GENEReviews

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Hyalinosis, Inherited Systemic

[*Includes: Infantile Systemic Hyalinosis, Juvenile Hyaline Fibromatosis*]

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Summary

Disease characteristics. Inherited systemic hyalinosis is characterized by hyaline deposits in the papillary dermis and other tissues. It typically presents 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) die in early childhood; some with a milder phenotype (previously called juvenile hyaline fibromatosis) survive into adulthood.

Diagnosis/testing. The diagnosis of inherited systemic hyalinosis is based on clinical findings. 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. *ANTXR2* (previously called *CMG2*) is the only gene currently known to cause inherited systemic hyalinosis. Molecular genetic testing is currently available on a research basis only.

Management. *Treatment of manifestations:* nonsteroidal anti-inflammatory drugs (NSAIDs), opiates, and possibly gabapentin for pain; consultation with a pain management specialist as needed; physiotherapy for joint contractures within the person's tolerance for pain; nasogastric tube or gastrostomy tube feeding under supervision of a gastroenterologist and nutritionist; hydration and albumin infusions for protein-losing enteropathy; lesions that obstruct the airway or interfere with feedings can be excised, but may recur. *Prevention of secondary complications:* Anesthesiologists need to be aware of potential difficulties with endotracheal intubation.

Genetic counseling. Inherited systemic hyalinosis is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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 an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. No laboratories offering molecular genetic testing for prenatal diagnosis of inherited systemic hyalinosis are listed in the GeneTests Laboratory Directory; however, prenatal testing may be possible through a laboratory offering custom prenatal testing for families in which the disease-causing mutations are known.

Diagnosis

Clinical Diagnosis

Inherited systemic hyalinosis is characterized by hyaline deposits in the papillary dermis and other tissues associated with the following distinctive clinical findings presented in order of their specificity for clinical diagnosis:

- **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.
- **Pain or excessive crying.** Severe pain with passive movement in infancy or early childhood is characteristic. Pathogenesis is unclear.
- **Gingival thickening.** Affected individuals develop masses in the gingiva, which enlarge over time.
- **Other skin 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 seem to develop and become more numerous over time. The skin is firm to palpation and has been described as thickened.
- **Unusual 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.
- **Failure to thrive.** Postnatal-onset growth deficiency is common. Some children develop chronic diarrhea and protein-losing enteropathy.

Testing

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 and imaging. Findings in biopsy specimens from individuals with prominent gastrointestinal symptoms include villous atrophy, edema, lymphangiectasia, and hyalinosis. Rapid transit time has been reported in real-time upper-gastrointestinal imaging studies.

Skeletal radiographs. Radiographic abnormalities include generalized osteopenia, periosteal reaction, and lucent lesions. These nonspecific findings may affect long bones as well as the axial skeleton and can support a clinical suspicion of inherited systemic hyalinosis.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *ANTXR2*, the capillary morphogenesis gene-2, is the only gene currently known to be associated with inherited systemic hyalinosis.

Research testing

- **Sequence analysis.** In 18 families with 30 affected individuals, Hanks et al (2003) sequenced *ANTXR2* exons and intron-exon boundaries. They identified 15 different mutations in 17 families. Although most individuals were homozygous for mutations in *ANTXR2*, compound heterozygotes were also noted. In four families with five affected individuals, Dowling et al (2003) identified homozygous mutations in three families and compound heterozygous mutations in one family with two affected children.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Hyalinosis, Inherited Systemic

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*ANTXR2* sequence variants	90% [1]	Research only [2]

1. Twenty mutations were identified in 21 families tested [Dowling et al 2003, Hanks et al 2003].
2. For clinical confirmation of mutations identified in research laboratories, see Testing.

Testing Strategy

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family and confirmation in a laboratory offering clinical confirmation of mutations identified in a research laboratory. See Testing.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family and may be available from laboratories offeing custom prenatal diagnosis. See Testing.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with *ANTXR2* mutations.

Clinical Description

Natural Hsitory

Inherited systemic hyalinosis, named for the characteristic hyaline deposits in the papillary dermis and other tissues of affected individuals, exhibits a broad spectrum of clinical severity [Mancini et al 1999, Urbina et al 2004]. Severely affected children often succumb in the first years of life; this severe phenotype was originally termed infantile systemic hyalinosis. Milder forms of the disease were originally described as juvenile hyaline fibromatosis (JHF); however, it has become clear that both the severe and mild forms occur on a continuum of clinical findings [Rahman et al 2002, Dowling et al 2003, Hanks et al 2003]. Thus, the term inherited systemic hyalinosis encompasses the entire spectrum of disease.

Inherited systemic hyalinosis presents 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 [Stucki et al 2001].

The degree of hyperpigmentation varies depending on the baseline pigmentation of the skin [Arbour et al 2001].

Pearly papules develop on the head and neck. Skin nodules, papules, and fleshy lesions develop especially periorally and perianally.

The gingivae are thickened and may reveal focal masses. Dental abnormalities include malpositioned teeth and curved dental roots.

Cognitive function is preserved; however, cases of delayed development have been reported [Nischal et al 2004].

Excessive diaphoresis is common.

Hepatomegaly may be present.

Susceptibility to fractures may be increased.

Failure to thrive is associated with difficulty in feeding and severe intractable protein-losing diarrhea, likely accompanying hyalinosis of the intestine.

Recurrent infections may develop for unclear reasons.

Individuals with severe disease succumb to infection or complications of protein-losing enteropathy.

Some individuals demonstrate a milder phenotype (previously described as JHF), which may be of later onset. Although joint contractures, skin hyperpigmentation, and lesions occur with the milder phenotype, the presentation is variable, the pain is less severe, the disability may be less pronounced, and affected individuals may live into adulthood. Pain may lessen with age. Short stature, limb shortening, and brachydactyly may be present. Intractable diarrhea is rare in milder forms of the disorder.

At least two individuals clinically diagnosed as having JHF developed squamous cell carcinoma [Kawasaki et al 2001, Shimizu et al 2005]; the *ANTXR2* mutation status in these individuals is unknown.

Other studies

- MRI of the brain is unremarkable.
- Ophthalmologic examination does not reveal any characteristic findings and can be used to differentiate inherited systemic hyalinosis from some lysosomal storage disorders.
- Myopathic changes on muscle biopsy may be evident [Zolkipli et al 2003].
- Laboratory studies may demonstrate a normal or slightly elevated ESR, anemia, and/or thrombocytosis.
- C3 and C4 lymphocyte subsets and ANA are unremarkable.

Pathology. Only a few post-mortem 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 with features of either infantile systemic hyalinosis or JHF:

- Those with at least one insertion/deletion in *ANTXR2* resulting in a translational frameshift had a severe phenotype (infantile systemic hyalinosis).
- All individuals with mutations situated in the von Willebrand domain had infantile systemic hyalinosis, suggesting that disruption of the protein-binding domain leads to serious clinical consequences.
- In-frame and missense mutations 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.

Nomenclature

Before the molecular basis of inherited systemic hyalinosis was understood, severe and milder forms of the disorder were described as separate conditions (infantile systemic hyalinosis and juvenile hyaline fibromatosis, respectively). Recent data indicate that both severe and mild forms of inherited systemic hyalinosis are caused by mutations in *ANTXR2*.

Prevalence

Inherited systemic hyalinosis is rare, but it has been recognized in families of various ethnic backgrounds on multiple continents [Felix et al 2004]. One report described multiple cases in the Arab population [Al-Mayouf et al 2005], reflecting the presence of consanguinity.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The following conditions exhibit some features similar to inherited systemic hyalinosis; however, inherited systemic hyalinosis can be distinguished by the characteristic associated pain, hyperpigmented skin lesions, and perianal and perioral masses:

- **Farber disease (Farber lipogranulomatosis)** [OMIM 228000] is a lysosomal storage disease caused by deficiency of the enzyme acid ceramidase. Affected individuals typically present with painful joint contractures and progressive hoarseness. Skin nodules develop, especially over bony prominences. However, most

of the reported cases have neurologic involvement, which helps distinguish Farber disease from inherited systemic hyalinosis. Furthermore, individuals with Farber disease do not have the hyperpigmented patches as seen in inherited systemic hyalinosis. The diagnosis of Farber disease can be made by assessing activity of the enzyme ceramidase in fibroblasts.

- **I-cell disease (mucolipidosis II)** [OMIM 252500] is a storage disorder associated with ineffective transport of enzymes into the lysosome accompanying a defect in the enzyme lysosomal phosphotransferase. Affected individuals develop gingival thickening and dysostosis multiplex. The facies are coarse and joint contractures develop over time. The distinctive skin findings of inherited systemic hyalinosis can help differentiate these disorders. Diagnosis is confirmed by enzyme analysis.
- **Non-accidental trauma.** Periosteal reaction or fractures on skeletal radiographs in systemic hyalinosis have been mistaken for nonaccidental 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.
- **Pseudo-Hurler polydystrophy (mucolipidosis IIIA)** [OMIM 252600] is caused by mutations in *GNPTAB*, the gene encoding N-acetylglucosamine-1-phophotransferase. The phenotype varies in severity; principal features include contractures and dysostosis multiplex. The skin findings of systemic hyalinosis distinguish the two conditions.
- **Winchester syndrome** [OMIM 277950] is characterized by short stature and osteolysis of the interphalangeal and metacarpal-phalangeal joints. Winchester syndrome has been proposed to be allelic with **nodulosis-arthropathy-osteolysis syndrome** (NAO) [OMIM 605156], a disorder resulting from mutations in *MMP2*, the gene encoding matrix metalloproteinase-2. **Torg syndrome** [OMIM 259600] has also been clinically classified as the same disorder as NAO. All three disorders lack the distinctive dermatologic features of inherited systemic hyalinosis.
- **Congenital generalized fibromatosis (infantile myofibromatosis)** [OMIM 228550] is associated with solitary, multiple, or generalized nodules composed of cells with features of differentiated fibroblasts and smooth muscle cells. Autosomal dominant inheritance has been suggested [Zand et al 2004].
- **Stiff skin syndrome** [OMIM 184900] is characterized by thickened skin and flexion contractures, with early lethality in some cases. Mucopolysaccharide deposition has been found in the skin but mucopolysacchariduria has not been detected.
- **Lipoid proteinosis of Urbach and Wiethe (hyaline cutis et mucosae)** [OMIM 247100] presents with hoarseness, followed by the development of papules around the eyelids. Other findings include facial papules, tongue enlargement, dental hypoplasia, and skin lesions (vesicles and crusted bullae evolving into waxy plaques) that are distinct from those in inherited systemic hyalinosis. Many cases have been reported from South Africa. Mutations in *ECM1*, the gene encoding extracellular matrix protein 1, have been observed in some affected individuals.
- **Caffey disease (infantile cortical hyperostosis)** [OMIM 114000] presents with irritability, poor feeding, fever, and soft tissue swelling. Radiographic hyperostoses are characteristic and can help differentiate Caffey disease from inherited systemic hyalinosis. Some individuals exhibit mutations in *COL1A1*, the gene encoding type 1, alpha 1 collagen.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with inherited systemic hyalinosis, complete nutritional evaluation and evaluation for intestinal malabsorption are recommended.

Treatment of Manifestations

Pain

- Nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates help control pain. Agents such as gabapentin should be considered.
- Gentle handling may reduce pain that is worsened with movement. Splinting of affected joints may provide comfort.
- When passive movement of joint contractures is painful, physiotherapy should be carried out with care; in some cases physiotherapy is not tolerated because of pain.
- Consultation with a pain management specialist may be helpful. Palliative care may be an option in severe cases.

Failure to thrive. Early consideration should be given to nasogastric tube or gastrostomy tube feeding. Formula should be tailored for the possibility for malabsorption. A nutritionist should follow affected individuals.

Protein-losing enteropathy. Chronic diarrhea and protein-losing enteropathy with subsequent edema are treated with hydration and albumin infusions; an effective long-term treatment is lacking.

Skin nodules, gingival thickening, and lesions of the mouth. Lesions that obstruct the airway or interfere with oral intake are particularly problematic. Surgical excision is an option, but lesions may recur.

Anesthesiologists should be aware of the diagnosis given the anatomic difficulty of endotracheal intubation in some affected individuals as a result of gingival thickening.

Dermatitis. Intertriginous, perianal, and neck areas seem particularly prone to dermatitis and should be treated appropriately.

Perianal masses may be excised, but may recur.

Joint contractures. Contractures are typically progressive. Treatment of contractures with physiotherapy should be performed with care because of pain.

Infections. Infections are treated in a standard manner based on the site of infection and causative agent. An immunology evaluation should be considered if there is a history of multiple infections; however, the etiology of multiple infections in some individuals is unclear.

Other

- Because hyalinosis of the heart has been reported, an echocardiogram should be considered.
- Given the chronic nature of this disorder in an individual with normal intelligence, family counseling should be considered in order to develop coping strategies for both the patient and the immediate family.

Surveillance

Routine nutritional assessment is appropriate.

Periodic assessment for gastrointestinal malabsorption may aid in optimizing nutritional status.

Testing 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 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Systemic hyalinosis is inherited in an autosomal recessive manner.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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.

- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with systemic hyalinosis are obligate heterozygotes (carriers) for a disease-causing mutation.

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

Carrier Detection

If the mutations have been identified in the family, carrier testing for at-risk family members is available on a clinical basis from laboratories offering clinical confirmation of mutations identified in research labs. See Testing.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being carriers.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when molecular genetic testing is available on a research basis only. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. No laboratories offering molecular genetic testing for prenatal diagnosis of inherited systemic hyalinosis are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Ultrasound examination. In general, prenatal ultrasound examination is not useful in diagnosis; however, in a pregnancy at risk, detection of decreased fetal activity and contractures could suggest recurrence.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hyalinosis, Inherited Systemic

Gene Symbol	Chromosomal Locus	Protein Name
ANTXR2	4q21	Anthrax toxin receptor 2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hyalinosis, Inherited Systemic

228600	FIBROMATOSIS, JUVENILE HYALINE
236490	HYALINOSIS, INFANTILE SYSTEMIC
608041	ANTHRAX TOXIN RECEPTOR 2; ANTXR2

Table C. Genomic Databases for Hyalinosis, Inherited Systemic

Gene Symbol	Entrez Gene	HGMD
ANTXR2	118429 (MIM No. 608041)	ANTXR2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: *ANTXR2* consists of 17 exons. Several polymorphisms have been described [Hanks et al 2003].

Pathologic allelic variants: Twenty different mutations were reported in 21 families representing ten different ethnic groups [Dowling et al 2003, Hanks et al 2003]:

- The milder phenotype, consistent with a diagnosis of juvenile hyaline fibromatosis, is more likely caused by mutations in the cytoplasmic domain (in-frame and missense) [Hanks et al 2003].
- The more severe phenotype, consistent with early onset and death in infancy or early childhood, is more likely to be caused by missense and truncating mutations in the extracellular domain, although truncating mutations in the transmembrane and cytoplasmic domains may also result in the severe phenotype.

Multiple affected individuals have had mutations involving the polycytosine tract in the region encoding the cytoplasmic domain, suggesting that this may be a hot spot for mutation.

Individuals with compound heterozygous mutations have been reported [Dowling et al 2003, Hanks et al 2003].

Deletions in *ANTXR2* may also exist [Shieh et al 2006].

Normal gene product: Anthrax toxin receptor 2 is a protein of 488 amino acids including a cytoplasmic, transmembrane, and extracellular domain. The extracellular latter domain contains a von Willebrand factor type A domain. *ANTXR2* is expressed in numerous tissues including heart, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, prostate, testis, ovary, small intestine, colon, and leukocytes. It is minimally or not expressed in the brain. It is induced during capillary morphogenesis and binds laminin and collagen IV via the von Willebrand domain. It is hypothesized that anthrax toxin receptor 2 plays an important role in basement membrane matrix homeostasis. Anthrax toxin receptor 2 has significant homology to tumor endothelium marker 8 *(TEM8*), which also acts as an anthrax receptor [Scobie et al 2003].

Abnormal gene product: Abnormalities in the anthrax toxin receptor 2 protein affect anthrax toxin receptor 2-laminin interaction, likely affecting basement membrane homeostasis [Dowling et al 2003, Hanks et al 2003].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

American Chronic Pain Association: Growing Pains
Growing Pains is a support group for chronically ill youth.
PO Box 850
Rocklin CA 95677
Phone: 800-533-3231
Fax: 916-632-3208
Email: ACPA@pacbell.net
Growing Pains

Association for the Care of Children's Health
Pain, Pain, Go Away: Helping Children with Pain Booklet

M.I.S.S. 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
Email: info@missfoundation.org
www.missfoundation.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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