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NLM Citation: Jacob P, Bhat V, Patil SJ. *HOXA1*-Related Disorders. 2024 Nov 14. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

HOXA1-Related Disorders

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Created: November 14, 2024.

Summary

Clinical characteristics

HOXA1-related disorders are characterized by ocular motility disorder (horizontal gaze palsy with or without Duane syndrome), bilateral sensorineural deafness, cerebrovascular malformations (predominantly involving the carotid arteries), motor delay, central hypoventilation, and intellectual disability. Additional common features include congenital heart disease, facial paresis, vocal cord paresis, and swallowing dysfunction. Some individuals have seizures.

Diagnosis/testing

The diagnosis of a *HOXA1*-related disorder is established in a proband with suggestive findings and biallelic pathogenic variants in *HOXA1* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment of Duane syndrome or horizontal gaze palsy includes orthoptic exercises, botulinum toxin injection, and surgery in those with severe manifestations; hearing aids, cochlear implants, speech therapy, educational support, and accommodations for those with sensorineural deafness; management of cerebrovascular anomalies per cardiovascular specialist with medications or surgical interventions; physical therapy, occupational therapy, and early intervention services for motor delay; educational and developmental support; mechanical ventilation with aminophylline and continuous monitoring of respiratory function in those with central hypoventilation; treatment of congenital heart disease includes medications, surgical intervention, and cardiac rehabilitation; medications, botulinum toxin injection, and physical therapy for facial twitching or paresis; tracheostomy, gastrostomy tube feedings, and pharmacologic therapies for gastroesophageal reflux in those with vocal cord paresis and swallowing dysfunction; social work and family support.

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Surveillance: Ophthalmologic examination every six to 12 months; assessment of visual acuity and ocular alignment and orthoptic and fundoscopic evaluation per ophthalmologist; audiology, speech, and auditory processing assessment annually or as needed; surveillance for cerebral vascular anomalies per neurologist and/or vascular surgeon; developmental and physical therapy evaluation annually; assess for need for early intervention services, educational support, and accommodations and for signs of intellectual disability annually; respiratory evaluation with pulmonary function tests and sleep studies annually; assess for central hypoventilation and respiratory manifestations annually; cardiac evaluation, EKG, and echocardiogram annually; neurologic examination for facial twitching, facial paresis, and seizures annually; brain MRI as clinically indicated; assess family needs at each visit.

Agents/circumstances to avoid: Avoid high altitude, especially among individuals with *HOXA1*-related Athabascan brainstem dysgenesis syndrome; avoid risk factors for stroke.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of surveillance and treatment.

Genetic counseling

HOXA1-related disorders are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *HOXA1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *HOXA1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

HOXA1-Related Disorders: Included Phenotypes
• Bosley-Salih-Alorainy syndrome (BSAS) • Athabascan brainstem dysgenesis syndrome (ABDS)

For synonyms and outdated names, see Nomenclature.

Diagnosis

Suggestive Findings

HOXA1-related disorders **should be suspected** in probands with the following clinical and imaging findings and family history.

Clinical findings

- Ocular motility disorder: horizontal gaze palsy with or without Duane syndrome (also referred to as Duane retraction syndrome)
- Bilateral sensorineural deafness
- Developmental delay
- Intellectual disability
- Central hypoventilation while awake or asleep requiring supplemental oxygen and/or mechanical ventilatory support
- Congenital heart malformations, cerebrovascular malformations
- Facial paresis, vocal cord paresis, and swallowing dysfunction leading to recurrent aspiration and pneumonia

- Seizure disorder
- Neurobehavioral/psychiatric manifestations

Imaging findings

- **Bosley-Salih-Alorainy syndrome** (See Figure 1.)
  - Cerebrovascular malformations often involving the carotid arteries
  - Abnormalities of inner ear structures
  - Variable absence of cranial nerves VI-XII, most commonly cranial nerve VI (abducens nerve)
  - Small petrous bones, likely due to absent carotid canal and inner ear structural abnormalities with patulous Meckel caves
- **Athabascan brainstem dysgenesis syndrome**
  - Generalized cerebral atrophy
  - Normal brainstem
  - Abnormalities of the cerebrovascular system
  - Abnormalities of inner ear structures
  - Variable absence of cranial nerves VI-XII

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of a *HOXA1*-related disorder **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *HOXA1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *HOXA1* variants of uncertain significance (or of one known *HOXA1* pathogenic variant and one *HOXA1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *HOXA1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Targeted analysis for a founder pathogenic variant can be performed first in individuals of Saudi Arabian ancestry (c.175dupG [p.Val59GlyfsTer119]) and individuals of Navajo and/or Apache ancestry (c.76C>T [p.Arg26Ter]) (see Table 7).

A congenital cranial dysinnervation disorders multigene panel that includes *HOXA1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain

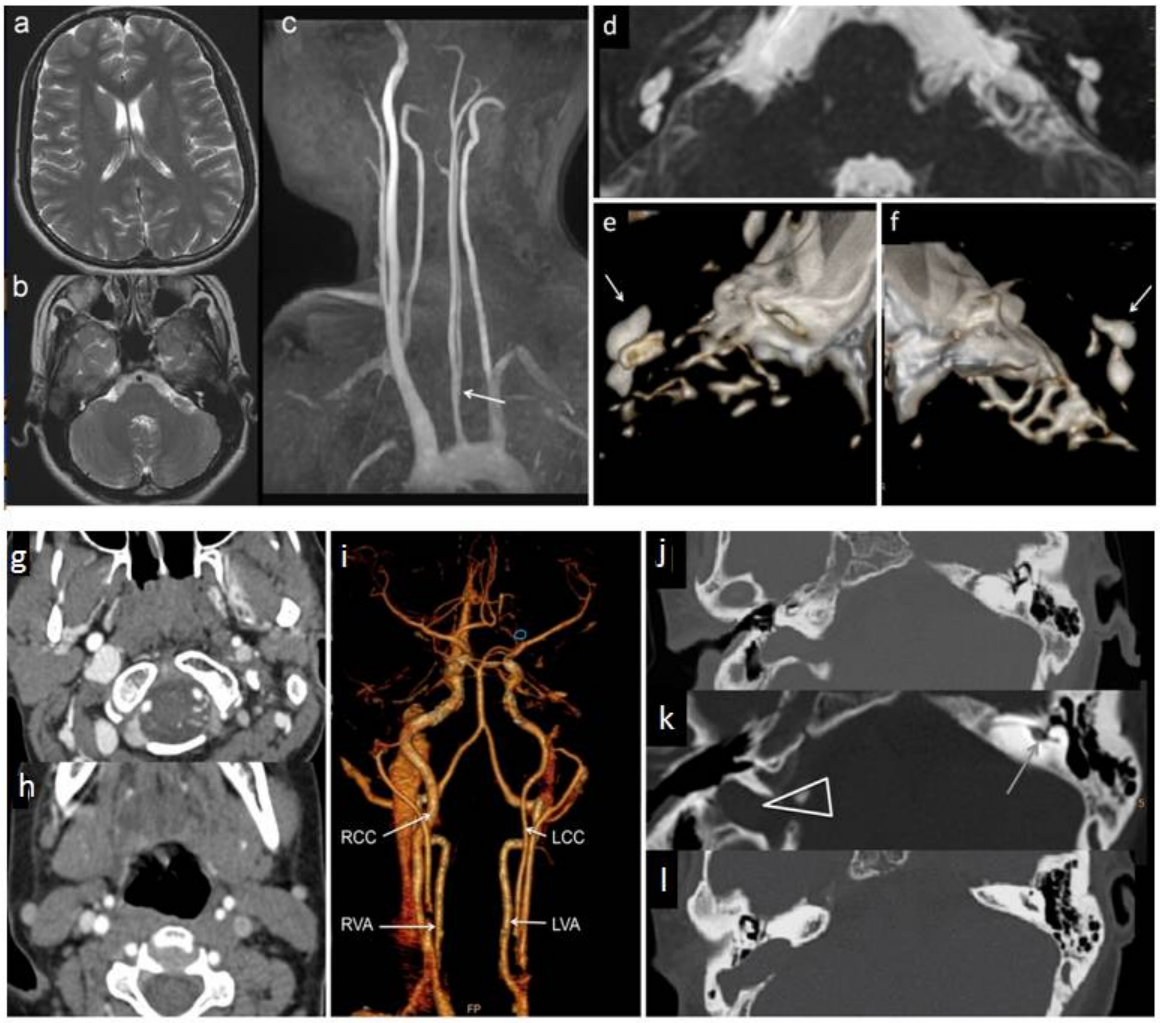

Figure 1. a-f. Brain and neck imaging of a female age 19 years with Bosley-Salih-Alorainy syndrome (BSAS). (a,b) Brain MRI: supratentorial and infratentorial axial T_2-weighted images show normal appearance of the cerebral and cerebellar hemispheres. (c) Time-of-flight (TOF) angiograph of the carotid arteries shows hypoplastic left common carotid artery and its early division into the external and internal carotid arteries (ICA) (arrow). Small-caliber ICA hypoplasia is extending into the cranium. Right common carotid artery and ICA is relatively large in caliber. (d) Maximum intensity projection (MIP) axial T_2-weighted image shows poorly developed cochlea bilaterally with single cystic structure representing the cochlea. Both vestibules are incompletely formed with small outpunching representing roots of the semicircular canal, which are not developed. Cochlear and superior vestibular nerves are present bilaterally, whereas abducens nerves are not visible. (e,f) 3D-rendered images of right and left vestibular cochlear apparatus (arrows) in coronal projections.

g-l. Brain and inner ear imaging of a male age 14 years with BSAS. (g,h) Brain MRI images at mid-cervical region show relatively small left carotid artery. (i) 3D image shows hypoplastic left common carotid artery and its divisions. The right common carotid artery and vertebral artery are relatively large. Right and left vertebral arteries (RVA, LVA) are symmetrical in caliber. (j,k,l) Images of inner ear structure show petrous bones at three levels showing normal external and middle ear structures. (k) Right carotid canal and jugular fossa (triangle) are large. Vestibulocochlear apparatus are not recognizable on the right side. Cochlea is not visualized on the left side; however, vestibule and semicircular canal are seen.

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the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that

includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of a *HOXA1*-related disorder has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *HOXA1*-Related Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
HOXA1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4, 6]

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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Bosley et al [2008], Patil et al [2020], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. To date, no large intragenic deletions/duplications have been reported in individuals with *HOXA1*-related disorders.

Clinical Characteristics

Clinical Description

HOXA1-related disorders are characterized by ocular motility disorder (horizontal gaze palsy with or without Duane syndrome), bilateral sensorineural deafness, variable cerebrovascular malformations (predominantly involving the carotid arteries), motor developmental delay, central hypoventilation, and intellectual disability. To date, 34 individuals have been identified with biallelic pathogenic variants in *HOXA1* [Holve et al 2003, Tischfield et al 2005, Bosley et al 2007, Bosley et al 2008, Higley et al 2011, Oystreck et al 2011, Ellsworth et al 2020, Patil et al 2020]. Two overlapping phenotypes have been described: Athabascan brainstem dysgenesis syndrome (ABDS) and Bosley-Salih-Alorainy syndrome (BSAS).

Table 2. *HOXA1*-Related Disorders: Frequency of Selected Features by Phenotype

Feature	% of Persons w/Feature by Phenotype [1]	
	ABDS	BSAS
Horizontal gaze palsy w/ or w/o Duane syndrome	14/14	18/20

Table 2. continued from previous page.

Feature	% of Persons w/Feature by Phenotype [1]	
	ABDS	BSAS
Sensorineural deafness	13/14	19/20
Cerebrovascular anomalies involving the carotid artery	3/3	13/13
Motor delay	12/14	13/20
Intellectual disability	13/13	3/20
Autism spectrum disorder	NA	3/20
Central hypoventilation	12/14	0/20
Congenital heart disease	10/14	5/20
Facial paresis or twitching	7/14	5/20
Seizures	4/14	2/20

Based on Tischfield et al [2005], Bosley et al [2007], Bosley et al [2008], Higley et al [2011], Oystreck et al [2011], Ellsworth et al [2020], Patil et al [2020]
ABDS = Athabascan brainstem dysgenesis syndrome; BSAS = Bosley-Salih-Alorainy syndrome; NA = not applicable
1. Denominator indicates number of appropriately evaluated individuals.

Ocular motility disorder. One of the most common clinical findings among affected individuals with ABDS and BSAS is horizontal gaze palsy with or without Duane syndrome due to underlying abducens nucleus / nerve abnormalities [Holve et al 2003, Tischfield et al 2005, Bosley et al 2007, Bosley et al 2008, Higley et al 2011, Oystreck et al 2011, Ellsworth et al 2020, Patil et al 2020]. Horizontal gaze palsy can be unilateral or bilateral and can be apparent from early infancy. Affected individuals have variable severity of abduction/adduction with or without refractive errors, nystagmus, vertical gaze involvement, strabismus (esotropia), and ptosis. Only two reported individuals with BSAS did not have the typical ocular motility disorder; one had mild ocular motility disorder and the other had normal ocular motility. Untreated eye complications can lead to amblyopia [Bosley et al 2008].

Inner ear anomalies / sensorineural deafness. Structural abnormalities within the inner ear accompanied by congenital profound sensorineural deafness are observed in most affected individuals (32/34 individuals). Structural abnormalities of the inner ear described in individuals with ABDS and BSAS can be unilateral or bilateral, including complete absence of the labyrinthine structure, common cavity deformity, and/or underdevelopment or absence of the cochlea [Holve et al 2003, Tischfield et al 2005, Bosley et al 2007, Bosley et al 2008, Higley et al 2011, Oystreck et al 2011, Ellsworth et al 2020, Patil et al 2020].

Cerebrovascular malformations. Cerebrovascular anomalies affecting the carotid arteries are frequently observed; the internal carotid arteries are most commonly involved [Bosley et al 2007, Bosley et al 2008]. These anomalies may be unilateral or bilateral, including carotid artery aplasia or hypoplasia, early branching of the common carotid artery, anterior cerebral artery aplasia, and duplication of the vertebral artery along with compensatory enlargement of the posterior communicating artery or the vestibulobasilar arterial system. Although a cerebrovascular malformation may increase the risk of stroke, in most individuals with ABDS and BSAS these vascular defects remain silent, except for two individuals. One individual with ABDS had a vertebral artery stroke and another individual with BSAS had a stroke following cardiac surgery [Holve et al 2003, Bosley et al 2008].

Developmental delay. Motor delay is noted in most affected individuals, which can be attributed to the absence of a vestibular system and congenital heart defects in individuals with BSAS rather than a widespread disturbance in the brain [Bosley et al 2008]. Most individuals with BSAS and motor delay achieved independent

ambulation [Bosley et al 2008, Patil et al 2020]. However, in individuals with ABDS, unsteady and wide-based gait was reported in those who became ambulatory along with dysmetria possibly related to cerebellar dysfunction [Holve et al 2003].

Learning difficulties / intellectual disability. Cognitive dysfunction is seen in all affected individuals with ABDS and is believed to result from chronic brain oxygen deficiency due to a combination of central hypoventilation, cerebrovascular abnormalities, and the elevated altitude where the Athabascan community resides [Bosley et al 2008]. Two individuals of 14 with ABDS are reported to have relatively mild cognitive impairment, possibly because they were raised at lower altitude.

Individuals with BSAS are reported to have variable developmental abilities and cognitive function ranging from isolated motor delay, learning difficulties, or behavioral issues to global developmental delay and autism spectrum disorder. Often neurologic assessment is confounded by the presence of profound sensorineural deafness and speech issues. Normal neurologic function has been reported in seven of 20 individuals with BSAS [Bosely et al 2007, Bosely et al 2008].

Central hypoventilation is the distinguishing feature in individuals with ABDS. Most children with ABDS had clinical features of central hypoventilation identified in early infancy (age <6 months). All reported individuals required supplemental oxygen either through mechanical ventilation or nasal cannula and aminophylline. Weaning of supplemental oxygen was possible in those who survived beyond infancy with improved respiratory drive with age. Central hypoventilation has been reported to be more severe during sleep. Some individuals only required supplemental oxygen at night [Holve et al 2003, Bosley et al 2008, Ellsworth et al 2020].

None of the individuals with BSAS have central hypoventilation.

Congenital heart disease. The majority of children with ABDS have congenital heart disease commonly involving the cardiac outflow tract including tetralogy of Fallot, coarctation of aorta, double aortic arch, transverse hypoplastic arch, aortic valve stenosis, aberrant left subclavian artery, patent ductus arteriosus, bicuspid aortic valve, ventricular septal defect, and total anomalous pulmonary venous return.

Some individuals with BSAS also have congenital heart disease including double outlet left ventricle, tetralogy of Fallot, and ventricular septal defect. One individual with BSAS was reported to have apparently isolated congenital heart disease without ocular motility disorder or hearing impairment [Bosely et al 2008].

Facial paresis, vocal cord paresis, and swallowing dysfunction are manifestations of hypoplasia and/or aplasia of certain cranial nerves. Variable facial paresis or twitching/spasms (unilateral or bilateral) have been documented in individuals with ABDS and BSAS, which is attributed to hypoplasia or aplasia of cranial nerve VII [Holve et al 2003, Tischfield et al 2005, Bosley et al 2008, Higley et al 2011]. Vocal cord paresis (2/10 individuals) and swallowing dysfunction (6/10 individuals) have also been reported in individuals with ABDS. Often these complications lead to recurrent aspirations requiring hospitalization and gastrostomy tube feeding [Holve er al 2003].

Seizures were reported in two individuals with BSAS and four individuals with ABDS [Holve et al 2003, Bosley et al 2008]. To date, further information regarding type of seizures is not available, except in one individual with ABDS described as having generalized tonic-clonic seizures (onset at age 3 years) [Holve et al 2003].

Other variable, less common clinical features [Bosley et al 2007, Bosley et al 2008]:

- External ear minor malformations (e.g., flattened ear helix, low-set ears) in four individuals with BSAS
- Clubfoot in three individuals
- Chronic constipation in two individuals with BSAS
- Frequent grimacing in two individuals with BSAS
- Facial asymmetry in one individual with BSAS and one individual with ABDS

- Multiple lentigines, hypertrichosis, polydactyly, brachydactyly, and duplex ureteral system with urethral stricture (1 individual each)

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Central hypoventilation has only been reported in individuals with ABDS, and high altitude is a suspected contributing factor [Holve et al 2003, Bosley et al 2008].

Nomenclature

ABDS was previously referred to as "Navajo brainstem syndrome." Holve et al [2003] proposed the term "Athabascan brainstem dysgenesis syndrome."

Prevalence

To date, 34 individuals have been reported with biallelic variants in *HOXA1*.

ABDS is prevalent in individuals of Navajo and Apache descent due to the *HOXA1* founder pathogenic variant c.76C>T (p.Arg26Ter). The incidence of ABDS was predicted to be 0.5-1:1,000 live births in the White River Apache Reservation and 1:3,000 live births in the Navajo population [Erickson et al 1999, Holve et al 2003].

BSAS has been reported in individuals from Middle Eastern populations including Saudi Arabia and Turkey due to the *HOXA1* founder pathogenic variant c.175dupG (p.Val59Ter).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *HOXA1*.

Differential Diagnosis

Athabascan brainstem dysgenesis syndrome (ABDS), most commonly reported in individuals of Navajo and Apache descent, must be distinguished from overlapping disorders with horizontal gaze palsy, sensorineural deafness, and/or central hypoventilation. Of note, the differential diagnosis of central hypoventilation includes congenital central hypoventilation syndrome (CCHS) (see Table 3) and other conditions associated with central hypoventilation in early infancy such as primary neuromuscular, pulmonary, or cardiac disease; brainstem lesion; hypoxic ischemic encephalopathy, asphyxia, infarction, and infection; and severe prematurity (see CCHS, Differential Diagnosis).

Bosley-Salih-Alorainy syndrome (BSAS), most commonly reported in individuals from Middle Eastern populations, must be distinguished from overlapping disorders with sensorineural deafness, horizontal gaze palsy, and/or carotid artery anomalies

Table 3. Genes of Interest in the Differential Diagnosis of *HOXA1*-Related Disorders

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/*HOXA1*-related disorders	Distinguishing from *HOXA1*-related disorders
PHOX2B	Congenital central hypoventilation syndrome	AD [1]	Central hypoventilation, restricted eye movements	Autonomic nervous system dysregulation, Hirschsprung disease

Table 3. continued from previous page.

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/*HOXA1*-related disorders	Distinguishing from *HOXA1*-related disorders
CHN1	*CHN1*-related isolated Duane syndrome	AD	Variable severity of ocular abduction/adduction	Absence of central hypoventilation, carotid artery anomalies, & deafness
FOXI3	Craniofacial microsomia 2 (OMIM 620444)	AD AR	Carotid artery anomalies, deafness	Mandibular hypoplasia, microtia
KIF21A	*KIF21A*-related CFEOM	AD	Variable vertical & horizontal eye movements	Bilateral blepharoptosis, ophthalmoplegia, bilateral ptosis, restricted vertical gaze
MAFB	*MAFB*-related isolated Duane syndrome	AD	Variable severity of ocular abduction/adduction	Absence of central hypoventilation, carotid artery anomalies, deafness
PHOX2A	*PHOX2A*-related CFEOM	AR	Variable vertical & horizontal eye movements	Bilateral ptosis, exotropia
PLXND1 *REV3L* (unknown in most affected persons) [2]	Moebius syndrome [2] (OMIM 157900)	Unknown in most; AD in small # of persons [2]	Limited ocular abduction & facial weakness	Limb abnormalities, musculoskeletal anomalies, feeding difficulties w/respect to lingual &/or pharyngeal dysfunction; intellectual disability uncommon
ROBO3	*ROBO3*-related horizontal gaze palsy w/progressive scoliosis (OMIM 607313)	AR	Horizontal gaze paralysis	Scoliosis
SALL4	*SALL4*-related disorders incl Duane-radial ray syndrome (DRRS) & acro-renal-ocular syndrome (AROS)	AD	Duane ocular anomaly	Limb anomalies incl triphalangeal, hypoplastic, or absent thumbs, microphthalmia, hypertelorism, cleft palate, & renal anomalies
TUBB3	*TUBB3*-related CFEOM	AD	Variable vertical & horizontal eye movements	Asymmetric ptosis, exotropia

AD = autosomal dominant; AR = autosomal recessive; CFEOM = congenital fibrosis of the extraocular muscles; MOI = mode of inheritance

1. Congenital central hypoventilation syndrome (CCHS) is typically inherited in an autosomal dominant manner (CCHS caused by biallelic reduced-penetrance *PHOX2B* pathogenic variants has been reported in 2 families).

2. Both genetic and environmental etiologies have been proposed. Additionally, prenatal exposure to misoprostol and other agents has been known to cause a Moebius syndrome phenotype. Heterozygous *de novo* pathogenic variants in *PLXND1* and *REV3L* have been described in a small number of individuals with congenital facial weakness associated with a variety of additional findings that overlap the Moebius syndrome spectrum [Tomas-Roca et al 2015].

Chromosome 8 abnormalities. Several individuals with Duane syndrome have been reported to have chromosome 8 abnormalities: abnormalities of the 8q13 DURS1 locus; mosaic trisomy 8 (2 individuals) [Connell et al 2004]; deletion 8q13-q21.2; a *de novo* reciprocal balanced translocation consisting of t(6:8)(q26;q13) disrupting *CPAH*; and a duplication (or microduplication) of 8q12 and 8p11.2 deletion. Three reports suggest that abnormal dosage of *CHD7* may cause the phenotype associated with 8q12 chromosome abnormalities. Individuals described in these reports manifest Duane syndrome with various associated

congenital abnormalities including other cranial nerve deficits, facial dysmorphisms, intellectual disabilities, and cardiac defects (see Duane syndrome.)

Management

No clinical practice guidelines for *HOXA1*-related disorders have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *HOXA1*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *HOXA1*-Related Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Ocular	• Complete neuro-ophthalmologic & orthoptic exams • Binocular vision tests	To evaluate for ocular motility disorder & vision
Auditory	Brainstem auditory evoked response test	To assess for hearing impairment
Cerebrovascular	Neck & brain MR TOF angiogram	To assess for anomaly of carotid artery & other arteries
Neurologic	• Neurologic exam • Brain MRI	Consider EEG if seizures are a concern.
Development	Developmental assessment incl Vineland Adaptive Behavior scale	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl behavioral issues &/or findings suggestive of ASD
Respiratory system	• Awake pulse oximetry • Sleep study • Arterial blood gases	To assess for central hypoventilation
Cardiac	• EKG • Echocardiogram	
Swallowing / Feeding / Weight gain	• Bronchoscopy • Swallow study	To assess for swallowing dysfunction, recurrent aspiration, & vocal cord paresis
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of a *HOXA1*-related disorder to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ASD = autism spectrum disorder; MOI = mode of inheritance; TOF = time-of-flight

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

Treatment of Manifestations

There is no cure for *HOXA1*-related disorders. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *HOXA1*-Related Disorders: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Duane syndrome / Horizontal gaze palsy	• Orthoptic exercises • Botulinum toxin injection • Surgery in those w/severe manifestations	• Treatment approach depends on severity & impact on visual function. • Surgical intervention may be considered if non-surgical options are insufficient.
Sensorineural deafness	• Hearing aids • Cochlear implants • Speech therapy • Consider educational support & accommodations.	Early intervention is crucial for speech & language development.
Cerebrovascular anomalies involving carotid artery	• Mgmt per cardiovascular specialist • Treatment may incl medications (e.g., antiplatelets, anticoagulants) or surgical intervention (e.g., angioplasty, stenting, surgical revascularization).	Collaborative care w/specialists to manage associated conditions (e.g., hypertension, hyperlipidemia)
Developmental delay (incl motor delay) / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	Individualized therapy plans to address specific motor delays & challenges
Central hypoventilation (in ABDS)	• Mechanical ventilation (e.g., positive pressure ventilation) w/aminophylline • Continuous monitoring of respiratory function	Lifelong mgmt w/respiratory support devices
Congenital heart disease	• Medications (e.g., diuretics, beta-blockers) • Surgical intervention (e.g., repair of structural defects) • Cardiac rehab	Close monitoring by pediatric cardiology team
Facial twitching or paresis	• Medications (e.g., anticonvulsants, muscle relaxants) • Botulinum toxin injection • Physical therapy	Identification & mgmt of underlying causes (e.g., seizures, nerve injury)
Vocal cord paresis / Swallowing dysfunction / Risk of recurrent aspirations	• Tracheostomy • Gastrostomy tube feeding • Pharmacologic therapies for gastroesophageal reflux	• Often these issues complicate central hypoventilation in children w/ABDS. • Usually these manifestations improve w/age (after infancy), allowing removal of gastrostomy tube & closure of tracheostomy.
Family / Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ABDS = Athabascan brainstem dysgenesis syndrome

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric 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 typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *HOXA1*-Related Disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Ophthalmologic	Ophthalmologic exam	Every 6-12 mos
	• Assessment of visual acuity & ocular alignment • Orthoptic eval (if applicable) • Fundoscopic exam	Per ophthalmologist or as clinically indicated
Audiologic	• Audiologic assessment • Assessment of hearing function & speech development • Monitor for signs of hearing loss or auditory processing deficits.	Annually or as clinically indicated

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Cerebrovascular anomalies	Surveillance as recommended by neurologist &/or vascular surgeon	Frequency per neurologist &/or vascular surgeon
Neurodevelopmental	• Developmental assessment incl assessment of motor development & musculoskeletal function • Physical therapy eval	Annually
	• Assess for need for early intervention services. • Assess for need for educational support & accommodations. • Monitor for signs of intellectual disability.	Annually or as clinically indicated
Respiratory / Central hypoventilation (in ABDS)	Respiratory eval (pulmonary function tests, sleep studies)	Annually
	• Assess for signs of central hypoventilation. • Monitor for respiratory manifestations or complications.	Annually or as clinically indicated
Cardiac	Assess for signs of arrhythmias or cardiac abnormalities.	Annually or as clinically indicated
	Cardiac eval incl EKG & echocardiogram	Annually
Neurologic	• Neurologic exam for facial twitching or facial paresis • Assess for development of seizures.	Annually or as clinically indicated
	Brain MRI	As clinically indicated (e.g., w/new seizure onset or manifestations of stroke)
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Agents/Circumstances to Avoid

It seems prudent to avoid high altitude, especially among individuals with ABDS, based on a few case studies [Bosely et al 2008], but this needs further study and confirmation. In addition, practical limitations would make avoiding high altitude challenging.

Avoid risk factors leading to stroke (lifestyle and drugs).

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of surveillance and treatment.

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

HOXA1-related disorders are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *HOXA1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *HOXA1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *HOXA1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has a *HOXA1*-related disorder or is a carrier (see **Family Planning**), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *HOXA1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *HOXA1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *HOXA1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk sibs for the purpose of early diagnosis and treatment.

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, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of individuals affected with a *HOXA1*-related disorder and individuals known to be carriers of a *HOXA1* pathogenic variant, particularly if consanguinity is likely and/or if both partners are of the same ethnic background (*HOXA1* founder variants have been identified in individuals of Navajo and Apache ancestry and individuals from Saudi Arabia [see Table 7]).

Prenatal Testing and Preimplantation Genetic Testing

Once the *HOXA1* pathogenic variants have 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **Human Disease Gene Website Series - Registry**
  HOXA1

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. HOXA1-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HOXA1	7p15.2	Homeobox protein Hox-A1	HOXA1 database	HOXA1	HOXA1

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 HOXA1-Related Disorders (View All in OMIM)

142955	HOMEOBOX A1; HOXA1
601536	ATHABASKAN BRAINSTEM DYSGENESIS SYNDROME; ABDS

Molecular Pathogenesis

Homeobox (HOX) genes occur in four clusters (A-D), located on different chromosomes. In each cluster, 3' HOX genes are expressed earlier and more anteriorly than 5' HOX genes [Lappin et al 2006]. HOX genes encode proteins that play an important role in specification of anterior-posterior patterning and lineage-specific cellular

differentiation [De Kumar et al 2017]. Pathogenic variants in HOX genes result in malformations reflecting the pattern of developmental expression. Homozygous *HOXA1* mutated mice show faulty development of hindbrain and associated structures [Mark et al 1993, Makki et al 2012].

To date, the reported biallelic pathogenic variants in *HOXA1* in the majority of affected individuals lead to loss of all functional domains. In one reported individual, preservation of the PBX binding domain (almost resembling isoform 3) has been observed [Patil et al 2020].

Mechanism of disease causation. Loss of function

Table 7. *HOXA1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005522.5 NP_005513.2	c.76C>T	p.Arg26Ter	Founder variant in persons of Navajo & Apache ancestry [Tischfield et al 2005]
	c.175dupG	p.Val59GlyfsTer119	Founder variant in persons from Saudi Arabia [Tischfield et al 2005]

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.

Chapter Notes

Author Notes

Dr Siddaramappa J Patil (drsjpatil@gmail.com) is keen to identify more individuals with *HOXA1*-related disorders to better characterize the phenotype and genotype. He and Dr Prince Jacob (princejacob@jssuni.edu.in) serve as moderators for the *HOXA1* entry in the Human Disease Genes website series.

Dr Patil and Dr Jacob are actively involved in clinical research regarding individuals with *HOXA1*-related disorders. They would be happy to communicate with persons who have any questions regarding diagnosis of *HOXA1*-related disorders or other considerations.

Dr Patil is also interested in hearing from clinicians treating families affected by inherited cardiovascular malformations in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Patil and Dr Jacob to inquire about review of *HOXA1* variants of uncertain significance.

Acknowledgments

We are thankful to Narayana Hrudayalaya Hospital / Mazumdar Shaw Medical Center and JSS Academy of Higher Research (JSSAHER) for providing the support and resources for conducting the study.

Revision History

- 14 November 2024 (sw) Review posted live
- 22 April 2024 (sp) Original submission

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