychiatric eval for severe behavioral issues.Consultation w/clinical geneticist &/or genetic counselorTable 4. Evaluations To Consider Following Initial Diagnosis of KBG SyndromeView in own windowSystem/ConcernEvaluationComment

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, kyphosisConsider 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 ManifestationsTable 5. Treatment of Manifestations in Individuals with KBG SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

Palatal anomalies

Surgical correction &/or speech therapy may be required.

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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

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Consider growth hormone therapy.

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Consider medication to arrest puberty, as per endocrinologist.GERD = gastroesophageal reflux diseaseDevelopmental Delay / Intellectual Disability Management IssuesThe 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 ConcernsChildren may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis

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Therapies Under InvestigationSearch 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 InheritanceKBG 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 MembersNon-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.

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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 IssuesConsiderations 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 TestingOnce 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.

Mode of InheritanceKBG 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.

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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.

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.

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.

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.

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.

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.

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.

Related Genetic Counseling IssuesConsiderations 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.

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 TestingOnce 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 RoadWest Jordan UT 84088Phone: 801-566-5949Fax: 801-566-5949Email: contact@KBGFoundation.com

www.kbgfoundation.com

MedlinePlus

KBG syndrome

Children's Craniofacial Association

Phone: 800-535-3643Email: contactCCA@ccakids.com

www.ccakids.org

FACES: National Craniofacial Association

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

www.faces-cranio.org

World Craniofacial Foundation

7777 Forest LaneSuite C-616Dallas TX 75230Phone: 800-533-3315Fax: 972-566-3850Email:

info@worldcf.org

www.worldcf.org

KBG Foundation

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Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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) View in own window

148050KBG SYNDROME; KBGS

611192ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 11; ANKRD11Molecular PathogenesisGene 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 GeneReviewView in own windowDNA Nucleotide ChangePredicted Protein ChangeReference Sequencesc.1903_1907delAAACAp.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].

Table A.KBG Syndrome: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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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

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KBG Syndrome: Genes and Databases

GeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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Table B.OMIM Entries for KBG Syndrome (View All in OMIM) View in own window

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OMIM Entries for KBG Syndrome (View All in OMIM)

148050KBG SYNDROME; KBGS

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