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Au-Kline Syndrome

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Summary

Clinical characteristics

Au-Kline syndrome is characterized by developmental delay and hypotonia with moderate-to-severe intellectual disability, and typical facial features that include long palpebral fissures, ptosis, shallow orbits, large and deeply grooved tongue, broad nose with a wide nasal bridge, and downturned mouth. There is frequently variable autonomic dysfunction (gastrointestinal dysmotility, high pain threshold, heat intolerance, recurrent fevers, abnormal sweating). Congenital heart disease, hydronephrosis, palate abnormalities, and oligodontia are also reported in the majority of affected individuals. Additional complications can include craniosynostosis, feeding difficulty, vision issues, osteopenia, and other skeletal anomalies.

Diagnosis/testing

The diagnosis of Au-Kline syndrome is established in a proband by identification of a heterozygous pathogenic variant in *HNRNPK* on molecular genetic testing.

Management

Treatment of manifestations: Physiotherapy support may be helpful for hypotonia; dysautonomia management per neurologist; standard treatment for congenital heart defects; cleft palate treatment per craniofacial specialists; early intervention, individualized education, and therapies for developmental delay; psychiatry referral for those with behavior issues; nasogastric or gastric-tube feeding as needed for significant feeding issues; treatment of hearing loss with hearing aids if necessary; standard treatment for refractive errors and keratopathy; standard dental and/or orthodontic care as needed; orthopedics referral for scoliosis as needed for bracing or surgical intervention; standard management for hypothyroidism; bisphosphonate treatment could be considered for recurrent fractures.

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Prevention of secondary complications: Anesthesia consultation is suggested prior to any sedation for surgery given potential airway issues from malocclusion and macroglossia and risk for prolonged intubation and ventilation.

Surveillance: Screen for craniosynostosis in infants at each health visit during the first few months of life; at all health visits and at least annually review developmental milestones and screen for seizure history, symptoms of dysautonomia, behavior concerns, and scoliosis; annual audiologic evaluation; echocardiography to monitor for aortic dilatation with frequency as per cardiologist; ophthalmologic evaluation with frequency as per ophthalmologist; periodic TSH and bone densitometry as needed.

Genetic counseling

Au-Kline syndrome is inherited in an autosomal dominant manner. All probands reported to date with Au-Kline syndrome have the disorder as a result of a *de novo HNRNPK* pathogenic variant. Each child of an individual with Au-Kline syndrome has a 50% chance of inheriting the *HNRNPK* pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if the *HNRNPK* pathogenic variant in the family is known.

Diagnosis

Formal diagnostic criteria for Au-Kline syndrome (AKS) have not been established.

Suggestive Findings

AKS **should be suspected** in individuals with the following clinical and imaging findings.

Clinical findings

- Characteristic facial features [Au et al 2015, Au et al 2018] (see Figure 1):
  - Long palpebral fissures
  - Ptosis
  - Shallow orbits
  - Deeply grooved tongue
  - Broad nose with wide nasal bridge
  - Downturned mouth, often described as an "M-shaped" Cupid's bow
- Craniosynostosis; typically sagittal and metopic sutures are affected. Metopic ridging is common.
- Palate abnormalities (e.g., cleft palate, high-arched palate, bifid uvula)
- Congenital heart malformations (e.g., ventricular septal defect, atrial septal defect, bicuspid aortic valve, and more complex malformations)
- Genitourinary anomalies (e.g., hydronephrosis, undescended testes)
- Skeletal anomalies (e.g., vertebral segmentation defects, scoliosis, congenital hip dysplasia)

Imaging findings

- **Brain MRI.** Individuals with AKS can have variable brain anomalies identified on MRI. More common findings include gray matter heterotopia and hypoplasia of the corpus callosum [Lange et al 2016, Au et al 2018].
- **Radiographs of the spine** may show vertebral segmentation defects [Au et al 2015, Au et al 2018].
- **Spine MRI.** Spinal syrinx may be identified, especially if scoliosis is present.

Establishing the Diagnosis

The diagnosis of Au-Kline syndrome **is established** in a proband by identification of a heterozygous pathogenic variant in *HNRNPK* on molecular genetic testing (see Table 1).

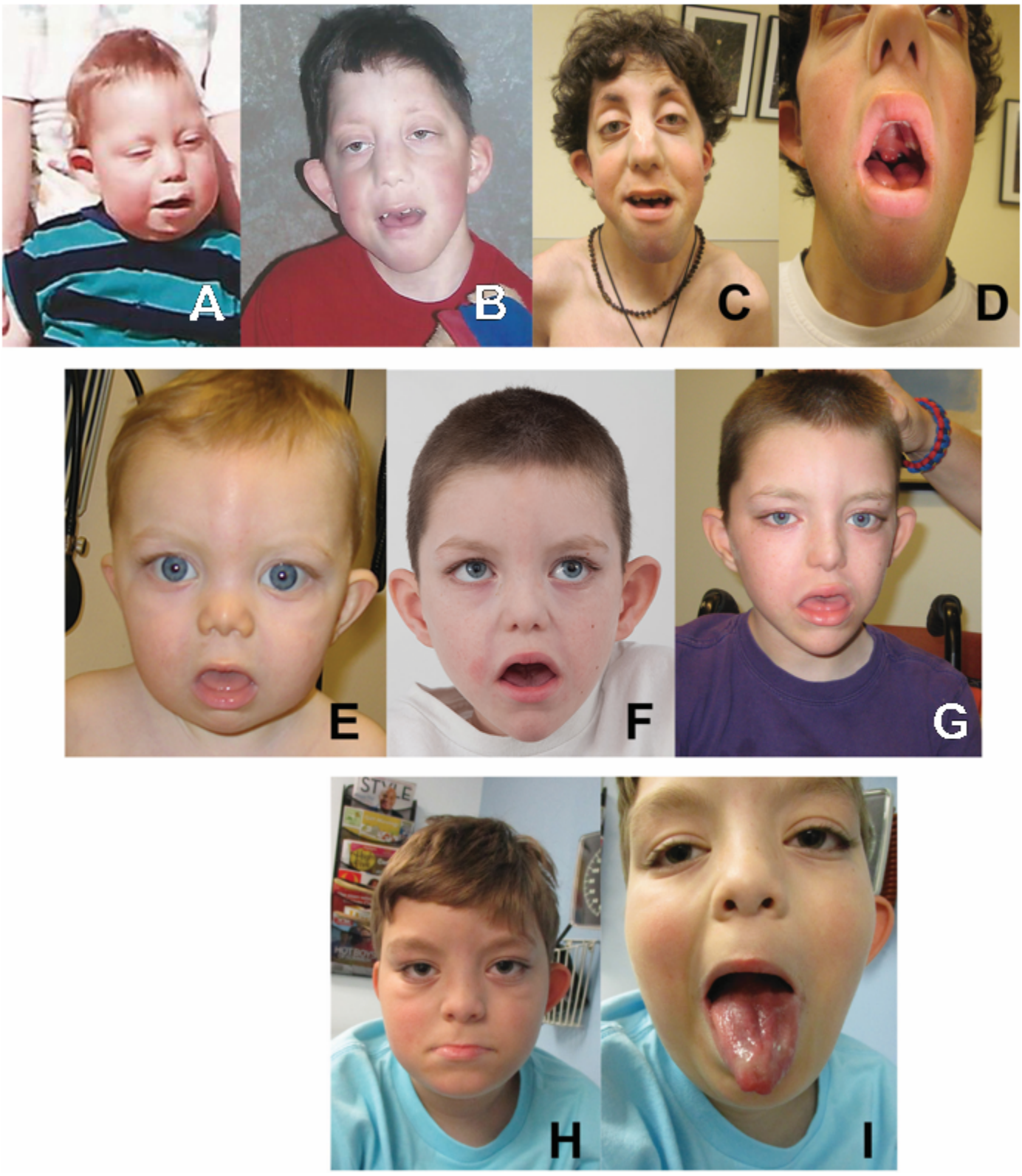

Figure 1. Three individuals with Au-Kline syndrome

A-C. Proband 1 at age 14 months, age 8 years, and age 19 years. Note long palpebral fissures, prominent eyes and shallow orbits, broad nasal ridge, and "M-shaped" Cupid's bow to upper lip. D. High-arched palate with bifid uvula and deeply grooved tongue present in proband 1.

E-G. Proband 2 at age 12 months, age 8 years, and age 11 years. Note presence of metopic ridging, long palpebral fissures with subtle lateral eversion, and characteristic shape to nose and mouth.

H. Proband 3 at age 7 years. I. Note deep midline groove in the tongue.
Adapted from Au et al [2018], used with permission of authors

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, exome array) depending on the phenotype.

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

Option 1

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

- **Single-gene testing.** Sequence analysis of *HNRNPK* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: Given the rarity of Au-Kline disorder, single-gene testing for *HNRNPK* may not be clinically available. A custom multigene panel or comprehensive genomic testing, or reanalysis of previous genomic testing data may be required for *HNRNPK* analysis.

- **A multigene panel** that includes *HNRNPK* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of Au-Kline syndrome, some panels for intellectual disability may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of Au-Kline syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

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 Au-Kline Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
HNRNPK	Sequence analysis [3]	16/17 [4]
	Gene-targeted deletion/duplication analysis [5]	1/17 [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Au et al [2015]; Lange et al [2016]; Miyake et al [2017]; Au et al [2018]; Dentici et al [2018]; Author, personal communication
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Pua et al [2014], Hancarova et al [2015], and Au et al [2018]) may not be detected by these methods.
6. Au et al [2018]

Clinical Characteristics

Clinical Description

Au-Kline syndrome, a recently described syndrome affecting multiple organ systems, is associated with moderate-to-severe intellectual disability. This section summarizes information from 20 individuals with Au-Kline syndrome (AKS), including published and unpublished reports [Au et al 2015; Lange et al 2016; Au et al 2018; Dentici et al 2018; Author, personal communication].

Growth. Most neonates with AKS have normal growth parameters. Approximately 50% of individuals demonstrate growth deficiency over time, affecting both height and weight. Age of onset of growth restriction has been variable. One third of individuals have microcephaly, and some may acquire microcephaly, which is usually noted by early childhood. Overgrowth has been observed in only two individuals [Au et al 2018].

Neurologic. Hypotonia has been reported in all known individuals with AKS. Reflexes are typically reduced or absent. Some individuals describe muscle weakness and/or easy fatigability. Muscle biopsy may be abnormal and has not been pursued in most individuals. Histologic findings have not been consistent, and have included type 1 fiber atrophy and mitochondrial complex 1 deficiency. Brain anomalies have been identified in several individuals. The most common abnormalities were heterotopia and thinning of the corpus callosum. Seizures have been reported in three individuals; absence seizures were reported in one individual and partial complex epilepsy in another. Seizures were controlled with anti-seizure medication in both individuals. The third individual had seizures that resolved. Several individuals have been diagnosed with autonomic dysfunction, presenting with gastrointestinal dysmotility, high pain threshold, heat intolerance, recurrent fevers, and abnormal sweating.

Cardiovascular. Congenital heart disease is present in approximately 75% of individuals with AKS. Ventricular septal defects are the most common anomaly. Complex congenital heart defects are rarely reported. Aortic dilatation has been identified in three individuals; the natural history of aortic dilatation in AKS is unclear.

Genitourinary. Hydronephrosis is present in up to 75% of individuals with AKS. It is often identified prenatally and typically associated with vesicoureteral reflux disease or obstructive uropathy. It can sometimes be severe, as in one individual who was affected with prune belly sequence [Au et al 2018].

Craniofacial. Craniosynostosis is present in approximately one third of individuals with AKS. Sagittal and metopic sutures are typically affected, and many individuals have metopic ridging without obvious or confirmed synostosis. Early detection and intervention for craniosynostosis may help with neurocognitive outcomes [Renier et al 1996], but this is unclear for AKS specifically. Approximately half of individuals with craniosynostosis have required surgical intervention.

Palate abnormalities, which include cleft palate, high-arched or narrow palate, and bifid uvula, are common.

There is a typical facial gestalt in AKS (see Figure 1). The face is often long. Orbits are often shallow. Palpebral fissures are long in almost 100% of individuals. There can be lateral lid eversion similar to Kabuki syndrome, but typically lid eversion is more subtle. Ptosis is common and can be asymmetric. Ears can be protruding, with a simplified helix. Preauricular pits are common. The nose often has a characteristic shape with broad nasal bridge and tip, and occasionally hypoplastic alae nasi. The mouth is frequently downturned and held in open position. The upper lip is often described as an "M-shaped" Cupid's bow [Dentici et al 2018]. Many individuals have a deep midline groove in the tongue, and bifid tip to the tongue has also been described. Many individuals also have macroglossia. Facial features may appear coarse.

Development. Individuals with loss-of-function *HNRNPK* variants typically have moderate-to-severe intellectual disability. More detailed developmental information is available for eight older individuals who were evaluated from age eight years to young adulthood. Independent ambulation was achieved by 5/8 individuals, although some still required assistive devices for longer distances. Seven individuals were able to communicate verbally, typically with single words. Four individuals were able to use phrases. Most older children and adults were able to use signs (up to several hundred) and devices to supplement their communication [Au et al 2018]. For example, of five individuals older than age eight years, one was able to speak in phrases and the others all had single words. 4/5 used signs, 5/5 used communication devices. Autism appeared to be rare. The neurodevelopmental outcomes for individuals with missense *HNRNPK* variants are not yet clear due to the limited number of individuals reported [Miyake et al 2017].

Gastrointestinal complications and feeding. Most newborns are able to feed normally. Some individuals struggle with feeding difficulty and may require short- or long-term support with tube feeding. These issues may be associated with bowel dysmotility (e.g., delayed gastric emptying, recurrent vomiting, pseudoobstruction). Constipation is common, and can be mild or severe.

Hearing. Hearing loss is present in approximately one third of individuals. Conductive hearing loss may be due to chronic middle ear effusion, but sensorineural hearing loss also occurs (described in 3 individuals).

Ophthalmologic. Myopia and hyperopia have both been reported in individuals with AKS. Optic nerve anomalies have been identified in several individuals, which may include hypoplasia of the optic nerve or the presence of a coloboma. There is theoretic risk for exposure keratopathy in individuals with particularly shallow orbits and long palpebral fissures, but it has not been observed in individuals with AKS.

Dental. The majority of individuals appear to have malocclusion, and some individuals have an open bite. Oligodontia is common. Bruxism is frequently observed.

Skeletal. More than half of individuals with AKS have scoliosis, which can range from mild to severe and require surgical intervention. Vertebral segmentation anomalies are present in some individuals and are more likely to be associated with severe scoliosis. Congenital hip dysplasia is observed in more than half of individuals with AKS. *Talipes equinovarus* and *pes planus* are also common. Some individuals have joint hypermobility.

Endocrine. Osteopenia has been identified in several individuals; fractures have been seen in two individuals with AKS. Hypothyroidism is also present in several individuals.

Respiratory. Most individuals with AKS have had normal sleep studies. One individual was found to hypoventilate at night and requires BiPAP.

Other. Postaxial polydactyly, branchial defects, inverted nipples, and supernumerary nipples have also been identified in individuals with AKS.

Genotype-Phenotype Correlations

At this time there are no clear genotype-phenotype correlations.

Penetrance

There is complete penetrance for AKS for loss-of-function variants in *HNRNPK*. No sex- or age-related differences have been observed. There is insufficient information regarding penetrance of missense variants in *HNRNPK*.

Prevalence

Prevalence is currently unknown. AKS is a rare disorder, only recently described in 2015. At this time the authors are aware of at least 25 affected individuals worldwide, with 12 individuals reported in the literature [Au et al 2015, Lange et al 2016, Miyake et al 2017, Au et al 2018, Dentici et al 2018].

Genetically Related (Allelic) Disorders

Larger microdeletions encompassing *HNRNPK* and adjacent genes have been reported in individuals with features of AKS in addition to other findings attributable to deletion of adjacent genes [Pua et al 2014, Hancarova et al 2015].

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Au-Kline Syndrome (AKS)

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/AKS	Distinguishing from AKS
Kabuki syndrome	*KDM6A* *KMT2D*	AD	• Postnatal growth deficiency • Congenital heart defects • Genitourinary anomalies • Elongated palpebral fissures, large prominent ears, cleft palate, & dental anomalies • ID (mild to moderate) • Skeletal anomalies	• Arched & broad eyebrows; short columella w/depressed nasal tip [1] • Cleft lip or lip pits • Immunodeficiency • Craniosynostosis is rare.
Shprintzen-Goldberg syndrome	*SKI*	AD	• Aortic dilatation • Sagittal craniosynostosis, shallow orbits, palate abnormalities, &/or bifid uvula • ID (mild to moderate) • Skeletal anomalies	• Absence of typical AKS facial gestalt [2] • Marfanoid body habitus • Arachnodactyly & camptodactyly

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/AKS	Distinguishing from AKS
Noonan syndrome	*PTPN11* *SOS1* *RAF1* *RIT1* *KRAS* *BRAF* *MAP2K1* [3]	AD	• Short stature • Genitourinary anomalies; cryptorchidism in males • Coarse facial features • Ptosis • Prenatal cystic hygroma or ↑ nuchal translucency	• Absence of typical AKS facial gestalt [2] • DD of variable degree [4] • Hypertrophic cardiomyopathy • Coagulation abnormalities • Myelodysplasia
Simpson-Golabi-Behmel syndrome type 1	*GPC3* *GPC4*	XL	• Coarse facial features & macroglossia • ID (mild to severe) • Postaxial polydactyly • Supernumerary nipples • Vertebral anomalies	• Absence of typical AKS facial gestalt [2] • Typically affects males • Pre- & postnatal overgrowth • Polyhdramnios • Macrostomia

AD = autosomal dominant; CHD = congenital heart defect; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Shallow orbits, coarse features, broad nasal ridge, open downturned mouth with macroglossia, and a deeply grooved tongue would be more suggestive of AKS.

2. See Clinical Description, **Craniofacial**.

3. Several additional genes associated with a Noonan syndrome-like phenotype in fewer than ten individuals have been identified.

4. Individuals with AKS caused by loss-of-function *HNRNPK* variants typically have moderate-to-severe intellectual disability.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Au-Kline syndrome (AKS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Au-Kline Syndrome

System/Concern	Evaluation	Comment
Constitutional	Evaluate growth.	
Neurologic	Brain MRI could be considered at time of diagnosis if neurologic symptoms (e.g., seizure); assessment for seizures & dysautonomia	Referral to neurologist as needed
Cardiovascular	Cardiac eval w/echocardiography	To evaluate for structural defects & dilatation of aorta
Genitourinary	Renal US; voiding cystourethrogram if needed	To evaluate for vesicoureteral reflux & obstructive uropathy
Craniofacial	In infants, evaluate for craniosynostosis w/clinical exam & imaging as needed.	Referral to neurosurgeon if craniosynostosis is suspected
	ENT evaluation	To identify palate anomalies & malocclusion
Neurodevelopmental/ Neuropsychiatric	Neuropsychiatric evaluation & assessment of developmental milestones	• Incl evaluation of motor, speech/language, general cognitive, & vocational skills. • Evaluate individuals age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Clinical evaluation of feeding	If there are feeding concerns or failure to thrive, consider GI referral & workup for dysmotility.
Hearing	Audiologic evaluation	To identify middle ear effusion & sensorineural hearing loss
Ophthalmologic	Ophthalmologic evaluation	To identify vision concerns & evaluate for keratopathy
Dental	Evaluation for malocclusion, oligodontia, & bruxism	
Musculoskeletal	• Spine x-rays for segmentation anomalies & scoliosis • Hip US or x-ray depending on age • Bone densitometry • Spine MRI to rule out spinal syrinx if indicated	Referral to orthopedist for congenital hip dysplasia or moderate-to-severe scoliosis
Endocrine	Monitor TSH.	To evaluate for hypothyroidism
	Bone densitometry	If fractures are reported
Respiratory	Polysomnogram	If concerns for sleep apnea
Other	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ENT = ear, nose, and throat; TSH = thyroid-stimulating hormone; US = ultrasound

Treatment of Manifestations

Treatment of the complications associated with AKS are standard and are not currently different from treatment in the general population.

Table 4. Treatment of Manifestations in Individuals with Au-Kline Syndrome

Manifestation/ Concern	Treatment	Considerations/ Other
Hypotonia	PT support may be helpful.	In those w/weakness & fatigue: anecdotal reports of benefit from creatine supplementation or mt vitamin cocktails incl coenzyme Q & carnitine; currently no published evidence to support these therapies
Dysautonomia	Referral to neurologist w/experience in management of autonomic dysfunction	Offer strategies for managing heat intolerance & abnormal sweating.
Congenital heart defects	Standard treatment per cardiologist	
Hydronephrosis	Referral to pediatric nephrologist & urologist for assessment of renal function & appropriate surgical repair	
Craniosynostosis	Referral to neurosurgeon for appropriate surgical intervention	
Cleft palate	Treatment by craniofacial team	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/ Other
Developmental delay	• Early intervention programs & individualized education programs • Speech therapy & OT to support use of sign language & assistive communication devices	
Behavior concerns	Formal eval w/psychiatrist	May be beneficial for children who exhibit more behavioral struggles
Feeding difficulties	Nasogastric or gastric-tube feeding may be necessary for significant feeding issues.	
Hearing loss	Treatment of SNHL & conductive hearing loss per ENT physician / audiologist; hearing aids if necessary	
Vision anomalies	Standard treatment for refractive errors & keratopathy	
Dental complications	Standard treatment per dentist &/or orthodontist	
Scoliosis	If scoliosis is progressive, referral to orthopedist for bracing or surgical intervention w/instrumentation may be required.	It is unclear at present whether certain interventions are more effective or beneficial for progressive scoliosis.
Hypothyroidism	Standard management for hypothyroidism	
Osteopenia	Bisphosphonate treatment could be considered for recurrent fractures.	

ENT = ear, nose, and throat; mt = mitochondrial; OT = occupational therapy; PT = physical therapy; SNHL = sensorineural hearing loss

Prevention of Secondary Complications

Anesthesia consultation is suggested prior to any sedation for surgery given potential airway issues from malocclusion and macroglossia. There is also potential risk that prolonged intubation and ventilation will be required, as occurred in one individual after surgery [Au et al 2018].

Surveillance

Table 5. Recommended Surveillance for Individuals with Au-Kline Syndrome

System/Concern	Evaluation	Frequency
Neurologic	Screen for seizure history & symptoms of dysautonomia.	At all health visits & at least annually
Cardiovascular	Echocardiography to monitor for aortic dilatation (in all patients, w/or w/out congenital heart defect)	Per cardiologist; frequency of eval may depend on size of aortic root & arch.
Craniofacial	Screen for craniosynostosis.	In infants, at all health visits during the first few months of life
Development	Review developmental milestones & screen for behavior concerns.	At all health visits & at least annually
Hearing	Audiologic eval	Annually
Refractive error &/or kerotopathy	Ophthalmologic eval	Frequency per ophthalmologist

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Scoliosis	Clinical exam for scoliosis	At all health visits & at least annually
Endocrine	TSH; bone densitometry	Periodic; frequency of bone densitometry may depend on severity & history of fracture.

TSH = thyroid-stimulating hormone

Evaluation of Relatives at Risk

Asymptomatic family members are not at risk for AKS.

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

Au-Kline syndrome (AKS) is inherited in an autosomal dominant manner and is typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with AKS whose parents have undergone molecular genetic testing have the disorder as a result of a *de novoHNRNPK* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *HNRNPK* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of germline mosaicism have been reported to date.
- Theoretically, if the parent is the individual in whom the *HNRNPK* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *HNRNPK* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Individuals with AKS are not known to reproduce; however, many of the reported probands are not yet of reproductive age.

Other family members. Given that all probands with AKS reported to date have the disorder as a result of a *de novo HNRNPK* pathogenic variant, the risk to other family members is presumed to be low.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a de novo *HNRNPK* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal testing and preimplantation genetic testing may be considered.

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.

- **MedlinePlus**
  Au-Kline 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
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Craniosynostosis

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. Au-Kline Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
HNRNPK	9q21.32	Heterogeneous nuclear ribonucleoprotein K	HNRNPK	HNRNPK

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 Au-Kline Syndrome (View All in OMIM)

600712	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN K; HNRNPK
616580	AU-KLINE SYNDROME; AUKS

Molecular Pathogenesis

Gene structure. *HNRNPK* has 17 exons and four alternative splice isoforms [Kimura et al 2010]. The longest transcript spans 3,123 base pairs and encodes the longest isoform. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Pathogenic variants associated with Au-Kline syndrome (AKS) are typically loss-of-function variants, which include nonsense, frameshift, and splice variants. Pathogenic variants identified to date have all been *de novo*. The variant c.257G>A (p.Arg86His) has been identified in two affected individuals. Although predicted to result in a missense change, this variant has been confirmed to be a splice variant, and cell-based functional studies have demonstrated decreased protein production consistent with haploinsufficiency [Au et al 2015]. The variant c.998dupA (p.Tyr333Ter) has now also been identified in two individuals [Dentici et al 2018; Author, personal communication].

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

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.257G>A	See footnote 1.	NM_002140.4 NP_002131.2
c.998dupA	p.Tyr333Ter	
c.464T>C	p.Leu155Pro	

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.
1. This variant is predicted to result in a missense variant (p.Arg86His) but has been shown to cause a splicing defect and decreased protein production.

Normal gene product. *HNRNPK* encodes heterogeneous ribonucleoprotein type K (hnRNP K). There are four isoforms reported in the literature. The longest isoform (isoform a) is 464 amino acids. The alternative protein isoforms have an either basic or acidic C terminus consisting of either ^{459}SGKFF^{463} or ^{459}ADVEGF^{464}, or they differ due to alternative splicing of exon 8, resulting in missing of residues p.Gly111-p.Asn134 [Kimura et al 2010].

HnRNP K is involved with binding single-stranded DNA or RNA, which is mediated through its three KH domains. There are two consecutive KH domains at the N terminus (encoded by exons 4-7 and 9-10) and a third located at the C terminus (encoded by exons 15-16). HnRNP K also acts as a docking platform for interaction of kinases and signal transduction factors that have roles in nucleic acid-related cellular activities, implicating hnRNP K in chromatin remodeling, transcriptional regulation, and translational regulation [Barboro et al 2014].

Abnormal gene product. Deletion of *HNRNPK* has been associated with the AKS disease phenotype, thus supporting haploinsufficiency as the underlying disease mechanism [Pua et al 2014, Hancarova et al 2015, Au et al 2018]. Most reported pathogenic single-nucleotide variants are expected to lead to nonsense-mediated decay and/or decreased or absent hnRNP K protein. Only one individual with an AKS phenotype with a *de novo* missense variant in *HNRNPK*, c.464T>C (p.Leu155Pro), has been reported in the literature [Miyake et al 2017]. It is not clear if this variant leads to reduction or loss of function.

Cancer and Benign Tumors

Somatic pathogenic variants in *HNRNPK* have been implicated in human myelodysplasia and leukemia, and mice that are haploinsufficient for *HNRNPK* are at higher risk for tumors [Barboro et al 2014, Gallardo et al 2015]. However, no hematologic abnormalities or malignancies have been identified in individuals with AKS. The oldest reported individual is age 19 years. Utility of screening for myelodysplasia is unknown and therefore no recommendations regarding cancer surveillance can be made.

Chapter Notes

Author Notes

There is an AKS Facebook group for affected individuals and families.

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