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SOST-Related Sclerosing Bone Dysplasias

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Summary

Clinical characteristics

SOST-related sclerosing bone dysplasias include sclerosteosis and van Buchem disease, both disorders of progressive bone overgrowth due to increased bone formation.

The major clinical features of sclerosteosis are progressive skeletal overgrowth, most pronounced in the skull and mandible, and variable syndactyly, usually of the second (index) and third (middle) fingers. Affected individuals appear normal at birth except for syndactyly. Facial distortion due to bossing of the forehead and mandibular overgrowth is seen in nearly all individuals and becomes apparent in early childhood with progression into adulthood. Hyperostosis of the skull results in narrowing of the foramina, causing entrapment of the seventh cranial nerve (leading to facial palsy) with other, less common nerve entrapment syndromes including visual loss (2nd cranial nerve), neuralgia or anosmia (5th cranial nerve), and sensory hearing loss (8th cranial nerve). In sclerosteosis, hyperostosis of the calvarium reduces intracranial volume, increasing the risk for potentially lethal elevation of intracranial pressure. Survival of individuals with sclerosteosis into old age is unusual, but not unprecedented.

The manifestations of van Buchem disease are generally milder than sclerosteosis and syndactyly is absent; life span appears to be normal.

Diagnosis/testing

The diagnosis of *SOST*-related sclerosing bone dysplasia is established in a proband with typical clinical and radiographic findings and identification of biallelic pathogenic variants in *SOST* (for sclerosteosis) or the presence of a biallelic 52-kb deletion downstream of *SOST* (for van Buchem disease) on molecular genetic testing.

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Management

No specific treatment is currently available, and management aims at relieving symptoms and preventing complications.

Treatment of manifestations: Surgical correction of syndactyly; surgical decompression of entrapped cranial nerves, notably the facial nerve; craniectomy and ventriculo-peritoneal drain for increased intracranial pressure; surgical reduction of mandibular overgrowth; hearing aids with middle ear surgery or cochlear implant depending on nature of hearing loss; spinal cord decompression for radiculopathy; orbital decompression for proptosis or glaucoma.

Surveillance: At least annual assessments from infancy for bone mass, evidence of cranial nerve entrapment and of increased intracranial pressure, vision issues, hearing loss, and tooth malalignment/malocclusion.

Agents to avoid: Agents known to suppress bone resorption (e.g., bisphosphonates, denosumab, selective estrogen receptor modulators) and agents known to stimulate bone formation (e.g., teriparatide, abaloparatide, romozosumab).

Genetic counseling

SOST-related sclerosing bone dysplasia is inherited in an autosomal recessive manner. 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. Prenatal diagnosis for pregnancies at increased risk and preimplantation diagnosis for *SOST*-related sclerosing bone dysplasias are possible if the pathogenic variants in the family have been identified. Ultrasound examination may detect syndactyly in fetuses at risk for sclerosteosis, but its absence on ultrasound examination does not rule out an affected fetus.

GeneReview Scope

SOST-Related Sclerosing Bone Dysplasias: Included Phenotypes [1]
• Sclerosteosis • van Buchem disease

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Sclerosteosis and van Buchem disease are both disorders of progressive bone overgrowth due to increased bone formation; they are clinically and radiographically similar disorders that are caused by pathogenic variants in *SOST* [Balemans et al 2001, Brunkow et al 2001, Balemans et al 2002, Staehling-Hampton et al 2002]. The two disorders differ in severity and in type of molecular genetic variants.

Suggestive Findings

SOST-related sclerosing bone dysplasias **should be suspected** in individuals with the following findings.

Clinical findings

- Generalized progressive skeletal overgrowth, most pronounced in the skull and mandible, leading to:
  - Potentially lethal elevation of intracranial pressure in childhood or early adulthood as a result of calvarial overgrowth
  - Entrapment of the seventh cranial nerve leading to recurrent 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, or 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. (Note: Syndactyly is not found in van Buchem disease.)
- Radial deviation of the terminal phalanges
- Dysplastic or absent nails

Radiographic findings

- 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
- High bone mineral density (Z-score >5) measured by dual energy x-ray absorptiometry (DXA) [van Lierop et al 2017]

Ethnicity and neonatal findings. The majority of persons affected with sclerosteosis are members of the Afrikaner (Dutch ancestry) population of South Africa. Within this population the diagnosis should be suspected in any neonate with syndactyly, or in the presence of fluctuating facial palsy.

Van Buchem disease is almost exclusively found within the Netherlands. There are no specific neonatal findings in patients with van Buchem disease, although facial palsy can already be present at birth [van Egmond et al 2012].

Establishing the Diagnosis

The diagnosis of *SOST*-related sclerosing bone dysplasia **is established** in a proband with typical clinical and radiographic findings and biallelic pathogenic variants involving *SOST* identified on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, 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. Because the phenotype of *SOST*-related sclerosing bone dysplasia is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical findings in whom the diagnosis of *SOST*-related sclerosing bone dysplasia has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *SOST*-related sclerosing bone dysplasia, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SOST* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *SOST* 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Note: A homozygous 52-kb deletion downstream of *SOST*, which does not overlap the coding region, has been described in all individuals with van Buchem disease [Balemans et al 2002, Staehling-Hampton et al 2002]. This defect will not be found with single-gene testing or in a multigene panel. However, because van Buchem disease is almost exclusively found in the Netherlands, it is recommended to test for this genetic defect in non-Dutch individuals only if no genetic defects were found in a multigene panel.

Option 2

When the diagnosis of *SOST*-related sclerosing bone dysplasia is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best 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 *SOST*-related Sclerosing Bone Dysplasia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SOST	Sequence analysis [3]	All reported [4]
	Gene-targeted deletion/duplication analysis [5]	See footnotes 6 and 7.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. All pathogenic variants associated with *SOST*-related sclerosteosis in 94/96 cases are detectable by sequencing [van Lierop et al 2017]. Note that 66/96 reported cases are homozygous for the c.69C>T (p.Gln24Ter) South African founder variant. See footnote 6 regarding the pathogenic variant associated with van Buchem disease.
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. A homozygous 52-kb deletion downstream of *SOST*, which does not overlap the coding region, has been described in all Dutch individuals with van Buchem disease [Balemans et al 2002, Staehling-Hampton et al 2002].
7. No additional data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Hypothesized to be allelic disorders [Beighton et al 1984], sclerosteosis and van Buchem disease were confirmed to be caused by pathogenic variants in the same gene in 2002 [Balemans et al 2002, Staehling-Hampton et al 2002]. The two disorders have very similar phenotypes caused by genetic deficiency of sclerostin; however, the manifestations of van Buchem disease are generally milder than those in sclerosteosis and syndactyly is absent (Table 2) [Beighton 1995]. Taken together, these two disorders are known as *SOST*-related sclerosing bone dysplasias.

Clinical Features of Sclerosteosis

Syndactyly, ranging from soft-tissue webbing to bony union of the phalanges, is found at birth in 66% of individuals. It most often affects the second and third fingers, although other fingers or toes can be affected as well.

More subtle deformity of the digits can also be seen, such as radial deviation of the phalanges or nail aplasia [Itin et al 2001].

Facial distortion due to bossing of the forehead and mandibular overgrowth is seen in 90% of individuals, with proptosis, hypertelorism, or midfacial hypoplasia found in some. These facial findings become apparent in early childhood and progress into adulthood [Hamersma et al 2003, van Lierop et al 2017].

Tall stature appears at school age. Longitudinal growth arrests at puberty, by which time individuals can reach heights exceeding two meters (6.5 feet).

Recurrent facial palsies are hallmark complications in sclerosteosis, affecting 93% of individuals. The first episodes develop in early childhood and in some cases within the first months of life. The palsies are caused by narrowing of the neural foramina due to bone overgrowth of the skull.

Other, less common nerve entrapment syndromes in sclerosteosis are visual loss (2nd cranial nerve), neuralgia or anosmia (5th cranial nerve), and sensory hearing loss (8th cranial nerve) [van Lierop et al 2017].

Hearing loss is also highly prevalent, affecting 94% of individuals. It starts as conductive hearing loss in childhood, but often progresses into mixed conductive, sensorineural hearing loss later in life [Hamersma et al 2003, van Lierop et al 2017].

Increased intracranial pressure can develop due to narrowing of the intracranial cavity by the thickening of calvaria. It often starts in late adolescence. In a recent study, it was reported in 71% of individuals with sclerosteosis, and was considered the cause of death in 12 out of 33 deceased individuals of Afrikaner background, while six additional individuals died due to perioperative complications [van Lierop et al 2017].

Clinical course of the disease. While syndactyly is the only symptom of sclerosteosis present at birth, other symptoms develop early in childhood. The disease progresses into adulthood but appears to stabilize in the third decade in the majority of those with sclerosteosis [van Lierop et al 2011, van Lierop et al 2013].

Clinical Features of van Buchem Disease

All of the above features can be found, except for syndactyly.

Overall there is a milder phenotype than observed in sclerosteosis. For example, increased intracranial pressure is rare in individuals with van Buchem disease [van Lierop et al 2010, van Lierop et al 2013].

Van Buchem disease also tends to stabilize in adulthood [van Lierop et al 2013].

Table 2. Distinguishing Features of Sclerosteosis and van Buchem Disease

	Sclerosteosis	van Buchem Disease
Reported cases	96	31
Prognosis	Potentially lethal	Comparatively benign
Habitus	Gigantism	Normal stature
Facies	Gross distortion	Prominent mandible
Teeth	Malaligned, w/malocclusion	Normal
Cranial nerve palsy	Very common	Common
Intracranial pressure	Raised	Inconsistent elevation
Syndactyly	Frequent	Absent
Nail hypoplasia	Frequent	Absent
Cranial hyperostosis	Gross	Moderate
Distortion of tubular bones of hands & feet	Marked	Mild

Modified from Beighton [1995], p 234

Laboratory Tests

Sclerostin. Serum levels of sclerostin are undetectable in sclerosteosis [van Lierop et al 2011], but low levels can be detected in patients with van Buchem disease [van Lierop et al 2013].

Bone formation markers. Levels of bone formation markers, such as procollagen type 1 aminoterminal propeptide (P1NP), alkaline phosphatase, or osteocalcin, are elevated in both sclerosteosis and van Buchem disease. Levels decline with age but remain elevated above the upper limit of normal in the majority of individuals [Wergedal et al 2003, van Lierop et al 2011, van Lierop et al 2013].

Bone resorption markers. Levels of the bone resorption marker serum collagen type 1 cross-linked C-telopeptide (sCTX) are increased in childhood, but levels decrease with age toward the lower end of the

reference range in adulthood [van Lierop et al 2011, van Lierop et al 2013]. Urinary cross-linker N-telopeptide (uNTX) was elevated in six individuals with van Buchem disease [Wergedal et al 2003].

Normal findings. Serum concentrations of calcium and phosphorus and levels of parathyroid hormone are normal [Epstein et al 1979, van Lierop et al 2011].

Bone Findings

Bone mineral density measured by DXA is greatly increased with Z-scores ranging from +7.7 to +14.4 at the spine and +7.8 to +11.5 at the hip in individuals with sclerosteosis [Balemans et al 2005, Piters et al 2010, Power et al 2010, van Lierop et al 2011], and from +5.4 to +12.3 at the spine and +5.2 to +12.1 at the hip, in individuals with van Buchem disease [van Lierop et al 2013].

Histologic examination of bone reveals increased bone volume and thickness of cortex and trabeculae, increased osteoblastic bone formation with normal or decreased osteoclastic bone resorption, and no abnormal mineralization of bone tissue [Stein et al 1983, van Lierop et al 2017, Hassler et al 2014].

The high bone density in sclerosteosis is not associated with increased mineralization [Hassler et al 2014], as is seen in osteopetrosis, but there is an increased biomechanical competence of the bone and resistance to fractures [van Lierop et al 2017].

The risk for fractures, osteomyelitis, or bone marrow failure is not increased.

Life Expectancy

Survival into old age is unusual in **sclerosteosis** but not unprecedented [Barnard et al 1980, van Lierop et al 2011, van Lierop et al 2013]. Life expectancy is reduced because of sudden deaths due to herniation of the brain stem, or perioperative complications from surgery to correct increased intracranial pressure. Mean age of death is 33 years [Hamersma et al 2003], but with increasing use of early craniectomy, longer-term survival is likely. The natural history of sclerosteosis has been reviewed in Beighton [1988], Beighton [1995], Hamersma et al [2003], and van Lierop et al [2017].

Life expectancy in **van Buchem disease** appears to be normal and individuals have had no significant comorbidities. Sudden death due to herniation of the brain stem has never been reported in patients with van Buchem disease. The oldest individual to be studied was 81 years old with type 2 diabetes mellitus, mild heart failure, and non-metastasized prostate cancer, comorbidities frequent in elderly populations [van Lierop et al 2017].

Genotype-Phenotype Correlations

There is no apparent difference in phenotype associated with any of the known *SOST* pathogenic variants. The phenotype of van Buchem disease, which is not caused by pathogenic variants in *SOST* itself but by a 52-kb deletion downstream of *SOST*, is milder than that of sclerosteosis.

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 is primarily found among the Afrikaner (Dutch ancestry) community of South Africa, where the carrier rate is estimated at 1:100 and prevalence at 1: 60.000 [Beighton & Hamersma 1979]. However, cases outside the Afrikaner population have been reported [van Lierop et al 2017]. With 96 cases reported worldwide up to 2017, of which 66 were from South Africa, sclerosteosis is an extremely rare disease outside South Africa.

There have been only 31 reported cases of van Buchem disease, of which 29 were from the Netherlands and two were from Germany [van Lierop et al 2017].

Genetically Related (Allelic) Disorders

Craniodiaphyseal dysplasia (CDD). In the autosomal dominant form of CDD (OMIM 122860) heterozygous *SOST* pathogenic variants have been documented in two affected children in Korea and Poland [Kim et al 2011]. Details of the phenotype in the latter child had been published previously [Bieganski et al 2007]. The main phenotypic features are progressive overgrowth of the craniofacial bones with deafness, facial palsy, and visual disturbance as a result of nerve entrapment. Choanal stenosis is a clinically significant complication. Radiologically the cranial and facial bones are hyperostotic while the diaphyses of the limb bones are expanded with thin cortices. In CDD, *SOST* pathogenic variants are located in the secretion signal of the gene and prevent sclerostin secretion possibly by a dominant negative mechanism [Kim et al 2011]. Since this report no other cases have been published.

Differential Diagnosis

SOST-related sclerosing bone dysplasia is included in the category of craniotubular hyperostoses, which need to be distinguished from other sclerosing bone dysplasias. These include:

- 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
- 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 *SOST*-related sclerosing bone dysplasia, this group of disorders includes the conditions summarized in Table 3.

Table 3. Other Craniotubular Hyperostoses to Consider in the Differential Diagnosis of *SOST*-Related Sclerosing Bone Dysplasias

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/*SOST*-related sclerosing bone dysplasias	Distinguishing from *SOST*-related sclerosing bone dysplasias
Endosteal hyperostosis, Worth form (OMIM 144750)	*LRP5*	AD	• Hyperostosis of long bones & skull • Cranial nerve impingement & hearing loss • Enlargement of the mandible	• Smooth or bony swellings may be on the palate (taurus palatinum). • Milder phenotype • Normal height • No syndactyly

Table 3. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/*SOST*-related sclerosing bone dysplasias	Distinguishing from *SOST*-related sclerosing bone dysplasias
Camurati-Engelmann disease (CED; progressive diaphyseal dysplasia)	*TGFB1* [1]	AD	• Hyperostosis of long bones, skull may be affected • Frontal bossing, enlargement of mandible & proptosis, & cranial nerve impingement resulting in facial palsy seen in severe cases later in life	• Proximal muscle weakness • Severe limb pain • Joint contractures • No syndactyly
Craniodiaphyseal dysplasia (CDD) (OMIM 122860)	See footnote 2.	AD	• Hyperostosis of skull • Facial deformity w/ hypertelorism • Cranial nerve impingement & hearing loss	• Severe progressive sclerosing bone dysplasia w/maximal involvement of the craniofacial skeleton Long bones, ribs, & pelvis less affected • Short stature • No syndactyly
Sclerosteosis-like phenotype (sclerosteosis 2) (OMIM 614305)	*LRP4*	AD AR	• Hyperostosis of long bones & skull • Facial deformity • Cranial nerve impingement & hearing loss • Tall stature	Normal or increased serum sclerostin levels

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. 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 in which mutation is known to cause CED. Sequence analysis identifies pathogenic variants in *TGFB1* in about 90% of affected individuals.

2. CDD is possibly heterogeneous. Heterozygous pathogenic variants in *SOST* have been demonstrated in two unrelated affected children [Kim et al 2011] (see Genetically Related Disorders).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with a *SOST*-related sclerosing bone dysplasia, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended:

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SOST*-Related Sclerosing Bone Dysplasia

System/Concern	Evaluation
Skeletal	• Radiographic & imaging studies incl bone densitometry • Assessment of necessity for surgical correction of syndactyly when present
Neurologic	Neurologic evaluation for consequences of cranial nerve entrapment
Ophthalmologic	Ophthalmologic evaluation for evidence of increased intracranial pressure &/or proptosis
Hearing	Formal audiologic evaluation
Other	Consultation w/clinical geneticist &/or genetic counselor

Treatment of Manifestations

No specific treatment for sclerosteosis or van Buchem disease is currently available, and management aims at relieving symptoms and preventing complications. Treatment of these disorders therefore mainly consists of surgical intervention to ameliorate complications.

In one adult case of severe van Buchem disease, treatment with glucocorticoids was successful in suppressing bone formation and disease progression [van Lierop et al 2010], although the individual still needed repeated surgery [Datema et al 2015]. In two children with van Buchem disease short courses of prednisolone were given during exacerbations of facial palsies. While biochemical bone turnover markers decreased during therapy, there was no clinical improvement of steroid treatment in these cases [van Egmond et al 2012] The long-term benefits of this treatment in sclerosteosis or van Buchem disease have not been studied.

Important note: 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.

Table 5. Treatment of Manifestations in Individuals with *SOST*-Related Sclerosing Bone Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Syndactyly	Surgical correction	May be necessary in early childhood to improve function & cosmetic appearance
Entrapped cranial nerves that can cause recurrent facial paralysis similar to Bell's palsy or facial pain	Surgical decompression	From age 2 yrs onwards
Elevated intracranial pressure	• Craniectomy • Ventriculo-peritoneal drain	• From age 5 yrs onwards but usually in young adulthood • In South Africa this procedure is undertaken at an increasingly young age.
Mandibular overgrowth	Surgical reduction	• May be performed for cosmetic reasons or if mouth closure is impaired due to mandible overgrowth • Tooth extraction may be difficult. • Management by an orthodontic or craniofacial team is recommended.
Hearing loss	• Hearing aids • Middle-ear surgery for conductive loss • Cochlear implant if obliteration of the internal auricular canal & damage to auditory nerve	
Radiculopathy	Spinal cord decompression	In adulthood
Proptosis & glaucoma	Orbital decompression	In adulthood

Surveillance

Table 6. Recommended Surveillance for Individuals with *SOST*-Related Sclerosing Bone Dysplasia

System/Concern	Evaluation	Frequency [1]
Bone mass	Bone mineral density measurement & biochemical markers of bone turnover	Annually at pediatric age, biennially at adult age

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency [1]
Neurologic	Examination for consequences of cranial nerve entrapment	Every 6 mos at pediatric age, annually at adult age
Ophthalmologic	Proptosis, eye pressure, & evaluation of the optic nerve papilla	Annually
Hearing	Audiologic assessment	Annually
Teeth	Dental & orthodontic evaluation of tooth malalignment & malocclusion	Annually at pediatric age, routine dental care at adult age

1. Note: Since no published guidelines are available, all suggested intervals are at the discretion of the treating physician.

Agents/Circumstances to Avoid

Agents known to suppress bone resorption:

- Bisphosphonates
- Denosumab
- Selective estrogen receptor modulators (SERMS)

Agents known to stimulate bone formation:

- Teriparatide
- Abaloparatide
- Romozosumab

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 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

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 obligate heterozygotes (carriers of one *SOST*-related pathogenic variant).
- Heterozygotes have increased bone mass and calvarial widening, but signs or symptoms of the disease have not been described.

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.
- Heterozygotes have increased bone mass and calvarial widening, but signs or symptoms of the disease have not been described.

Offspring of a proband

- The offspring of an individual with *SOST*-related sclerosing bone dysplasia are obligate heterozygotes (carriers) for a pathogenic variant in *SOST*.
- If the reproductive partner of the proband is heterozygous for an *SOST* pathogenic variant, each offspring has a 50% chance of inheriting two copies of an *SOST* pathogenic variant and being affected. Reproductive partners are more likely to be carriers of an *SOST* pathogenic variant if they are related to the proband or are members of populations with a high carrier frequency (e.g., the Afrikaner community in South Africa). See Prevalence.

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

Carrier Detection

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

Related Genetic Counseling Issues

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

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.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *SOST* pathogenic variants have been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing are possible.

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 sclerosteosis, but its absence is not indicative of an unaffected fetus.

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 Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org

deafchildren.org

- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
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Molecular Genetics

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

Table A. SOST-Related Sclerosing Bone Dysplasias: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SOST	17q21.31	Sclerostin	SOST @ LOVD	SOST	SOST

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 SOST-Related Sclerosing Bone Dysplasias (View All in OMIM)

239100	VAN BUCHEM DISEASE; VBCH
269500	SCLEROSTEOSIS 1; SOST1
605740	SCLEROSTIN; SOST

Molecular Pathogenesis

SOST encodes for the 190-residue glycoprotein sclerostin, which is predominantly secreted by osteocytes. Sclerostin acts as an inhibitor of bone formation through suppressing the canonic Wnt signaling pathway in cells of the osteoblast lineage. Sclerostin binds to the Wnt-signaling coreceptors LRP5 and LRP6, thereby disabling the binding of Wnt particles to these receptors. For this mode of action sclerostin is reliant on its own coreceptor, LRP4.

Mechanism of disease causation: loss of function

- Sclerosteosis, caused by loss of sclerostin expression, results in bone formation being less restrained, resulting in progressive generalized hyperostosis.
- Individuals with van Buchem disease, caused by a large deletion of regulatory elements only necessary for postnatal SOST transcription downstream of *SOST*, do not develop syndactyly.

Table 7. Notable *SOST* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_025237.2 NP_079513.1	c.69C>T	p.Gln24Ter	Founder variant in South Africa [Brunkow et al 2001]
	c.79C>T	p.Gln27Ter	Observed homozygous in an individual from Morocco [Belkhribchia et al 2014]

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.87dupC	p.Lys30GInfsTer3	Observed homozygous in individuals in Egypt [Fayez et al 2015]
	c.220+1G>C		Observed homozygous in individuals in Germany [Kim et al 2008]
	c.220+3A>T		Observed homozygous in an individual from Senegal [Balemans et al 2001]
	c.296dupC	p. Val100fsTer128	Observed homozygous in an individual from India [Bhadada et al 2013]
	c.371G>A	pTrp124Ter	Observed homozygous in an individual from Turkey [Yagi et al 2015]
	c.372G>A	p.Trp124Ter	Founder variant in Brazil [Balemans et al 2001, Kim et al 2008]
	c.376C>T	p.Arg126Ter	Founder variant in US (one kindred of mixed ancestry from Maryland) [Balemans et al 2001]
	c.444_445delinsAA	p.Cys148Ter	Observed homozygous in an individual from China [He et al 2016]
	c.499T>C	p.Cys167Arg	Founder variant in Turkey [Piters et al 2010]

References

Literature Cited

Balemans W, Cleiren E, Siebers U, Horst J, Van Hul W. A generalized skeletal hyperostosis in two siblings caused by a novel mutation in the SOST gene. Bone. 2005;36:943–7. PubMed PMID: 15869924.

Balemans W, Ebeling M, Patel N, Van Hul E, Olson P, Dioszegi M, Lacza C, Wuyts W, Van Den Ende J, Willems P, Paes-Alves AF, Hill S, Bueno M, Ramos FJ, Tacconi P, Dikkers FG, Stratakis C, Lindpaintner K, Vickery B, Foernzler D, Van Hul W. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet. 2001;10:537–43. PubMed PMID: 11181578.

Balemans W, Patel N, Ebeling M, Van Hul E, Wuyts W, Lacza C, Dioszegi M, Dikkers FG, Hildering P, Willems PJ, Verheij JB, Lindpaintner K, Vickery B, Foernzler D, Van Hul W. Identification of a 52 kb deletion downstream of the SOST gene in patients with van Buchem disease. J Med Genet. 2002;39:91–7. PubMed PMID: 11836356.

Barnard AH, Hamersma H, Kretzmar JH, Beighton P. Sclerosteosis in old age. S Afr Med J. 1980;58:401–3. PubMed PMID: 7404164.

Beighton P. Sclerosteosis. J Med Genet. 1988;25:200–3. PubMed PMID: 3351908.

Beighton P. Sclerosteosis. In: Donnai D, Winter RM, eds. *Congenital Malformation Syndromes*. London, UK: Chapman and Hall Medical Books Ltd; 1995:230-5.

Beighton P, Barnard A, Hamersma H, van der Wouden A. The syndromic status of sclerosteosis and van Buchem disease. Clin Genet. 1984;25:175–81. PubMed PMID: 6323069.

Beighton P, Hamersma H. Sclerosteosis in South Africa. S Afr Med J. 1979;55:783–8. PubMed PMID: 223247.

Belkhribchia MR, Collet C, Laplanche JL, Hassani R. Novel SOST gene mutation in a sclerosteosis patient from Marocco: a case report. Eur. J. Med. Genet. 2014;57:133–7. PubMed PMID: 24594238.

Bieganski T, Baranska D, Miastkowska I, Kobielski A, Gorska-Chrzastek M, Kozlowski K. A boy with severe craniodiaphyseal dysplasia and apparently normal mother. Am J Med Genet A. 2007;143A:2435–43. PubMed PMID: 17853455.

Bhadada SK, Rastogi A, Steenackers E, Boudin E, Arya A, Dhiman V, Bhansali A, Van Hul W. Novel SOST gene mutation in a sclerosteosis patient and her parents. Bone. 2013;52:707–10. PubMed PMID: 23079137.

Brunkow ME, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, Proll S, Skonier JE, Zhao L, Sabo PJ, Fu Y, Alisch RS, Gillett L, Colbert T, Tacconi P, Galas D, Hamersma H, Beighton P, Mulligan J. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. Am J Hum Genet. 2001;68:577–89. PubMed PMID: 11179006.

Datema M, Appelman-Dijkstra NM, Hoyng SA, Verstegen MJ, Koot RW. Decompressive surgery in a patient with hyperostosis corticalis generalisata for relief of cognitive disability and dysaesthesia. Acta Neurochir (Wien). 2015;157:1215–8. PubMed PMID: 25976340.

du Plessis JJ. Sclerosteosis: neurosurgical experience with 14 cases. J Neurosurg. 1993;78:388–92. PubMed PMID: 8433139.

Epstein S, Hamersma H, Beighton P. Endocrine function in sclerosteosis. S Afr Med J. 1979;55:1105–10. PubMed PMID: 225834.

Fayez A, Aglan M, Esmaiel N, El Zanaty T, Abdel Kader M, El Ruby MA. Novel loss of sclerostin function mutation in a first Egyptian family with sclerosteosis. Biomed. Res. Int. 2015;2015:517815. PubMed PMID: 25984533.

Hamersma H, Gardner J, Beighton P. The natural history of sclerosteosis. Clin Genet. 2003;63:192–7. PubMed PMID: 12694228.

Hassler N, Roschger A, Gamsjaeger S, Kramer I, Lueger S, van Lierop A, Roschger P, Klaushofer K, Paschalis EP, Kneissel M, Papapoulos S. Sclerostin deficiency is linked to altered bone composition. J Bone Miner Res. 2014;29:2144–51. PubMed PMID: 24753092.

He WT, Chen C, Pan C, Zhang MX, Yu XF, Wang DW, Hu SW. Sclerosteosis caused by a novel nonsense mutation of SOST in a consanguineous family. Clin Genet. 2016;89:205–9. PubMed PMID: 26283468.

Itin PH, Keserü B, Hauser V. Syndactyly/brachyphalangy and nail dysplasias as marker lesions for sclerosteosis. Dermatology. 2001;202:259–60. PubMed PMID: 11385236.

Kim CA, Honjo R, Bertola D, Albano L, Oliveira L, Jales S, Siqueira J, Castilho A, Balemans W, Piters E, Jennes K, Van Hul W. A known SOST gene mutation causes sclerosteosis in a familial and an isolated case from Brazilian origin. Genet Test. 2008;12:475–9. PubMed PMID: 19072561.

Kim SJ, Bieganski T, Sohn YB, Kozlowski K, Semënov M, Okamoto N, Kim CH, Ko AR, Ahn GH, Choi YL, Park SW, Ki CS, Kim OH, Nishimura G, Unger S, Superti-Furga A, Jin DK. Identification of signal peptide domain SOST mutations in autosomal dominant craniodiaphyseal dysplasia. Hum Genet. 2011;129:497–502. PubMed PMID: 21221996.

Piters E, Culha C, Moester M, van Bezooijen R, Adriaensen D, Mueller T, Weidauer S, Jennes K, de Freitas F, Löwik C, Timmermans JP, Van Hul W, Papapoulos S. First missense mutation in the SOST gene causing sclerosteosis by loss of sclerostin function. Hum Mutat. 2010;31:E1526–43. PubMed PMID: 20583295.

Power J, Poole KE, van Bezooijen R, Doube M, Caballero-Alías AM, Lowik C, Papapoulos S, Reeve J, Loveridge N. Sclerostin and the regulation of bone formation: effects in hip osteoarthritis and femoral neck fracture. J Bone Miner Res. 2010;25:1867–76. PubMed PMID: 20200987.

Staehling-Hampton K, Proll S, Paeper BW, Zhao L, Charmley P, Brown A, Gardner JC, Galas D, Schatzman RC, Beighton P, Papapoulos S, Hamersma H, Brunkow ME. A 52-kb deletion in the SOST-MEOX1 intergenic region on 17q12-q21 is associated with van Buchem disease in the Dutch population. Am J Med Genet. 2002;110:144–52. PubMed PMID: 12116252.

Stein SA, Witkop C, Hill S, Fallon MD, Viernstein L, Gucer G, McKeever P, Long D, Altman J, Miller NR, Teitelbaum SL, Schlesinger S. Sclerosteosis: neurogenetic and pathophysiologic analysis of an American kinship. Neurology. 1983;33:267–77. PubMed PMID: 6681869.

van Egmond ME, Dikkers FG, Boot AM, van Lierop AH, Papapoulos SE, Brouwer OF. A rare cause of facial nerve palsy in children: hyperostosis corticalis generalisata (Van Buchem disease). Three new pediatric cases and a literature review. Eur J Paediatr Neurol. 2012;16:740–3. PubMed PMID: 22445802.

van Lierop AH, Appelman-Dijkstra NM, Papapoulos SE. Sclerostin deficiency in humans. Bone. 2017;96:51–62. PubMed PMID: 27742500.

van Lierop AH, Hamdy NA, Hamersma H, van Bezooijen RL, Power J, Loveridge N, Papapoulos SE. Patients with sclerosteosis and disease carriers: human models of the effect of sclerostin on bone turnover. J Bone Miner Res. 2011;26:2804–11. PubMed PMID: 21786318.

van Lierop AH, Hamdy NA, Papapoulos SE. Glucocorticoids are not always deleterious for bone. J Bone Miner Res. 2010;25:2796–800. PubMed PMID: 20549703.

van Lierop AH, Hamdy NA, van Egmond ME, Bakker E, Dikkers FG, Papapoulos SE. Van Buchem disease: clinical, biochemical, and densitometric features of patients and disease carriers. J Bone Miner Res. 2013;28:848–54. PubMed PMID: 23074140.

Wergedal JE, Veskovic K, Hellan M, Nyght C, Balemans W, Libanati C, Vanhoenacker FM, Tan J, Baylink DJ, Van Hul W. Patients with Van Buchem disease, an osteosclerotic genetic disease, have elevated bone formation markers, higher bone density, and greater derived polar moment of inertia than normal. J Clin Endocrinol Metab. 2003;88:5778–83. PubMed PMID: 14671168.

Yagi H, Takagi M, Hasegawa Y, Kayserili H, Nishimura G. Sclerosteosis (craniotubular hyperostosis-syndactyly) with complex hyperphalangy of the index finger. Pediatr. Radiol. 2015;45:1239–43. PubMed PMID: 25835322.

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- 21 March 2019 (ha) Comprehensive update posted live
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