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Xia-Gibbs Syndrome

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Summary

Clinical characteristics

The main features of Xia-Gibbs syndrome (XGS), present in a majority of affected individuals, include delayed motor milestones, speech delay with severely limited or absent speech, moderate-to-severe cognitive impairment, hypotonia, structural brain anomalies, and nonspecific dysmorphic features. Other features may include sleep apnea, movement disorders (ataxia, tremors, and bradykinesias) that often become apparent in childhood or adolescence, short stature, seizures, eye anomalies, behavioral concerns, autism spectrum disorder, scoliosis, and laryngomalacia.

Diagnosis/testing

The diagnosis of XGS is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *AHDC1* that is predicted to lead to a truncated protein, identified by molecular genetic testing

Management

Treatment of manifestations: Treatment is symptomatic and can include: speech, occupational, and physical therapy; specialized educational programs depending on individual needs; standard treatment of behavioral concerns (ADHD, anxiety) and autism spectrum disorders; treatment of movement disorders by a neurologist familiar with movement disorders; standard treatment of seizures, feeding difficulties, gastroesophageal reflux disease, obstructive sleep apnea; stridor/disordered breathing, scoliosis, ophthalmologic/vision issues, and hearing loss; consideration of growth hormone therapy in those with short stature who also have growth hormone deficiency.

Surveillance: At each visit monitor growth and nutrition, occupational and physical therapy needs; assess for seizures, movement disorders, developmental progress, behavioral issues, gastrointestinal issues, respiratory issues, and family needs. Clinical assessment for scoliosis at each visit in childhood until skeletal maturity. Annual vision and hearing assessments. Measurement of growth hormone level in those with poor growth velocity.

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Genetic counseling

XGS is an autosomal dominant disorder typically caused by a *de novo* pathogenic truncating variant in *AHDC1*. The risk to other family members is presumed to be low, but parental testing should be done when possible to confirm that the variant is *de novo*. Once an *AHDC1* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Xia-Gibbs syndrome (XGS) have been published.

Suggestive Findings

XGS **should be considered** in individuals with the following clinical and brain MRI findings.

Clinical findings. Early-onset moderate-to-profound developmental delay (DD) or intellectual disability (ID) AND any of the following features presenting in infancy or childhood:

- Neurologic issues, including:
  - Generalized hypotonia of infancy
  - Epilepsy
  - Ataxia
  - Nystagmus
- Developmental issues, including:
  - Delayed motor milestones
  - Speech delay
  - Autism spectrum disorder (ASD)
- Respiratory issues, including:
  - Obstructive sleep apnea
  - Tracheomalacia
  - Laryngomalacia
- Scoliosis
- Short stature
- Strabismus
- Dysmorphic features (See Clinical Description.)

Brain MRI findings

- Thinning of the corpus callosum
- Posterior fossa cyst
- Delayed myelination

Family history. Because XGS is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of XGS **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *AHDC1* that is predicted to lead to a truncated protein, identified by molecular genetic testing (see Table 1 and Molecular Genetics).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous missense *AHDC1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with chromosomal microarray analysis (CMA). Other options include use of a multigene panel or exome/genome sequencing. Note: Single-gene testing (sequence analysis of *AHDC1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability (ID) or developmental delay (DD) multigene panel** that includes *AHDC1* and other genes of interest (see Differential Diagnosis) limits identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. However, given the rarity of XGS, some panels for ID or DD may not include *AHDC1,* and this should be considered ahead of testing. 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; therefore, present inclusion of *AHDC1* does not guarantee that the gene was included when a given individual underwent testing. (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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel – with the added advantage that it includes genes recently identified as causing ID, whereas some multigene panels may not. Historically, trio whole-exome sequencing has been the genetic test that typically identifies *de novo AHDC1* pathogenic variants that are predicted to lead to truncation of protein synthesis [Xia et al 2014, Yang et al 2015, García-Acero & Acosta 2017, Jiang et al 2018, Ritter et al 2018, Cheng et al 2019, Díaz-Ordoñez et al 2019, Murdock et al 2019, Yang et al 2019, Cardoso-Dos-Santos et al 2020, Gumus 2020, He et al 2020].

  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 Xia-Gibbs Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
AHDC1	Sequence analysis [3]	97%-98% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7, 8, 9]

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. From Xia et al [2014], Yang et al [2015], Jiang et al [2018], Ritter et al [2018], Khayat et al [2021b], and data derived from DECIPHER [Firth et al 2009] and the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Most individuals so far reported have pathogenic truncating or missense variants in *AHDC1*.
6. 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.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. There have been reports of large deletions of 1p36.11 that include *AHDC1*, with features overlapping with XGS. This accounts for up to 2%-3% of individuals identified with a pathogenic variant involving *AHDC1*. However, all known cases to date include adjacent genes as well, for which mutation can independently result in developmental disorders [Park et al 2017, Jiang et al 2018, Ritter et al 2018, Wang et al 2020].
9. Deletions have been reported in the DECIPHER database, but the reported deletions are large and involve many genes, and there is not sufficient evidence to narrow down the cause to a single gene [Firth et al 2009]. Therefore, the evidence supporting the pathogenicity of *AHDC1* deletions is incomplete and warrants further investigation.

Clinical Characteristics

Clinical Description

To date, approximately 280 individuals have been identified with a pathogenic variant in *AHDC1* [Jiang et al 2018]. The striking features of XGS include delayed motor milestones, speech delay, cognitive impairment, hypotonia, structural brain anomalies, dysmorphic features, and sleep apnea, in addition to variable presentation of secondary features [Xia et al 2014, Yang et al 2015, García-Acero & Acosta 2017, Park et al 2017, Jiang et al 2018, Ritter et al 2018, Díaz-Ordoñez et al 2019, Cardoso-Dos-Santos et al 2020, Wang et al 2020, Khayat et al 2021b]. The following description of the phenotypic features associated with this condition is based on these published reports.

Table 2. Select Features of Xia-Gibbs Syndrome

Feature	% of Persons w/Feature	Comment
DD	94%	Delayed motor milestones
Speech delay	94%	Most are nonverbal or have very limited speech.
Hypotonia	88%	Sometimes reported as "low muscle tone"
ID	88%	Moderate to severe
Dysmorphic features	80%	Typically nonspecific
Ataxia	65%	
Short stature	50%	
Seizures	45%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Sleep apnea	41%	Often obstructive in nature
Eye anomalies / vision issues	40%	Strabismus is the most common finding
ASD	30%	
Behavioral concerns	30%	Impulsiveness, aggression, self-injury, anxiety, poor social interaction, sleep disturbances, ADHD
Scoliosis	26%	
Laryngomalacia	20%	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability

Developmental delay (DD) and intellectual disability (ID). Delayed developmental milestones have been reported in the first year in concert with generalized hypotonia.

- Motor development delay is usually accompanied by poor coordination and gait disturbances, typically starting in early childhood.
- The median age when walking begins is 2.5 years (range ~1.5-6 years) [Jiang et al 2018].
- The majority of affected individuals function in the moderate-to-severe range of intellectual disability, although individuals with mild intellectual disability have also been reported [Xia et al 2014].

Speech delay. All individuals with XGS have delayed speech and language development. Most are nonverbal or have very limited speech.

- In one study the average age of using a first word was 2.75 years and the median age for using two words together was 3.5 years [Jiang et al 2018].
- Language delay was more pronounced in males than females, with one small study of 20 affected individuals demonstrating that affected males were statistically significantly more likely to be nonverbal compared to affected females ($p<.01$) [Jiang et al 2018]. Expressive language development was more severely impaired than receptive language skills [Jiang et al 2018].

Autism spectrum disorder (ASD). About one third of affected individuals either have a clinical diagnosis of an ASD or were assessed for an ASD based on a "high risk" score on the M-CHAT [Jiang et al 2018, Khayat et al 2021b]. A female presenting with high-functioning autism spectrum without intellectual disability has been reported [Della Vecchia et al 2021]. This individual also had attention deficit, motor dyspraxia, and a disharmonic intelligence profile, with better verbal performance. Other reports of individuals with XGS who displayed autistic symptoms with poor social interaction, or who had been diagnosed with ASD, have been documented [Yang et al 2015, Díaz-Ordoñez et al 2019, Faergeman et al 2021, Mubungu et al 2021].

Behavioral problems. Yang et al [2015] reported one individual with aggression and self-injury and another with self-injurious behavior. Self-injurious behavior has also been reported in several other individuals with XGS [Jiang et al 2018, Díaz-Ordoñez et al 2019, Murdock et al 2019, Cardoso-Dos-Santos et al 2020, Faergeman et al 2021]. Other common behavioral problems reported in individuals with XGS include the following [Xia et al 2014, Jiang et al 2018, Murdock et al 2019, Cardoso-Dos-Santos et al 2020, Della Vecchia et al 2021, Faergeman et al 2021, Mubungu et al 2021]:

- Impulsiveness
- Anxiety
- Poor social interaction

- Sleep disturbances
- Attention-deficit/hyperactivity disorder (ADHD)

Behavioral issues in affected individuals is an ongoing active area of study. The degree of manifestation of these behavioral features is variable among individuals with XGS, and not all affected individuals will display these features.

Neurologic

- **Abnormal muscle tone.** Generalized hypotonia may be noted during the first months of life and typically does not improve significantly over time. Oral hypotonia has also been reported [Yang et al 2015, Jiang et al 2018, Ritter et al 2018, Gumus 2020].
- **Movement disorders**. Ataxia, tremors, and bradykinesia have been frequently associated with XGS, typically first noted in childhood or adolescence [Yang et al 2015, Murdock et al 2019].
- **Seizures** occur in about half of affected individuals and can range from generalized tonic-clonic seizures to absence seizures, including febrile seizures, atonic, sleep-related, and startle-induced atonic seizures [Xia et al 2014, Yang et al 2015, Murdock et al 2019, Cardoso-Dos-Santos et al 2020].
  - The median age of seizure onset is four years (range 9 months to ~12 years) [Jiang et al 2018].
  - Abnormal EEG recordings have been reported in about 50% of individuals. This can include capturing seizures on EEG, but could also include individuals with diffuse slowing or other EEG abnormalities.
  - Seizures typically respond to standard anti-seizure medication.

Neuroimaging. More than half of affected individuals have delayed myelination or hypomyelination on brain magnetic resonance imaging (MRI). Other findings in those studied have included hypoplasia of the corpus callosum, posterior fossa cysts, and dysmorphic sulci-gyri [Xia et al 2014, Yang et al 2015, Jiang et al 2018, Ritter et al 2018, García-Acero & Acosta 2017, Gumus 2020].

Growth and feeding issues. Many individuals with XGS have a history of growth problems including short stature (length and/or height >-2 SD) and feeding difficulties [Yang et al 2015].

- Most affected individuals have a normal birth weight but have poor postnatal growth due to feeding issues during infancy.
- Specific feeding problems may include difficulties with suck and swallowing, recurrent vomiting, and gastroesophageal reflux disease [Yang et al 2015, Jiang et al 2018, Ritter et al 2018, Gumus 2020].
- Growth hormone deficiency was revealed as the cause for short stature in two affected individuals, who eventually responded well to growth hormone replacement therapy [Cheng et al 2019].

Dysmorphic features. Nonspecific dysmorphic facial features are a common finding in affected individuals [Xia et al 2014, Yang et al 2015, García-Acero & Acosta 2017, Jiang et al 2018, Ritter et al 2018, Cardoso-Dos-Santos et al 2020] and generally include:

- Broad forehead
- Horizontal eyebrows
- Widely spaced eyes
- Downslanted or upslanted palpebral fissures
- Mild ptosis
- Depressed nasal bridge
- Low-set ears
- Thin vermilion of the upper lip
- Micrognathia
- Transverse palmar crease

Sleep apnea and respiratory abnormalities. Sleep apnea is present in about 45% of affected individuals and is mostly obstructive in nature [Xia et al 2014, Yang et al 2015, Jiang et al 2018, Ritter et al 2018, Cardoso-Dos-Santos et al 2020, Khayat et al 2021b].

- Sleep disturbance is also a common finding with some affected individuals reported to have abnormal breathing patterns, breath-holding episodes, and irregular breathing patterns at night.
- Many use respiratory support. CPAP, BiPAP, and supplementary oxygen have been used during sleep at night.
- Some affected individuals also have structural airway issues, including laryngomalacia and tracheomalacia. Surgical intervention may be pursued in some cases.
- These occurrences suggest the need for close monitoring of airway function and consideration of referral to pulmonology (see Management).

Scoliosis. Scoliosis is common.

- About one fifth of affected individuals who participated in a XGS registry had scoliosis (at ages 10~21 years) [Jiang et al 2018] - significantly higher than the prevalence in the general population (i.e., 5%).
- Some individuals have required surgery for scoliosis.
- In a male age 55 years with XGS and loose soft skin, scoliosis was ascribed to connective tissue abnormalities [Murdock et al 2019].
- Timely identification, intervention, and management of scoliosis is recommended to prevent life-threatening complications [Murdock et al 2019, Goyal et al 2020] (see Management).

Eyes/vision. Strabismus has been described in more than half of individuals with XGS [Yang et al 2015, Jiang et al 2018, Ritter et al 2018, Gumus 2020].

- Some affected individuals have nystagmus, myopia, hyperopia, and/or ptosis.
- The severity of eye anomalies varies among individuals with XGS, with visual problems requiring correction and many affected individuals wearing glasses.

Hearing. Sensorineural hearing loss has been reported in one individual [Ritter et al 2018].

Other associated features

- **Skin.** Almost half of the individuals with XGS have an abnormality in the skin and in other connective tissues. Specifically, cutis aplasia and soft loose skin have been frequently reported [Ritter et al 2018, Murdock et al 2019].
- **Craniosynostosis.** Craniosynostosis has been reported in a few individuals with XGS. The type of sutures reported include coronal, bicoronal, and metopic [Yang et al 2015, Miller et al 2017, Gumus 2020].

Prognosis. It is unknown whether life span in Xia-Gibbs syndrome is abnormal. One reported individual is alive at age 55 years, demonstrating that survival into adulthood is possible [Murdock et al 2019]. Data on possible progression of behavior abnormalities or neurologic findings are still limited. Since many adults with DD or ID issues have not undergone advanced genetic or genomic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Truncating pathogenic variants (frameshift or stop-gain) have been reported to span across the length of the gene.

- Truncating pathogenic variants that arise near the N terminus of the protein have been associated with a statistically significant higher risk of developing seizures and scoliosis [Khayat et al 2021b].

- Similarly, truncating pathogenic variants at the C terminus of the protein are less likely to be associated with the development of seizures or scoliosis.

Missense variants. There are at least ten individuals with clinical features of XGS who have *de novo* missense variants within *AHDC1* that are presumed to be pathogenic (see Molecular Genetics) [Khayat et al 2021a].

Prevalence

The prevalence of XGS in the general population is estimated to be more than one in 80,000 live births with more than 270 individuals reported worldwide. Since many individuals with XGS may go undiagnosed due to lack of genomic testing (particularly in developing countries), the incidence may be greater than the current estimate.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *AHDC1*.

Differential Diagnosis

Because the clinical presentation of Xia-Gibbs syndrome (XGS) is typically nonspecific developmental delay (DD) and intellectual disability (ID), the phenotypic features alone are not sufficient to diagnose this condition.

XGS should be considered as a differential diagnosis for individuals presenting with unexplained ID and DDs. All disorders associated with ID without other distinctive findings and childhood onset behavior disorder (particularly when associated with mild dysmorphic features, sleep apnea, seizures, or scoliosis) should be considered in the differential diagnosis.

See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Xia-Gibbs Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	• To assess for growth deficiency & short stature • Consider targeted assessment for growth hormone deficiency in those w/poor growth velocity.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ behavioral concerns	Neuropsychiatric eval	For those age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Neurologic	Neurologic eval incl assessment for mvmt disorders	• To incl consideration of brain MRI if clinically indicated • EEG if seizures suspected

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• Eval of aspiration risk & nutritional status • History of constipation & GERD • Consider need for gastric tube placement.
Sleep disorder	Assessment by polysomnography for sleep disturbance &/or evidence of sleep apnea	To assess for obstructive sleep apnea
Respiratory	Assessment for noisy breathing (stridor) & irregular breathing patterns	Consider referral to pulmonologist.
Musculoskeletal/ Hypotonia	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Clinical exam for scoliosis	AP & lateral radiographs of spine if scoliosis suspected
Eyes	Ophthalmologic eval	To assess for ↓ vision, strabismus, & nystagmus
Hearing [1]	Audiology eval	To assess for sensorineural &/or conductive hearing loss
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of XGS in order to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as XGS Society; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; XGS = Xia-Gibbs syndrome

1. Although hearing loss is not commonly described in association with this condition, screening for occult hearing loss is often recommended in those who have developmental delay / intellectual disability that includes speech delay.

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

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Xia-Gibbs Syndrome

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Behavioral concerns (ADHD, anxiety, autism)	• Provide specialized instruction, OT, PT, & speech/behavioral therapies if indicated. • Standard treatment for ADHD (may incl medication) • Psychiatric consultation & therapy for those w/anxiety	ABA therapy may be indicated for those w/autistic features.
Epilepsy	Standardized treatment w/ASMs by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for XGS. • Education of parents/caregivers [1]

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Movement disorders (ataxia, tremors, bradykinesia)	Standard treatment per neurologist	Mgmt by neurologist familiar w/mvmt disorders recommended
Feeding difficulties	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
GERD	Standard treatment	May incl positioning &/or medications
Growth hormone deficiency	Growth hormone therapy if growth hormone deficient	Consultation w/endocrinologist recommended
Obstructive sleep apnea	Standard treatment per otolaryngologist &/or sleep medicine specialist	May incl removal of tonsils/adenoids &/or supportive breathing assistance through CPAP
Stridor or disordered breathing	Standard treatment per pulmonologist	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT	Consider need for positioning & mobility devices, disability parking placard.
Scoliosis	Standard treatment per orthopedist	
Reduced vision &/or strabismus	Standard treatment per ophthalmologist	Community vision services through early intervention or school district
Hearing loss	Hearing aids may be helpful; per otolaryngologist & audiologist.	Community hearing services through early intervention or school district
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.

ABA = applied behavioral therapy; ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication; CPAP = continuous positive airway pressure; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

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 can safely 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.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and 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 ADHD, when necessary.

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

Surveillance

Table 5. Recommended Surveillance for Individuals with Xia-Gibbs Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters	At each visit
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Neurologic	Monitor those w/seizures.	
	Assess for new manifestations, e.g., seizures, changes in tone, mvmt disorders.	
Feeding	• Eval of nutritional status & safety of oral intake • Assess for signs & symptoms of GERD	
Respiratory	Monitor for signs & symptoms of respiratory insufficiency & sleep apnea.	
Endocrine	Measurement of growth hormone level	In those w/poor growth velocity
Musculoskeletal	Clinical assessment for scoliosis	At each visit in childhood until skeletal maturity
Eyes	Ophthalmology eval	Annually or as clinically indicated
Hearing	Audiology eval	Annually in childhood or as clinically indicated
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

GERD = gastroesophageal reflux disease

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Xia-Gibbs syndrome (XGS) is an autosomal dominant disorder typically caused by a *de novo* pathogenic truncating variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with XGS whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo AHDC1* pathogenic truncating variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to assess risk of recurrence.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [He et al 2020]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the *AHDC1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *AHDC1* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Sib recurrence due to presumed maternal germline mosaicism has been reported in one family [He et al 2020].

Offspring of a proband

- Each child of an individual with XGS has a 50% chance of inheriting the *AHDC1* pathogenic variant.
- Individuals with XGS are generally not known to reproduce; however, most are not yet of reproductive age.

Other family members. Given that most probands with XGS reported to date have the disorder as the result of a *de novo AHDC1* 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

Once the *AHDC1* pathogenic variant 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.

- **Xia-Gibbs Society**

  Xia-Gibbs Society is a not-for-profit corporation formed in the USA for charitable purposes. Our mission is to support and advocate for those with Xia-Gibbs Syndrome (XGS) and their families, to raise awareness and to assist with scientific and medical research.

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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. Xia-Gibbs Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
AHDC1	1p36.11-p35.3	Transcription factor Gibbin	AHDC1	AHDC1

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 Xia-Gibbs Syndrome (View All in OMIM)

615790	AT-HOOK DNA-BINDING MOTIF-CONTAINING PROTEIN 1; AHDC1
615829	XIA-GIBBS SYNDROME; XIGIS

Molecular Pathogenesis

AHDC1 contains a total of seven exons with a single coding exon. Little is known about the normal function of the AHDC1 protein or how mutation of *AHDC1* leads to the clinical features seen in individuals with XGS. The gene encodes a protein containing three AT-hooks, which likely function in DNA binding. In individuals with clinical features of XGS who have *de novo* missense variants in *AHDC1*, it is hypothesized that the missense variants are in regions that are predicted to be functional motifs [Khayat et al 2021a].

Mechanism of disease causation. The mechanism by which *AHDC1* pathogenic variants result in XGS is unknown, with prior suggestions of both haploinsufficiency and dominant-negative effects [Khayat et al 2021b]. While loss-of-function (protein-truncation) pathogenic variants are consistent with either mechanism, Khayat et al [2021b] reported variable effects depending on the position of the truncating pathogenic variant, consistent with a dominant-negative effect. Further, pathogenic missense variants that result in XGS are expected to result in full-length protein products and are therefore more likely to act in a dominant-negative or other gain-of-function manner. Consequently, the available data support a dominant-negative model, but do not exclude the possibility of either haploinsufficiency (loss of function) or other gain-of-function mechanisms.

Table 6. Notable *AHDC1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001029882.3 NP_001025053.1	c.2373_2374delTG	p.Cys791TrpfsTer57	Recurring pathogenic variants [Jiang et al 2018, Khayat et al 2021b]
	c.2773C>T	p.Arg925Ter	
	c.2908C>T	p.Gln970Ter	

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.

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