U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Shieh JTC, Hoyme HE, Arbour LT. Hyaline Fibromatosis Syndrome. 2008 Feb 27 [Updated 2023 May 11]. 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/

Hyaline Fibromatosis Syndrome

Synonyms: Inherited Systemic Hyalinosis, *ANTXR2*-Related Hyaline Fibromatosis Syndrome

Joseph TC Shieh, MD, PhD,[1] H Eugene Hoyme, MD,[2] and Laura T Arbour, MD[3]

Created: February 27, 2008; Revised: May 11, 2023.

Summary

Clinical characteristics

Hyaline fibromatosis syndrome (HFS) is characterized by hyaline deposits in the papillary dermis and other tissues. It can present at birth or in infancy with severe pain with movement, progressive joint contractures, and often with severe motor disability, thickened skin, and hyperpigmented macules/patches over bony prominences of the joints. Gingival hypertrophy, skin nodules, pearly papules of the face and neck, and perianal masses are common. Complications of protein-losing enteropathy and failure to thrive can be life threatening. Cognitive development is normal. Many children with the severe form (previously called infantile systemic hyalinosis) have a significant risk of morbidity or mortality in early childhood; some with a milder phenotype (previously called juvenile hyaline fibromatosis) survive into adulthood.

Diagnosis/testing

The diagnosis of HFS is established in a proband with characteristic clinical features and/or biallelic pathogenic (or likely pathogenic) variants in *ANTXR2* identified by molecular genetic testing. Skin biopsy may reveal hyaline material accumulation in the dermis or nondiagnostic findings; intestinal biopsy may demonstrate villous atrophy and lymphangiectasia. Skeletal x-rays may reveal osteopenia, periosteal reaction, and lucent lesions.

Management

Treatment of manifestations: Possible nasogastric tube, gastrostomy tube feeding, or parenteral nutrition under supervision of a gastroenterologist and nutritionist; nutrition tailored for the possibility of malabsorption or lymphangiectasia; hydration and albumin infusions for protein-losing enteropathy; physiotherapy for joint contractures can be considered although pain may be problematic; nonsteroidal anti-inflammatory drugs, opiates, and possibly gabapentin for pain; gentle handling; splinting may reduce pain; consultation with a pain

Author Affiliations: 1 Division of Medical Genetics, Department of Pediatrics, Institute for Human Genetics, University of California San Francisco, San Francisco, California; Email: joseph.shieh2@ucsf.edu. 2 Department of Pediatrics, Sanford School of Medicine, University of South Dakota; Sanford Children's Hospital, Sioux Falls, South Dakota. 3 Department of Medical Genetics, Island Medical Program, University of British Columbia, Victoria, British Columbia, Canada.

management specialist as needed; lesions that obstruct the airway or interfere with feedings can be excised, but may recur; anesthesiologists need to be aware of potential difficulties with endotracheal intubation; perianal masses may be resected; treatment of skin nodules as recommended by dermatology and/or plastic surgery; infections are treated based on the site of infection and causative agent; consider family counseling to manage chronic medical condition.

Surveillance: The following as needed based on clinical presentation: antibody levels and serum albumin; evaluation for gastrointestinal malabsorption; nutrition assessment; history and examination for contracture progression and pain; examination for concerning lesions; examination for oral lesions that affect feeding/nutrition and dental complications; cardiac assessment.

Genetic counseling

HFS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ANTXR2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being unaffected and a carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible once the *ANTXR2* pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Hyaline fibromatosis syndrome (HFS) **should be suspected** in probands with the following clinical, laboratory, histopathology, and radiographic features. Clinical features are presented in order of their specificity for clinical diagnosis.

Clinical features

- **Hyperpigmented skin over bony prominences.** Purplish patches develop over the medial and lateral malleoli of the ankles, metacarpophalangeal joints, spine, and elbows.
- **Progressive contractures** (e.g., hip, knee and elbow flexion, ankle dorsiflexion, wrist extension with flexion of proximal interphalangeal and distal interphalangeal joints) that may be congenital and/or cause decreased intrauterine movement. Some individuals have only mild contractures.
- **Possible pain or excessive crying** with passive movement
- **Failure to thrive.** Postnatal-onset growth deficiency is common. Some children develop chronic diarrhea and protein-losing enteropathy.
- **Gingival thickening**
- **Skin nodules** (e.g., pearly papules on the head and neck; skin nodules, papules, and fleshy lesions periorally and perianally)
- **Characteristic facies.** A depressed nasal bridge, variable ear malformations (large, simple or low-set ears, and preauricular skin tags), and a slightly coarse facial appearance may be present.
- **Normal ophthalmologic examination** can be used to differentiate HFS from some lysosomal storage disorders.

Laboratory features

- Serum albumin may be low.
- Normal or slightly elevated ESR, anemia, and/or thrombocytosis
- Immunoglobulin levels may be low and cellular immune responses depressed.
- CD3 and CD4 lymphocyte subsets and ANA are unremarkable.

Histopathology

- **Skin biopsy.** Light microscopy demonstrates hyaline material in the dermis.

  Note: This finding may not be evident in the early stages of the disease [Arbour et al 2001]. The hyaline material appears as an amorphous eosinophilic substance that is periodic acid-Schiff (PAS) positive. It is thought to contain glycoproteins and collagen. The spindle-shaped fibroblasts dispersed in abundant amounts of hyaline material render a "chondroid appearance."

  Electron microscopy demonstrates cells filled with fine, fibrillary material with an enlarged endoplasmic reticulum and Golgi apparatus.

- **Intestinal biopsy.** Villous atrophy, edema, lymphangiectasia, and hyalinosis may be seen in individuals with prominent gastrointestinal symptoms.

Radiographic features

- Skeletal radiographs. Generalized osteopenia, periosteal reaction, and lucent lesions are nonspecific findings that may affect long bones as well as the axial skeleton.
- Upper-gastrointestinal imaging studies may show rapid transit time.
- Brain MRI is unremarkable.

Establishing the Diagnosis

The diagnosis of HFS **is established** in a proband with the above suggestive findings and/or biallelic pathogenic (or likely pathogenic) variants in *ANTXR2* identified by molecular genetic testing (see Table 1).

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 biallelic *ANTXR2* variants of uncertain significance (or of one known *ANTXR2* pathogenic variant and one *ANTXR2* 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, exome array, genome sequencing) depending on the phenotype.

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

Option 1

Single-gene testing. Sequence analysis of *ANTXR2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. 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.

A multigene panel that includes *ANTXR2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to

change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (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 HFS is not immediately recognized, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is the most likely option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Hyaline Fibromatosis Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ANTXR2	Sequence analysis [3]	95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [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 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. Dowling et al [2003], Hanks et al [2003], El-Kamah et al [2010], Denadai et al [2012], Casas-Alba et al [2018], Cozma et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Shieh et al [2006], Denadai et al [2012]

Clinical Characteristics

Clinical Description

Hyaline fibromatosis syndrome (HFS), named for the characteristic hyaline deposits in the papillary dermis and other tissues including the gastrointestinal tract of affected individuals, exhibits a broad spectrum of clinical severity [Casas-Alba et al 2018, Cozma et al 2019]. Individuals may present at birth or in infancy with severe pain with movement, progressive joint contractures, skin that is firm to palpation, and characteristic hyperpigmented macules/patches over bony prominences of the joints, especially the ankles, wrists, and metacarpal-phalangeal joints [Shieh et al 2006, El-Kamah & Mostafa 2009, Hammoudah & El-Attar 2016, Schussler et al 2018]. Severely affected children can die in the first years of life, possibly from gastrointestinal involvement. Some individuals demonstrate a milder phenotype, which may be of later onset. Adults with significant symptoms have also been reported.

To date, at least 93 individuals have been identified with a pathogenic variant in *ANTXR2* [Cozma et al 2019, Härter et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Features of Hyaline Fibromatosis Syndrome

Feature	% of Persons w/Feature	Comment [1]
Skin nodules	>80%	Can be diagnostic
Hyperpigmented skin over bony prominences, thickened skin	Common	Can be diagnostic
Contractures	~60%	Variable depending on severity
Gingival enlargement	93%	
Protein-losing enteropathy	Unknown	Diarrhea, reported in >50%, is likely more common than reported.
Immunodeficiency	~33%	Variable; may be underreported.

1. Presence of findings may be age dependent.

Skin nodules and other manifestations. Skin nodules and white-to-pink pearly papules that are a few millimeters in size are common on the face and neck. Fleshy lesions may appear in the perianal region. These lesions appear to develop and become more numerous over time. The skin is firm to palpation and has been described as thickened. Excessive diaphoresis is common.

Hyperpigmented skin over bony prominences. Characteristic purplish patches develop over the medial and lateral malleoli of the ankles, the metacarpophalangeal joints, spine, and elbows. The degree of hyperpigmentation varies depending on the baseline pigmentation of the skin [Arbour et al 2001].

Progressive contractures. Affected individuals can present with congenital contractures. Some mothers report deficient fetal activity during the pregnancy of the affected infant, and many parents note decreased passive and/or active movement of the extremities of their child. Contractures are progressive, and extremities become fixed with the hips and knees flexed and the ankles dorsiflexed. The elbows exhibit flexion contractures, and the wrists are typically positioned in extension with flexion contractures of the proximal interphalangeal and distal interphalangeal joints. Some individuals demonstrate milder features [Shieh et al 2006].

Pain or excessive crying. Severe pain with passive movement in infancy or early childhood is characteristic. Pathogenesis is unclear.

Failure to thrive. Postnatal-onset growth deficiency is common. Villous atrophy, edema, and lymphangiectasia of the intestine can lead to malabsorption. Some children develop severe intractable protein-losing diarrhea, likely due to hyalinosis of the intestine. The clinical progression of severe cases has been delayed with regular gastrointestinal evaluation and nutritional support [Shieh, unpublished].

Gingival manifestations. The gingivae are thickened. Affected individuals develop masses in the gingiva, which enlarge over time. Lesions that obstruct the airway or interfere with oral intake are particularly problematic. Lesions may recur after surgical excision.

Dental abnormalities include malpositioned teeth, curved dental roots, or other dental abnormalities.

Characteristic facies. A depressed nasal bridge, variable ear malformations (large, simple, or low-set ears; preauricular skin tags), and a slightly coarse facial appearance may be present.

Other

- Cognitive function is preserved; however, individuals with delayed development have been reported [Nischal et al 2004].
- Hepatomegaly may be present.
- Susceptibility to fractures may be increased.
- Recurrent infections may develop due to impaired cellular immune responses and reduced immunoglobulin levels [Klebanova & Schwindt 2009].
- At least two clinically diagnosed individuals developed squamous cell carcinoma [Kawasaki et al 2001, Shimizu et al 2005] and an adult has been reported with colon cancer. The *ANTXR2* mutation status in these individuals is unknown.
- Cardiovascular involvement is largely unknown. One instance of atrial thrombus has been reported.

Prognosis

- Individuals with severe disease can succumb to infection or complications of protein-losing enteropathy.
- Some individuals demonstrate a milder phenotype, which may be of later onset with potential survival into adulthood.
- A clinical grading system for HFS has been proposed [Denadai et al 2012] with grades from mild to severe/lethal. All grades have skin and/or gingival involvement, while increasing grades have joint and/or bone and internal organ involvement. Sepsis or organ failure is associated with the most severe forms.

Milder phenotype. Although joint contractures, skin hyperpigmentation, and skin lesions occur with the milder phenotype, the presentation is variable and disability may be less pronounced. Pain is less severe and may decrease with age. Short stature, limb shortening, and brachydactyly may be present. Intractable diarrhea is rare in milder forms of the disorder.

Pathology. Myopathic changes on muscle biopsy may be evident [Zolkipli et al 2003]. Only a few postmortem examinations have been reported. Hyaline deposition has been documented in the dermis, the small and large intestine, skeletal muscle, lymph nodes, thymus, spleen, thyroid, adrenals, and myocardium. Interstitial parenchymal fibrosis of the pancreas, skeletal muscle, lung, and liver was observed [Criado et al 2004].

Genotype-Phenotype Correlations

Hanks et al [2003] reported on genotype/phenotype correlations in 17 families:

- Those with at least one insertion/deletion in *ANTXR2* resulting in a translational frameshift had a severe phenotype (infantile systemic hyalinosis).
- In-frame and missense variants in the cytoplasmic domain were associated with a milder phenotype, with survival to adulthood without recurrent infections, diarrhea, or multiorgan failure. Skeletal manifestations, however, were variably present.

A review of *ANTXR2* variant type and disease grade was published by Casas-Alba et al [2018]; missense variants in the cytoplasmic domain were found to be less severe.

Nomenclature

Before the molecular basis of HFS was understood, severe and milder forms of the disorder were described as separate conditions (infantile systemic hyalinosis and juvenile hyaline fibromatosis, respectively). It is now known that both severe and mild forms of HFS are caused by pathogenic variants in *ANTXR2*.

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], HFS is referred to as *ANTXR2*-related hyaline fibromatosis syndrome and is included in the genetic inflammatory or rheumatoid-like osteoarthropathies group.

Prevalence

HFS is rare, but it has been recognized in families of various ethnic backgrounds on multiple continents.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ANTXR2*.

Differential Diagnosis

The conditions summarized in Table 3 exhibit some features similar to hyaline fibromatosis syndrome (HFS); however, HFS can be distinguished by the characteristic associated pain, hyperpigmented skin lesions, and perianal and perioral masses.

Table 3. Other Genes and Conditions of Interest in the Differential Diagnosis of Hyaline Fibromatosis Syndrome

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/HFS	Differentiating from HFS
ASAH1	Farber disease (See *ASAH1* Disorders.)	AR	Typically presents w/painful joint contractures & progressive hoarseness; skin nodules develop, esp over bony prominences.	Neurologic involvement in most persons; absence of hyperpigmented patches
COL1A1	Caffey disease (infantile cortical hyperostosis)	AD	Presents w/irritability, poor feeding, fever, & soft tissue swelling	Characteristic radiographic hyperostoses
ECM1	Lipoid proteinosis	AR	Presents w/hoarseness, followed by development of papules around eyelids	Facial papules, tongue enlargement, dental hypoplasia, & distinct skin lesions (vesicles & crusted bullae evolving into waxy plaques)

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/HFS	Differentiating from HFS
FBN1	Stiff skin syndrome (OMIM 184900)	AD	Thickened skin & flexion contractures; mucopolysaccharide deposition has been found in the skin but mucopolysaccharidurias has not been detected.	Absence of characteristic HFS skin findings
GNPTAB	Mucolipidosis II (See *GNPTAB* Disorders.)	AR	Gingival thickening & dysostosis multiplex; facies are coarse & joint contractures develop over time.	
	Mucolipidosis IIIα/β (See *GNPTAB* Disorders.)	AR	Phenotype varies in severity; principal features: contractures & dysostosis multiplex.	
MMP2	Multicentric osteolysis nodulosis & arthropathy [1]	AR	Short stature & osteolysis of interphalangeal & metacarpal-phalangeal joints	
PDGFRB	Congenital generalized fibromatosis (OMIM 228550)	AD	Solitary, multiple, or generalized nodules composed of cells w/features of differentiated fibroblasts & smooth muscle cells	

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; HFS = hyaline fibromatosis syndrome; MOI = mode of inheritance

1. In addition to multicentric osteolysis nodulosis and arthropathy (MONA), this phenotype has been reported in the literature as Torg syndrome, Winchester-Torg (or Torg-Winchester) syndrome, and nodulosis-arthropathy-osteolysis (NAO) syndrome. All of these conditions have been shown to be caused by biallelic pathogenic variants in *MMP2* with no discernible genotype-phenotype correlation.

Note: Periosteal reaction or fractures on skeletal radiographs in systemic hyalinosis have been mistaken for **non-accidental trauma**. The hyperpigmented skin lesions may mistakenly be considered post-traumatic, and the perianal masses can resemble condylomata, prompting a workup for an infectious etiology.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hyaline fibromatosis syndrome (HFS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) should be considered.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Hyaline Fibromatosis Syndrome

System/Concern	Evaluation	Comment
GI/Nutrition	Complete GI & nutritional eval	Incl eval for intestinal malabsorption & protein-losing enteropathy
Musculoskeletal	Consider pain management eval, orthopedic eval.	For contractures
Immunologic	Consider immunology eval.	To evaluate for immune deficiency both cellular & humoral; protein-losing enteropathy
Cardiac	Consider echocardiogram.	To evaluate cardiac function
Endocrine	Consider endocrine eval.	Possible osteopenia, recurrent fractures

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Dental	Consider dental eval.	For gingival hypertrophy & dental abnormalities
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of HFS in order to facilitate medical & personal decision-making

GI = gastrointestinal; HFS = hyaline fibromatosis syndrome; MOI= mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Hyaline Fibromatosis Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Failure to thriv	• Early consideration of nasogastric tube or gastrostomy tube feeding or parenteral nutrition • Nutrition should be tailored for possibility of malabsorption or lymphangiectasia.	A nutritionist should follow affected persons.
Protein-losing enteropathy	Diarrhea & protein-losing enteropathy w/subsequent edema should be treated w/hydration & albumin infusions.	An effective long-term treatment is lacking; the effectiveness of dietary therapies w/intestinal lymphangiectasia is not known.
Joint contractures	PT assessment	When passive movement of joint contractures is painful, PT should be carried out w/care; in some cases PT is not tolerated because of pain.
Pain	Nonsteroidal anti-inflammatory drugs & opiates	Agents such as gabapentin should also be considered.
	• Gentle handling may ↓ pain that is worsened w/ movement. • Splinting of affected joints may provide comfort.	• Consultation w/a pain mgmt specialist may be helpful. • Palliative care consultation may be an option in severe cases.
Skin nodules, gingival thickening, & lesions of the mouth	• Surgical excision is an option. • Anesthesiologists should be aware of difficulty of endotracheal intubation & mgmt in some affected persons [Pollard et al 2008, Qasem et al 2012].	• Lesions may recur after excision. • Significant complication w/anesthesia has been reported [El-Kamah & Mostafa 2009].
Perianal masses	Surgical excision is possible.	Masses may recur after excision.
Skin nodules	• Dermatology eval • Plastic surgery eval	Intertriginous, perianal, & neck areas are prone to masses / hypertrophic skin lesions.
Immune deficiency	• Treatment of infection based on site & causative agent • Consider humoral & cellular immune workup.	
Psychosocial	Consider family counseling.	To develop coping strategies for affected person & family

PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with Hyaline Fibromatosis Syndrome

System/Concern	Evaluation	Frequency
Gastrointestinal/ Nutrition	• Assessment of antibody levels, albumin • Assessment for GI malabsorption • Nutrition assessment	As needed based on clinical presentation
Musculoskeletal	Clinical history & exam for contracture progression & pain	
Integument	Exam for concerning lesions	
Immune system	Assessment of antibody levels	
ENT/Dental	Exam for oral lesions affecting feeding/nutrition & → dental complications	
Cardiology	Cardiac assessment	

GI = gastrointestinal

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

Hyaline fibromatosis syndrome (HFS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ANTXR2* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ANTXR2* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing HFS.

Sibs of a proband

- If both parents are known to be heterozygous for an *ANTXR2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being unaffected and a carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing HFS.

Offspring of a proband. The offspring of an individual with HFS are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ANTXR2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ANTXR2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *ANTXR2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Ultrasound examination/imaging. The utility of prenatal ultrasound examination is unclear; however, in a pregnancy at increased risk, detection of decreased fetal activity and contractures could suggest recurrence. (Note: One or both of these findings should also prompt consideration of HFS in a pregnancy not previously known to be at increased risk for the disorder.)

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.

- **American Chronic Pain Association: Growing Pains**

  Growing Pains is a support group for chronically ill youth.

  PO Box 346

Putnam Valley NY 10579

Phone: 800-533-3231

Email: GrowingPainsACPA@aol.com; ACPA@pacbell.net

Growing Pains

- **MISS Foundation**

  International organization which provides immediate and ongoing support to grieving families after the death of a baby or young child from any cause

  PO Box 5333

  Peoria AZ 85385-5333

  Phone: 888-455-6477 (toll-free); 623-979-1000

  Fax: 623-979-1001

  Email: info@missfoundation.org

  www.missfoundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hyaline Fibromatosis Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ANTXR2	4q21.21	Anthrax toxin receptor 2	ANTXR2 database	ANTXR2	ANTXR2

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 Hyaline Fibromatosis Syndrome (View All in OMIM)

228600	HYALINE FIBROMATOSIS SYNDROME; HFS
608041	ANTHRAX TOXIN RECEPTOR 2; ANTXR2

Molecular Pathogenesis

ANTXR2 encodes a transmembrane protein that is expressed in numerous organs in the body. ANTXR2 acts as a receptor and binds to subtrates such as collagen VI, which may lead to phosphorylation or ubiquitination. It also binds to laminin. ANTXR2 may activate matrix metalloproteinases such as MT1-MMP. ANTXR2 reduces proliferation of endothelial cells in culture. Knockout of *Antxr2* in mice led to uterine fibrosis [Reeves et al 2012, Bürgi et al 2017]. The cytoplasmic domain of ANTXR2 is also important in its function. Hyalinosis of the gastrointestinal tract may lead to protein-losing enteropathy [Shieh et al 2006, Alreheili et al 2012].

ANTXR2 is also known as *CMG2*, or capillary morphogenesis gene 2.

Mechanism of disease causation. Loss of function

Chapter Notes

Revision History

- 11 May 2023 (sw) Revision: "*ANTXR2*-Related Hyaline Fibromatosis Syndrome" added as a synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature
- 23 July 2020 (sw) Comprehensive update posted live
- 11 April 2013 (me) Comprehensive update posted live
- 27 February 2008 (me) Review posted live
- 5 May 2004 (la) Original submission

References

Literature Cited

Alreheili K, AlMehaidib A, Alsaleem K, Banemi M, Aldekhail W, Al-Mayouf SM. Intestinal lymphangiectasia in a patient with infantile systemic hyalinosis syndrome: a rare cause of protein-losing enteropathy. Ann Saudi Med. 2012;32:206–8. PubMed PMID: 22366835.

Arbour L, Reilly C, McGillivray B, Prendiville J, Dimmick J. Infantile systemic hyalinosis: A rare syndrome of progressive, painful contractures with peculiar hyperpigmentation and death in infancy. Greenwood, SC: Proceedings of the Greenwood Genetic Center; 2001.

Bürgi J, Kunz B, Abrami L, Deuquet J, Piersigilli A, Scholl-Bürgi S, Lausch E, Unger S, Superti-Furga A, Bonaldo P, van der Goot FG. CMG2/ANTXR2 regulates extracellular collagen VI which accumulates in hyaline fibromatosis syndrome. Nat Commun. 2017;8:15861. PubMed PMID: 28604699.

Casas-Alba D, Martínez-Monseny A, Pino-Ramírez RM, Alsina L, Castejón E, Navarro-Vilarrubí S, Pérez-Dueñas B, Serrano M, Palau F, García-Alix A. Hyaline fibromatosis syndrome: Clinical update and phenotype-genotype correlations. Hum Mutat. 2018;39:1752–63. PubMed PMID: 30176098.

Cozma C, Hovakimyan M, Iurașcu MI, Makhseed N, Selim LA, Alhashem AM, Ben-Omran T, Mahmoud IG, Al Menabawy NM, Al-Mureikhi M, Martin M, Demuth L, Yüksel Z, Beetz C, Bauer P, Rolfs A. Genetic, clinical and biochemical characterization of a large cohort of patients with hyaline fibromatosis syndrome. Orphanet J Rare Dis. 2019;14:209. PubMed PMID: 31455396.

Criado GR, González-Meneses A, Cañadas M, Rafel E, Yanes F, De Terreros IG. Infantile systemic hyalinosis: a clinicopathological study. Am J Med Genet A. 2004;129A:282–5. PubMed PMID: 15326628.

Denadai R, Raposo-Amaral CE, Bertola D, Kim C, Alonso N, Hart T, Han S, Stelini RF, Buzzo CL, Raposo-Amaral CA, Hart PS. Identification of 2 novel ANTXR2 mutations in patients with hyaline fibromatosis syndrome and proposal of a modified grading system. Am J Med Genet A. 2012;158A:732–42. PubMed PMID: 22383261.

Dowling O, Difeo A, Ramirez MC, Tukel T, Narla G, Bonafe L, Kayserili H, Yuksel-Apak M, Paller AS, Norton K, Teebi AS, Grum-Tokars V, Martin GS, Davis GE, Glucksman MJ, Martignetti JA. Mutations in capillary morphogenesis gene-2 result in the allelic disorders juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet. 2003;73:957–66. PubMed PMID: 12973667.

El-Kamah GY, Fong K, El-Ruby M, Afifi HH, Clements SE, Lai-Cheong JE, Amr K, El-Darouti M, McGrath JA. Spectrum of mutations in the ANTXR2 (CMG2) gene in infantile systemic hyalinosis and juvenile hyaline fibromatosis. Br J Dermatol. 2010;163:213–5. PubMed PMID: 20331448.

El-Kamah GY, Mostafa MI. Heterogeneity and atypical presentation in infantile systemic hyalinosis with severe labio-gingival enlargement: first Egyptian report. Dermatol Online J. 2009;15:6.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Hanks S, Adams S, Douglas J, Arbour L, Atherton DJ, Balci S, Bode H, Campbell ME, Feingold M, Keser G, Kleijer W, Mancini G, McGrath JA, Muntoni F, Nanda A, Teare MD, Warman M, Pope FM, Superti-Furga A, Futreal PA, Rahman N. Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet. 2003;73:791–800. PubMed PMID: 14508707.

Hammoudah SA, El-Attar LM. Infantile systemic hyalinosis: Report of two severe cases from Saudi Arabia and review of the literature. Intractable Rare Dis Res. 2016;5:124–8. PubMed PMID: 27195198.

Härter B, Benedicenti F, Karall D, Lausch E, Schweigmann G, Stanzial F, Superti-Furga A, Scholl-Bürgi S. Clinical aspects of hyaline fibromatosis syndrome and identification of a novel mutation. Mol Genet Genomic Med. 2020;8:e1203. PubMed PMID: 32196989.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Kawasaki G, Yanamoto S, Mizuno A, Fujita S. Juvenile hyaline fibromatosis complicated with oral squamous cell carcinoma: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;91:200–4. PubMed PMID: 11174598.

Klebanova Y, Schwindt C. Infantile systemic hyalinosis: a case report of compromised cellular and humoral branches of the immune system leading to infections. Pediatr Asthma Allergy Immunol. 2009;22:127–30. PubMed PMID: 20563226.

Nischal KC, Sachdev D, Kharkar V, Mahajan S. Juvenile hyaline fibromatosis. J Postgrad Med. 2004;50:125–6. PubMed PMID: 15235211.

Pollard M, Ollite EM, Walker RW. The anesthetic management of a child with infantile systemic hyalinosis. Paediatr Anaesth. 2008;18:1123–4. PubMed PMID: 18673317.

Qasem F, Abotaiban A, Ahmad H. Airway management in a patient with infantile systemic hyalinosis. J Anesth Clin Res. 2012;3:263.

Reeves CV, Wang X, Charles-Horvath PC, Vink JY, Borisenko VY, Young JA, Kitajewski JK. Anthrax toxin receptor 2 functions in ECM homeostasis of the murine reproductive tract and promotes MMP activity. PLoS One. 2012;7:e34862. PubMed PMID: 22529944.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Schussler E, Linkner RV, Levitt J, Mehta L, Martignetti JA, Oishi K. Protein-losing enteropathy and joint contractures caused by a novel homozygous ANTXR2 mutation. Adv Genomics Genet. 2018;8:17–21. PubMed PMID: 30050362.

Shieh JTC, Swidler P, Martignetti JA, Ramirez MC, Balboni I, Kaplan J, Kennedy J, Abdul-Rahman O, Enns GM, Sandborg C, Slavotinek A, Hoyme HE. Systemic hyalinosis: a distinctive early childhood-onset disorder characterized by mutations in the anthrax toxin receptor 2 gene (ANTXR2). Pediatrics. 2006;118:e1485–92. PubMed PMID: 17043134.

Shimizu K, Ogawa F, Hamasaki Y, Murota H, Katayama I. A case of bullous pemphigoid arising in juvenile hyaline fibromatosis with oral squamous cell carcinoma. J Dermatol. 2005;32:650–3. PubMed PMID: 16334866.

Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Sillence D, Simon M, Sutton VR, Warman ML, Superti-Furga A. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A. 2023;191:1164–209. PubMed PMID: 36779427.

Zolkipli Z, Longman C, Brown S, Rahman N, Holder SE, Muntoni F. Skeletal muscle involvement in infantile systemic hyalinosis. Eur J Paediatr Neurol. 2003;7:401–6. PubMed PMID: 14623219.

License