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SOST-Related Sclerosing Bone Dysplasias

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Summary

Disease characteristics. *SOST*-related sclerosing bone dysplasias include sclerosteosis and van Buchem disease; both are disorders of osteoblast hyperactivity. The major clinical features of sclerosteosis are progressive skeletal overgrowth and variable syndactyly, usually of the second (index) and third (middle) fingers. Affected individuals appear normal at birth except for syndactyly. Distinctive facial features including asymmetric mandibular hypertrophy, frontal bossing, and midface hypoplasia are usually apparent by mid-childhood. Hyperostosis of the skull results in narrowing of the foramina, causing entrapment of the seventh cranial nerve often leading to facial palsy, and entrapment of the eighth cranial nerve, often resulting in deafness in mid-childhood. In sclerosteosis, hyperostosis of the calvarium reduces intracranial volume, increasing the risk for potentially lethal elevation of intracranial pressure in adulthood. Survival of individuals with sclerosteosis into old age is unusual. The manifestations of van Buchem disease are generally milder than sclerosteosis and syndactyly is absent.

Diagnosis/testing. The diagnoses of sclerosteosis and van Buchem disease are based upon recognition of the characteristic clinical and radiographic features. Radiographic findings include widening (hyperostosis) and increased density (sclerosis) of the calvarium, the base of the skull, and the shafts of the tubular bones. *SOST* is the only gene known to be associated with sclerosteosis and van Buchem disease. Molecular genetic testing is available on a clinical basis.

Management. *Treatment of manifestations:* surgical decompression of entrapped cranial nerves; craniectomy for increased intracranial pressure; middle ear surgery for conductive hearing loss; hearing aids; spinal cord decompression for backache; surgical correction of syndactyly; surgical reduction of mandibular overgrowth. *Prevention of Secondary Complications:* Tooth extraction may be difficult; management by an orthodontic or craniofacial team is recommended. *Surveillance:* annual assessments from infancy for hearing,

evidence of increased intracranial pressure, and evidence of nerve entrapment. *Testing of relatives at risk:* clinical appraisal, lateral skull radiograph if indicated.

Genetic counseling. The *SOST*-related sclerosing bone dysplasias are inherited in an autosomal recessive manner. Each sib of a proband 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. Prenatal diagnosis for pregnancies at 25% risk is possible if both mutant alleles have been identified in an affected family member or if linkage has been established. Ultrasound examination may detect syndactyly, but its absence on ultrasound examination is not indicative of an unaffected fetus.

Diagnosis

Clinical Diagnosis

Sclerosteosis and van Buchem disease are clinically and radiographically similar disorders that are caused by mutations in the *SOST* gene [Balemans et al 2001; Brunkow et al 2001; Balemans, Patel et al 2002; Staehling-Hampton et al 2002].

Sclerosteosis. The diagnosis of sclerosteosis is based upon characteristic clinical and radiographic features and a family history consistent with autosomal recessive inheritance.

Clinical features include the following:

- Generalized progressive skeletal overgrowth, most pronounced in the skull and mandible, leading to:
  - Potentially lethal elevation of intracranial pressure in early adulthood as a result of calvarial overgrowth
  - Entrapment of the seventh cranial nerve leading to facial palsy that is initially intermittent and eventually constant resulting in impaired facial movements in adulthood
  - Conductive hearing loss in childhood followed by additional entrapment of the eighth cranial nerve and closure of the oval and round windows leading to sensorineural hearing loss in adulthood
  - Distortion of the face with asymmetric mandibular hypertrophy, frontal bossing, midface hypoplasia, and proptosis
  - Tall stature with accelerated bone growth beginning in childhood
- Variable cutaneous or bony syndactyly of fingers two (index) and three (middle), and occasionally fingers three and other fingers. The syndactyly is usually bilateral but not necessarily symmetric.
- Radial deviation of the terminal phalanges
- Dysplastic or absent nails

The majority of persons affected with sclerosteosis are members of the Afrikaner (Dutch ancestry) population of South Africa. The diagnosis should be suspected in any neonate in this population with syndactyly of the second and third fingers particularly in the presence of fluctuating facial palsy, which later may become permanent.

Radiographic findings include the following:

- Widening (hyperostosis) and increased density (sclerosis) of the calvarium, the base of the skull, and the shafts of the tubular bones

- Undermodeling of the shafts of the tubular bones of the metacarpals and phalanges
- Broad and dense clavicles and ribs
- Sclerosis of the scapulae and pelvis without an increase in size
- Relative sparing of the spine [Beighton, Cremin et al 1976; Hamersma et al 2003]

Van Buchem disease. This disorder is milder than sclerosteosis. Neurologic complications are less common and syndactyly does not occur.

Testing

Serum concentration of calcium and phosphorus are normal in individuals with sclerosteosis and van Buchem disease.

Serum concentration of alkaline phosphatase may be elevated.

Urinary cross-linked N-telopeptide was significantly elevated in one study of six individuals with van Buchem disease [Wergedal et al 2003]. Serum procollagen peptide and osteocalcin concentrations were also significantly elevated in these individuals.

Histologic examination of the bone reveals increased bone density with thicker than normal trabeculae and cortices.

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. *SOST* is the only gene currently known to be associated with sclerosteosis and van Buchem disease.

- **Sclerosteosis.** Four mutations in the *SOST* gene have been reported thus far in individuals with sclerosteosis: three distinct stop mutations in families of Afrikaner, Brazilian, and mixed descent (Caucasian/Native American/African American) and a splicing mutation in an individual of African heritage from Senegal [Balemans et al 2001, Brunkow et al 2001].
- **Van Buchem disease.** Balemans, Patel et al (2002) and Staehling-Hampton et al (2002) identified a 52-kb homozygous deletion downstream of the *SOST* gene in all Dutch individuals affected with van Buchem disease studied to date. The deletion does not appear to overlap the coding region of *SOST* or any other gene and potentially results in reduced *SOST* gene transcription by "cis regulatory action or a position effect." None of the Dutch individuals affected with van Buchem disease in these studies were found to have mutations within the *SOST* gene. A putative disease-causing splicing mutation in *SOST* was found in a brother and sister of German origin who were diagnosed with van Buchem disease [Balemans, Cleiren et al 2005].

Clinical uses

- Diagnostic confirmation
- Carrier testing

Clinical testing

- **Targeted mutation analysis.** Targeted mutation analysis for the 52-kb deletion downstream of the *SOST* gene is available on a clinical basis. It is not clear what percentage of individuals with van Buchem disease (or potentially sclerosteosis) have this mutation.
- **Sequence analysis.** Sequence analysis can detect the more common *SOST* mutations as well as rare, private mutations. The clinical sensitivity of sequence analysis has not been established (testing data collected thus far cannot differentiate between individuals testing negative for *SOST* mutations because they either are not affected with sclerosteosis/van Buchem disease or have *SOST* mutations that are not detected by the genetic assay].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *SOST*-Related Sclerosing Bone Dysplasias

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Targeted mutation analysis	52-kb deletion downstream of *SOST* gene	Unknown	Clinical Testing
Sequence analysis	*SOST* sequence variants		

1. Proportion of affected individuals with a mutation(s) as classified by test method

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

No other simple genetic disorders are known to be associated with mutations in *SOST*. However, common non-coding polymorphisms in the gene were found to moderately affect bone mineral density in the elderly, suggesting a role for the *SOST* gene product in the complex disorder, osteoporosis [Uitterlinden et al 2004].

Clinical Description

Natural History

Hypothesized to be allelic disorders, sclerosteosis and van Buchem disease were confirmed to be caused by mutations in the same gene in 2002 [Balemans, Patel et al 2002; Staehling-Hampton et al 2002]. The manifestations of van Buchem disease are generally milder than those in sclerosteosis and syndactyly is absent (Table 2) [Beighton et al 1984].

Table 2. Distinguishing Features of Sclerosteosis and van Buchem Disease

	Sclerosteosis	van Buchem Disease
Reported cases	±80	±20
Age of clinical presentation	Early childhood	Puberty
Prognosis	Potentially lethal	Comparatively benign
Habitus	Gigantism	Normal stature
Facies	Gross distortion	Prominent mandible
Teeth	Irregular, with malocclusion	Normal
Cranial nerve palsy	Very common	Inconsistent
Intracranial pressure	Raised	Normal
Syndactyly	Frequent	Absent
Nail hypoplasia	Frequent	Absent
Cranial hyperostosis	Gross	Moderate
Distortion of tubular bones of hands and feet	Marked	Mild

From Beighton 1995, p 234

Sclerosteosis. The major clinical features of sclerosteosis are progressive skeletal overgrowth and variable syndactyly, usually of the second (index) and third (middle) fingers. Affected individuals appear normal at birth except for the syndactyly (seen in 76%) and ocular hypertelorism. The distinctive facial features are usually apparent by age five years. The risk for fractures, osteomyelitis, or bone marrow failure is not increased.

Hyperostosis of the skull results in narrowing of the foramina, causing entrapment of the seventh cranial nerve often leading to facial palsy. Entrapment of the eighth cranial nerve resulting in deafness in mid-childhood occurs in 82% of affected individuals [Hamersma et al 2003]. Anosmia may develop in adulthood. Lingual hemiparesis has been reported.

Asymmetric overgrowth of the mandible and malalignment of the teeth are common [Stephen et al 2001], occurring in 73% in one study [Hamersma et al 2003]. Proptosis is common (25%).

Hyperostosis of the calvarium reduces intracranial volume, leading to potentially lethal elevation of intracranial pressure in adulthood. Affected individuals typically experience headache from brain compression. Sudden death can result from compression of the medulla at the level of the foramen magnum. Thus, even though the occipital frontal circumference (OFC) may be at the 95th centile, the intracranial volume is typically smaller than normal. The calvarial bone itself can be up to 3-4 cm thick.

Dual x-ray absorptiometry in seven affected persons revealed markedly increased bone mineral density (BMD). In 18 phenotypically normal heterozygotes, the BMD was above the mean values of age-matched controls [Gardner et al 2005].

Survival into old age is unusual but not unprecedented [Barnard et al 1980]. Mean age of death is 33 years [Hamersma et al 2003]. The natural history of sclerosteosis has been reviewed in Beighton (1988), Beighton (1995), and Hamersma et al (2003).

Van Buchem disease. Individuals with van Buchem disease have normal stature and no syndactyly. The course of the disorder is similar to that of sclerosteosis but generally milder. Facial distortion is less severe and the frequency of neurologic complications is lower.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

In the past, sclerosteosis and van Buchem disease have been grouped with other dense bone disorders under nonspecific general terms including marble bones, osteopetrosis, and Albers-Schönberg disease. Diagnostic precision and syndromic delineation followed and the term "sclerosteosis" became established. Similarly, van Buchem and his colleagues employed the designation "hyperostosis corticalis generalisata familiaris" for the condition that is now known as "van Buchem disease." In the nosology of the dense bone disorders, sclerosteosis and van Buchem disease have been categorized as "craniotubular hyperostoses." With the elucidation of the molecular basis of these conditions, they are now classified together as *SOST*-related sclerosing bone dysplasias.

Prevalence

Sclerosteosis. During the last 35 years, sclerosteosis has been recognized in more than 70 persons in the Afrikaner (Dutch ancestry) community of South Africa [Beighton & Hamersma 1979]. In the Afrikaner population of South Africa, the carrier rate for the single founder-derived mutation is approximately one in 100 [Gardner 1999].

Simplex cases (i.e., a single affected individual in a family) or occurrences of familial sclerosteosis have been recorded in the following populations:

- United States [Higinbotham & Alexander 1941, Kelley & Lawlah 1946, Stein et al 1983]
- Germany [Pietruschka 1958]
- Japan [Sugiura & Yasuhara 1975]
- Brazil [Freire de Paes Alves et al 1982]
- Spain [Bueno et al 1994]
- Senegal [Tacconi et al 1998]
- Greek Cypriot [Itin et al 2001]

Van Buchem disease. Van Buchem disease has been recognized predominantly in the Dutch population (±20 cases). Several of the affected families have ancestral origins on the former island of Urk in the Zuider Zee. In addition, a brother and sister of German origin were described with a possible diagnosis of van Buchem disease [Balemans, Cleiren et al 2005].

Differential Diagnosis

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

Sclerosteosis and van Buchem disease are included in the category of craniotubular hyperostoses, which need to be distinguished from other sclerosing bone dysplasias. These include (1) the osteoscleroses, notably osteopetrosis, characterized by increased bone density with no bone overgrowth and little or no disturbance of the contours of the bones, and (2) the craniotubular dysplasias, characterized by abnormal modeling of the skeleton and moderate sclerosis of the calvarium and base of the skull.

The predominant feature of the craniotubular hyperostoses is overgrowth of bone, which leads to alterations of contours and increase in radiologic density of the skeleton. The bones are often

very resistant to trauma. In addition to sclerosteosis and van Buchem disease, this group of disorders includes:

- **Endosteal hyperostosis, Worth form.** This much milder disorder is inherited in an autosomal dominant manner and can be caused by mutation in the *LRP5* gene. Affected individuals may develop palsies of the seventh and eighth cranial nerves but are otherwise asymptomatic. Smooth bony swellings may be present on the palate (torus palatinus) as in sclerosteosis.
- **Camurati-Engelmann disease (CED).** CED (progressive diaphyseal dysplasia) is characterized by hyperostosis of the long bones and the skull, proximal muscle weakness, severe limb pain, and joint contractures. Frontal bossing, enlargement of the mandible, proptosis, and cranial nerve impingement resulting in facial palsy are seen in severe cases later in life. Diagnosis of CED is based on physical examination and radiographic findings and can be confirmed by molecular genetic testing. Bone and muscle histology are nonspecific. *TGFB1* is the only gene known to be associated with CED. Sequence analysis identifies mutations in *TGFB1* in about 90% of affected individuals. Inheritance is autosomal dominant.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *SOST*-related sclerosing bone dysplasias, the following evaluations are recommended:

- Formal audiologic evaluation
- Neurologic evaluation for consequences of nerve entrapment
- Ophthalmologic evaluation for evidence of increased intracranial pressure and/or proptosis
- Assessment of the necessity for surgical correction of syndactyly in individuals with sclerosteosis
- Radiographic and imaging studies
- Dental assessment

Treatment of Manifestations

The bones in sclerosteosis are thick and dense; surgical intervention may be difficult and prolonged. Standard neurosurgical instruments may not be sufficient (i.e., drill bits may be too short and power tools may be damaged by the dense bone) [du Plessis 1993]. In addition, bone regrowth occurs and may cause recurrence of symptoms.

Management is based upon surgical decompression of the entrapped cranial nerves that can cause recurrent facial paralysis similar to Bell's palsy (from age two years onwards). Trigeminal nerve decompression can help if facial pain is severe.

Craniectomy is required if intracranial pressure becomes elevated (from age five years onwards but usually in young adulthood).

Middle ear surgery to correct conductive hearing loss and the provision of hearing aids may be helpful.

Spinal cord decompression may occasionally be needed in adulthood to alleviate backache.

Surgical correction of syndactyly may be necessary in early childhood in order to improve function and cosmetic appearance in those with sclerosteosis.

Mandible reduction may be performed for cosmetic reasons or if mouth closure is impaired as a result of overgrowth of the mandible. Tooth extraction may be difficult. Management by an orthodontic or craniofacial team, if available, is recommended.

Surveillance

Annually from infancy onwards for the following:

- Audiologic assessment
- Assessment for increased intracranial pressure and medullary compression
- Neurologic examination for consequences of nerve entrapment

Malocclusion is evaluated on an individual basis.

Testing of Relatives at Risk

Clinical appraisal and lateral skull radiograph are appropriate as indicated.

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

Surgery for proptosis has not been successful [De Villiers & du Plessis 1995].

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

The *SOST*-related sclerosing bone dysplasias are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are heterozygotes (carriers).
- In sclerosteosis, some heterozygotes have calvarial widening.

Sibs of a proband

- At conception, each sib of a proband 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 chance of his/her being a carrier is 2/3.

Offspring of a proband

- The offspring of an individual with sclerosteosis or van Buchem disease are obligate heterozygotes (carriers) for a disease-causing mutation in the *SOST* gene.
- If the reproductive partner of the proband is heterozygous for an *SOST* mutation, each offspring has a 50% chance of inheriting two copies of an *SOST* mutation and being affected. Reproductive partners are more likely to be carriers of an *SOST* mutation if they are related to the proband or are members of populations with a high carrier frequency.
- **Sclerosteosis.** In the Afrikaner population of South Africa, the carrier rate is approximately 1:100.
- **Van Buchem disease.** The Dutch population is the only population known to have an elevated carrier rate for mutations in the *SOST* gene.

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

Carrier Detection

Carrier testing for at-risk relatives is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy.

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 in situations in which the sensitivity of currently available testing is less than 100%. 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 *SOST*-related sclerosing bone dysplasias are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing

mutations have been identified. For laboratories offering custom prenatal testing, see Testing.

Ultrasound examination. Ultrasound examination may be able to detect syndactyly in fetuses at risk for sclerosteosis. This finding is variable in sclerosteosis and therefore its presence in an at-risk fetus is indicative of SCL, but its absence is not indicative of an unaffected fetus.

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 SOST-Related Sclerosing Bone Dysplasias

Gene Symbol	Chromosomal Locus	Protein Name
SOST	17q12-q21	Sclerostin

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 SOST-Related Sclerosing Bone Dysplasias

239100	HYPEROSTOSIS CORTICALIS GENERALISATA
269500	SCLEROSTEOSIS; SOST
605740	SCLEROSTIN; SOST

Table C. Genomic Databases for SOST-Related Sclerosing Bone Dysplasias

Gene Symbol	Entrez Gene	HGMD
SOST	50964 (MIM No. 605740)	SOST

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Sclerosteosis is a disorder of bone modeling and remodeling, especially of the skull and diaphyseal region of the long bones. Current evidence supports a deficiency of sclerostin, a novel secreted protein expressed in osteoblasts and osteocytes, resulting in the increased bone density observed in sclerosteosis and van Buchem disease.

Normal allelic variants: Normal allelic variants within the sclerostin signal sequence as well as in the non-coding sequence flanking the two-exon *SOST* gene have been reported [Balemans, Foernzler et al 2002; Uitterlinden et al 2004].

Pathologic allelic variants: Consistent with the autosomal recessive inheritance pattern of the disorder, all *SOST* mutations reported thus far result in loss of function of the gene product, either by introduction of a termination codon or by splicing mutations [Balemans et al 2001; Brunkow et al 2001; Balemans, Cleiren et al 2005]. A 52-kb downstream deletion potentially resulting in altered regulation of the *SOST* gene was shown to be associated with van Buchem disease in Dutch individuals studied by Balemans, Patel et al (2002) and Staehling-Hampton et al (2002). The inhibitory effect of this deletion on *SOST* gene expression was demonstrated in a transgenic mouse model [Loots et al 2005]. See Genomic Databases table above.

Normal gene product: The *SOST* gene encodes a 213-amino acid propeptide (sclerostin) with a cysteine-knot motif that participates in dimerization and receptor binding and a signal sequence for secretion. It is a secreted bone morphogenetic protein (BMP) antagonist, thought to be derived from either osteoblasts/osteocytes after onset of mineralization [Winkler et al 2003, Van Bezooijen et al 2004, Poole et al 2005] or from osteoclasts [Kusu et al 2003]. For reviews, see van Bezooijen, Papapoulos et al (2005) and van Bezooijen, ten Dijke et al (2005). Sclerostin has been shown to dimerize with the BMP antagonist noggin, suggesting an exquisite mechanism for the fine-tuning of BMP activity and bone formation [Winkler et al 2004]. One study found that expression of sclerostin effected apoptosis of osteoblasts in a differentiating culture [Sutherland, Geoghegan, Yu, Turcott et al 2004]. It is also thought to negatively regulate Wnt signalling through its association with the Wnt co-receptors LRP5 and LRP6 [Li et al 2005, Semenov et al 2005]. The expression of *SOST* is positively influenced by the presence of specific BMPs [Ohyama et al 2004; Sutherland, Geoghegan, Yu, Winkler et al 2004] and may be a direct target of the osteoblast-specific transcription factor Cbfa1/RUNX2 (see Cleidocranial Dysplasia) [Sevetson et al 2004].

Abnormal gene product: Unknown

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.

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Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

American Society for Deaf Children
3820 Hartzdale Drive
Camp Hill PA 17011
Phone: 800-942-2732 (parent hotline); 717-703-0073 (business V/TTY)
Fax: 717-909-5599
Email: asdc@deafchildren.org
www.deafchildren.org

National Association of the Deaf
8630 Fenton Street Suite 820
Silver Spring MD 20910
Phone: 301-587-1788 (voice); 301-587-1789 (TTY)
Fax: 301-587-1791
Email: NADinfo@nad.org
www.nad.org

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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

- 5 October 2007 (cd) Revision: sequence analysis available on a clinical basis
- 2 February 2007 (me) Comprehensive update posted to live Web site
- 23 September 2004 (me) Comprehensive update posted to live Web site
- 4 June 2002 (tk/me) Review posted to live Web site
- 5 February 2002 (phb) Original submission