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SOST-Related Sclerosing Bone Dysplasias

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Summary

Clinical characteristics

SOST-related sclerosing bone dysplasias include *SOST*-related sclerosteosis and *SOST*-related endosteal hyperostosis, van Buchem type (van Buchem disease), both disorders of progressive bone overgrowth due to increased bone formation.

The major clinical features of *SOST*-related 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 frontal bossing 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 sensorineural hearing loss (8th cranial nerve). In *SOST*-related sclerosteosis, hyperostosis of the calvarium reduces intracranial volume, increasing the risk for potentially lethal elevation of intracranial pressure. Survival of individuals with *SOST*-related sclerosteosis into old age is unusual but not unprecedented.

The manifestations of van Buchem disease are generally milder than *SOST*-related sclerosteosis. Stature is typically normal, cranial nerve entrapment of the seventh and eighth cranial nerves are common, and increased intracranial pressure is rare, seen only in severely affected individuals. Individuals with van Buchem disease do not have syndactyly or other digit deformities. Life span appears not to be altered.

Diagnosis/testing

The diagnosis of a *SOST*-related sclerosing bone dysplasia is established in a proband with typical clinical and radiographic findings and biallelic pathogenic variants in *SOST* (in individuals with *SOST*-related sclerosteosis)

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or a biallelic 52-kb deletion downstream of *SOST* (in individuals with van Buchem disease) identified on molecular genetic testing.

Management

Treatment of manifestations: Hearing aids with middle ear surgery or cochlear implant depending on the nature of the hearing loss; surgical decompression as needed for entrapped facial nerves; surgical reduction of mandibular overgrowth; orbital decompression for proptosis; treatment of dental manifestations per orthodontist and/or craniofacial team; craniectomy and ventriculoperitoneal drain for increased intracranial pressure; surgical correction of syndactyly.

Surveillance: Intermittent assessment of bone mineral density and biochemical markers of bone turnover until age 18 years and then every five years in adulthood; annual audiologic assessment in childhood and as needed in adults; examination for evidence of cranial nerve entrapment and increased intracranial pressure every six months until age 18 years and then annually in adulthood; annual ophthalmology examination to assess for proptosis, intraocular pressure, and evaluation of the optic nerve papilla; annual dental and orthodontic evaluation to assess for tooth malalignment and malocclusion until age 18 years; routine dental screening in adults.

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 dysplasias are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a pathogenic variant associated with a *SOST*-related sclerosing bone dysplasia, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the pathogenic variants associated with a *SOST*-related sclerosing bone dysplasia have been identified in an affected family member, carrier testing for at-risk family members and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

SOST-Related Sclerosing Bone Dysplasias: Included Phenotypes
• *SOST*-related sclerosteosis [1] • *SOST*-related endosteal hyperostosis, van Buchem type (van Buchem disease)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of this phenotype see Differential Diagnosis.

Diagnosis

SOST-related sclerosteosis and *SOST*-related endosteal hyperostosis, van Buchem type (van Buchem disease) are clinically and radiographically similar disorders of progressive bone overgrowth due to increased bone formation. The 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 present in individuals with 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 standard deviations above the mean) measured by dual-energy x-ray absorptiometry [van Lierop et al 2017]

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Note: The majority of persons affected with ***SOST*-related sclerosteosis** are 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 in individuals from the **Netherlands**.

Establishing the Diagnosis

The diagnosis of a *SOST*-related sclerosing bone dysplasia **is established** in a proband with typical clinical and radiographic findings and biallelic pathogenic (or likely pathogenic) variants in *SOST* (in individuals with *SOST*-related sclerosteosis) or a biallelic 52-kb deletion downstream of *SOST* (in individuals with van Buchem disease) identified on molecular genetic testing (see Table 1).

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

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel, targeted deletion analysis) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the clinical and radiographic findings suggest the diagnosis of ***SOST*-related sclerosteosis**, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *SOST* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *SOST* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

In individuals from the Netherlands with suspected **van Buchem disease**, **targeted deletion analysis** for the 52-kb deletion downstream of *SOST*, which does not overlap the coding region, should be considered. Note: (1) This downstream deletion cannot be identified on *SOST* single-gene testing or a multigene panel. (2) Van Buchem disease is almost exclusively found in individuals from the Netherlands; testing for this deletion in non-Dutch individuals is only recommended if no pathogenic variants were found on a multigene panel.

Option 2

When the diagnosis of a *SOST*-related sclerosing bone dysplasia is not considered because an individual has atypical clinical and/or radiographic 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.

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 Dysplasias

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method	
		Sclerosteosis	Van Buchem disease
SOST	Sequence analysis [3]	100% [4]	None reported
	Targeted deletion analysis for 52-kb del downstream of *SOST* [5]	None reported	100% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. SOST pathogenic variants were identified on sequence analysis in 94 of 96 individuals with sclerosteosis; two individuals did not undergo molecular testing and were diagnosed based on clinical and radiographic features [van Lierop et al 2017]. Note: Sixty-six of the 94 individuals who underwent molecular testing were homozygous for the South African founder variant c.70C>T (p.Gln24Ter).
5. Targeted deletion analysis 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 the 52-kb deletion downstream of *SOST*.
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 and the two affected individuals from Germany [Balemans et al 2002, Staehling-Hampton et al 2002, van Lierop et al 2017].

Clinical Characteristics

Clinical Description

SOST-related sclerosteosis and *SOST*-related endosteal hyperostosis, van Buchem type (van Buchem disease) have very similar phenotypes. However, the manifestations of van Buchem disease are generally milder than those in sclerosteosis (see Table 2). To date, more than 100 individuals have been identified with biallelic pathogenic variants in *SOST* or a biallelic 52-kb deletion downstream of *SOST*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *SOST*-Related Sclerosing Bone Dysplasias: Comparison of Phenotypes by Select Features

Feature	Sclerosteosis **(n=96)**	Van Buchem Disease **(n=31)**	Comment
Linear overgrowth	100%	0%	Normal stature in van Buchem disease
Hearing loss	94%	78%	
Facial palsies	93%	89%	
Cranial hyperostosis causing facial distortion	90%	68%	Typically only prominent mandible in van Buchem disease
Increased intracranial pressure	71%	16%	
Syndactyly	66%	0%	No syndactyly in van Buchem disease

Modified from Beighton [1995] and van Lierop et al [2017]

Clinical Features of *SOST*-Related Sclerosteosis

Tall stature. Accelerated linear growth becomes evident in early childhood. Longitudinal growth arrests at puberty, by which time individuals can reach heights exceeding two meters (6.5 feet).

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

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

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

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

Dental manifestations. Teeth can be malaligned with malocclusion due to mandibular hyperostosis.

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 *SOST*-related sclerosteosis and was considered the cause of death in 12 of 33 deceased individuals of Afrikaner background, and six additional individuals died due to perioperative complications [van Lierop et al 2017].

Digit and nail abnormalities / 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].

Prognosis. The complications of *SOST*-related sclerosteosis progress into adulthood but appear to stabilize in the third decade in the majority of affected individuals [van Lierop et al 2011, van Lierop et al 2013]. Survival into old age is unusual in *SOST*-related 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 *SOST*-related sclerosteosis has been reviewed in various reports, most recently in van Lierop et al [2017].

Clinical Features of Van Buchem Disease

Stature is typically normal in individuals with van Buchem disease; linear overgrowth is not typical.

Hearing loss is conductive and sensorineural with onset in childhood.

Cranial nerve entrapment syndromes due to bone overgrowth of the skull such as visual loss (2nd cranial nerve), neuralgia or anosmia (5th cranial nerve), facial palsy (7th cranial nerve), and sensorineural hearing loss (8th cranial nerve) can occur but are less common than in *SOST*-related sclerosteosis.

Cranial hyperostosis typically only manifests as mandibular overgrowth, which becomes apparent in young adulthood. Teeth are not typically affected.

Increased intracranial pressure is rare in individuals with van Buchem disease [van Lierop et al 2010, van Lierop et al 2013]. Sudden death due to herniation of the brain stem has never been reported in individuals with van Buchem disease.

Digit and nails typically appear normal without syndactyly. Mild distortion of tubular bones of hands and feet can be seen on radiographs.

Prognosis. Van Buchem disease also tends to stabilize in adulthood [van Lierop et al 2013]. Life expectancy in van Buchem disease appears to be normal, and reported individuals have had no significant comorbidities. The oldest individual to be studied was age 81 years with diabetes mellitus type 2, mild heart failure, and non-metastasized prostate cancer, comorbidities frequent in elderly populations [van Lierop et al 2017].

Laboratory Tests

Sclerostin. Serum concentration of sclerostin is undetectable in individuals with *SOST*-related sclerosteosis [van Lierop et al 2011], but low serum sclerostin concentration can be detected in individuals with van Buchem disease [van Lierop et al 2013].

Bone formation markers. Serum concentration of bone formation markers, such as procollagen type 1 amino terminal propeptide (P1NP), alkaline phosphatase, or osteocalcin, are elevated in individuals with *SOST*-related 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. Serum concentration of the bone resorption marker type I collagen cross-linked C-terminal telopeptide (CTX) is increased in childhood, but concentration decreases with age toward the lower end of the reference range in adulthood [van Lierop et al 2011, van Lierop et al 2013]. Urinary concentration of type I collagen cross-linked N-terminal telopeptide (NTX) was elevated in six individuals with van Buchem disease [Wergedal et al 2003].

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

Bone Findings

Bone mineral density measured by dual-energy x-ray absorptiometry (DXA) is greatly increased, with z scores ranging from 7.7 to 14.4 standard deviations (SD) above the mean at the spine and 7.8 to 11.5 SD above the mean at the hip in individuals with *SOST*-related 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 SD above the mean at the spine and 5.2 to 12.1 SD above the mean 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, Hassler et al 2014, van Lierop et al 2017].

The high bone density in *SOST*-related 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.

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 caused by a **52-kb deletion downstream of *SOST***, is milder than that of *SOST*-related sclerosteosis.

Nomenclature

In the 2023 revision of the Nosology of Genetic Skeletal Disorders, the *SOST*-related sclerosing bone dysplasias are included in the osteosclerotic disorders group, and van Buchem disease is referred to as *SOST*-related endosteal hyperostosis, van Buchem type [Unger et al 2023].

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.

Prevalence

SOST-related sclerosteosis is primarily found among the Afrikaner (Dutch ancestry) community of South Africa due to a founder variant; the carrier rate is estimated at 1:100 and prevalence at 1:60,000 [Beighton & Hamersma 1979]. However, individuals with *SOST*-related sclerosteosis outside the Afrikaner population have been reported [van Lierop et al 2017]. Founder variants have also been reported in individuals from Brazil and Turkey (see Table 7). With 100 individuals reported worldwide, of which 66 were from South Africa, *SOST*-related sclerosteosis is an extremely rare disease outside South Africa.

There have been only 31 reported individuals with van Buchem disease, of which 29 were from the Netherlands and two were from Germany [van Lierop et al 2017]. Three additional affected individuals are known to the authors [N Appelman-Dijkstra, personal observation].

Genetically Related (Allelic) Disorders

***SOST*-related craniodiaphyseal dysplasia (CDD).** Autosomal dominant CDD (OMIM 122860) caused by heterozygous *SOST* pathogenic variants has been documented in two affected children in Korea and Poland [Kim et al 2011]. Details of the phenotype in the latter child were 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 long bones are expanded with thin cortices. In *SOST*-related 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]. To date, no other individuals with *SOST*-related CDD have been reported.

Differential Diagnosis

SOST-related sclerosing bone dysplasias must be distinguished from other sclerosing bone dysplasias, including:

- The osteoscleroses, notably osteopetrosis, characterized by increased bone density with no bone overgrowth and little or no disturbance of the contours of the bones;
- 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 dysplasias, 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

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/*SOST*-related sclerosing bone dysplasias	Distinguishing from *SOST*-related sclerosing bone dysplasias
LRP4	*LRP4*-related sclerosteosis (OMIM 614305)	AD AR	• Hyperostosis of long bones & skull • Facial deformity • Cranial nerve impingement & hearing loss • Tall stature	Normal or ↑ serum sclerostin concentration
LRP5	Endosteal hyperostosis, Worth type (OMIM 144750)	AD	• Hyperostosis of long bones & skull • Cranial nerve impingement & hearing loss • Enlargement of mandible	• Smooth or bony swellings of palate (taurus palatinum) • Milder phenotype • Normal height • No syndactyly
SOST [1]	*SOST*-related craniodiaphyseal dysplasia	AD	• Hyperostosis of skull • Facial deformity w/hypertelorism • Cranial nerve impingement & hearing loss	• Severe progressive sclerosing bone dysplasia w/maximal involvement of craniofacial skeleton • Long bones, ribs, & pelvis less affected • Short stature • No syndactyly
SP7 [2]	*SP7*-related craniodiaphyseal dysplasia	AR	• Facial dysmorphism • Severe hyperostosis of calvarium, skull base, & mandible	• Short stature & lean body habitus • Broad clavicles & ribs, scoliosis, & diaphyseal expansion of long bones • 1 of 2 persons reported had recurrent fractures.
TGFB1 [3]	*TGFB1*-related Camurati-Engelmann diaphyseal dysplasia (See Camurati-Engelmann Disease.)	AD	• Hyperostosis of long bones • Frontal bossing, enlargement of mandible, proptosis, & cranial nerve impingement later in life in those w/severe disease	• Proximal muscle weakness • Severe limb pain • Joint contractures • No syndactyly

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

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

2. Hendrickx et al [2023]

3. Diagnosis of Camurati-Engelmann disease (CED) is established in a proband with the characteristic radiographic findings or (if radiographic findings are inconclusive) a heterozygous pathogenic variant in *TGFB1* identified by molecular genetic testing.

Management

No clinical practice guidelines for *SOST*-related sclerosing bone dysplasias have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with these disorders.

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. *SOST*-Related Sclerosing Bone Dysplasias: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Skeletal	• Radiographs of affected areas • DXA scan • Assessment of necessity for surgical correction of syndactyly when present	
Hearing	Formal audiologic eval	
Neurologic	• Neurologic eval for consequences of cranial nerve entrapment • Assessment for manifestations of ↑ intracranial pressure	
Ophthalmologic	Ophthalmologic eval for evidence of ↑ intracranial pressure &/or proptosis	
Dental	Dental &/or orthodontic eval for malalignment & malocclusion in children	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *SOST*-related sclerosing bone dysplasias to facilitate medical & personal decision making

DXA = dual-energy x-ray absorptiometry; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

No specific treatment for *SOST*-related sclerosteosis or *SOST*-related endosteal hyperostosis, van Buchem type (van Buchem disease) is currently available, and management aims at relieving symptoms and preventing complications. Treatment of these disorders mainly consists of surgical intervention to ameliorate complications.

In one adult with 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 with steroid treatment in these individuals [van Egmond et al 2012] The long-term benefits of this treatment in *SOST*-related sclerosteosis or van Buchem disease have not been studied.

Note: The bones in individuals with *SOST*-related 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. *SOST*-Related Sclerosing Bone Dysplasias: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Hearing loss	• Hearing aids • Middle ear surgery for conductive loss • Cochlear implant if obliteration of internal auricular canal & damage to auditory nerve is present	
Cranial nerve entrapment	Surgical decompression as needed for recurrent facial paralysis or facial pain	May be needed from age 2 yrs onward

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
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. • Mgmt by an orthodontic or craniofacial team is recommended.
Proptosis	Orbital decompression	In adulthood
Dental manifestations	Treatment per orthodontist &/or as part of craniofacial team	
Increased intracranial pressure	• Craniectomy • Ventriculoperitoneal drain	• From age 5 yrs onward, but usually in young adulthood • In South Africa this procedure is undertaken at an increasingly young age.
Syndactyly	Surgical correction	May be necessary in early childhood to improve function & cosmetic appearance

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *SOST*-Related Sclerosing Bone Dysplasias: Recommended Surveillance

System/Concern	Evaluation	Frequency [1]
Bone mass	DXA scan to assess bone mineral density [2]	• Intermittently until age 18 yrs • Every 5 yrs in adults
	Biochemical markers of bone turnover: [3] • Serum P1NP, alkaline phosphatase, & osteocalcin • Urine NTX & serum CTX	
Hearing	Audiologic assessment	• Annually in childhood • As needed in adults
Neurologic	Exam for evidence of cranial nerve entrapment & ↑ intracranial pressure	• Every 6 mos until age 18 yrs • Annually in adults
Ophthalmologic	Ophthalmologic exam to assess for proptosis, intraocular pressure, & eval of optic nerve papilla	Annually
Teeth	Dental & orthodontic eval of tooth malalignment & malocclusion	Annually until age 18 yrs
	Routine dental screening	Annually in adults

CTX = type I collagen cross-linked C-terminal telopeptide; NTX = type I collagen cross-linked N-terminal telopeptide; P1NP = procollagen type 1 amino terminal propeptide

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

2. Frequent measurement of bone mineral density has little clinical consequence in individuals with *SOST*-related sclerosing bone dysplasias.

3. Measurement of bone markers can be helpful to evaluate effect of treatment with glucocorticoids. During childhood bone markers are difficult to interpret in individuals with *SOST*-related sclerosing bone dysplasias. In adulthood they may help detect disease stabilization.

Agents/Circumstances to Avoid

Avoid agents known to suppress bone resorption:

- Bisphosphonates
- Denosumab
- Selective estrogen receptor modulators

Avoid 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 (*SOST*-related sclerosteosis and *SOST*-related endosteal hyperostosis, van Buchem type [van Buchem disease]) are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an individual with *SOST*-related sclerosteosis are presumed to be heterozygous for a pathogenic variant in *SOST*. The parents of an individual with van Buchem disease are presumed to be heterozygous for a 52-kb deletion downstream of *SOST*.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for the genetic alteration identified in the proband and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the genetic alterations identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;

- Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the genetic alteration in the proband.
- Heterozygotes have increased bone mass and calvarial widening, but signs and symptoms of a *SOST*-related sclerosing bone dysplasia have not been described.

Sibs of a proband

- If both parents are known to be heterozygous for a genetic alteration associated with a *SOST*-related sclerosing bone dysplasia, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial genetic alterations.
- Heterozygotes have increased bone mass and calvarial widening, but signs and symptoms of a *SOST*-related sclerosing bone dysplasia have not been described.

Offspring of a proband

- Unless an affected individual's reproductive partner also has an *SOST*-related sclerosing bone dysplasia or is a carrier, offspring will be obligate heterozygotes (carriers) for a genetic alteration associated with a *SOST*-related sclerosing bone dysplasia.
- If the reproductive partner of the proband is heterozygous for a genetic alteration associated with a *SOST*-related sclerosing bone dysplasia, each offspring has a 50% chance of inheriting biallelic genetic alterations and being affected. Reproductive partners are more likely to be carriers of a genetic alteration associated with a *SOST*-related sclerosing bone dysplasia 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 a genetic alteration associated with a *SOST*-related sclerosing bone dysplasia.

Carrier Detection

Carrier testing for at-risk family members requires prior identification of the genetic alterations associated with the *SOST*-related sclerosing bone dysplasia in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of known carriers and for the reproductive partners of individuals affected with a *SOST*-related sclerosing bone dysplasia, particularly if both partners are of the same ancestral background. Founder variants have been identified in several populations (see Table 7).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the genetic alterations associated with a *SOST*-related sclerosing bone dysplasia have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American 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)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

Molecular Genetics

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

Table A. 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 the 190-residue glycoprotein sclerostin, which is predominantly secreted by osteocytes. Sclerostin acts as an inhibitor of bone formation by 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

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

Table 7. *SOST* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_025237.3 NP_079513.1	c.70C>T (69C>T)	p.Gln24Ter	Founder variant in South Africa [Brunkow et al 2001]
	c.372G>A	p.Trp124Ter	Founder variant in Brazil [Balemans et al 2001, Kim et al 2008]
	c.499T>C	p.Cys167Arg	Founder variant in Turkey [Piters et al 2010]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

Dr Natasha Appelman-Dijkstra would be happy to communicate with persons who have any questions regarding *SOST*-related sclerosing bone dysplasias.

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

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

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.

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.

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.

Hendrickx G, Boudin E, Steenackers E, Collet C, Mortier GR, Geneviève D, Van Hul W. A recessive form of craniodiaphyseal dysplasia caused by a homozygous missense variant in SP7/Osterix. Bone. 2023;167:116633. PubMed PMID: 36436818.

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

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A,

Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

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.

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

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.

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

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.

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