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Osteopathia Striata with Cranial Sclerosis

Synonyms: Horan-Beighton Syndrome, OS-CS, *AMER1*-Related Osteopathia Striata with Cranial Sclerosis

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Summary

Clinical characteristics

Most females with osteopathia striata with cranial sclerosis (OS-CS) present with macrocephaly and characteristic facial features (frontal bossing, hypertelorism, epicanthal folds, depressed nasal bridge, and prominent jaw). Approximately half have associated features including orofacial clefting and hearing loss, and a minority have some degree of developmental delay (usually mild). Radiographic findings of cranial sclerosis, sclerosis of long bones, and metaphyseal striations (in combination with macrocephaly) can be considered pathognomonic.

Males can present with a mild or severe phenotype.

Mildly affected males have clinical features similar to affected females, including macrocephaly, characteristic facial features, orofacial clefting, hearing loss, and mild-to-moderate learning delays. Mildly affected males are more likely than females to have congenital or musculoskeletal anomalies. Radiographic findings include cranial sclerosis and sclerosis of the long bones; Metaphyseal striations are more common in males who are mosaic for an *AMER1* pathogenic variant.

The severe phenotype manifests in males as a multiple-malformation syndrome, lethal in mid-to-late gestation, or in the neonatal period. Congenital malformations include skeletal defects (e.g., polysyndactyly, absent or hypoplastic fibulae), congenital heart disease, and brain, genitourinary, and gastrointestinal anomalies. Macrocephaly is not always present and longitudinal metaphyseal striations have not been observed in severely affected males, except for those who are mosaic for the *AMER1* pathogenic variant.

Diagnosis/testing

The diagnosis of OS-CS is established in a female proband with characteristic features and a heterozygous pathogenic variant in *AMER1* identified by molecular genetic testing. The diagnosis of OS-CS is established in a

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male proband with characteristic features and a hemizygous pathogenic variant in *AMER1* identified by molecular genetic testing.

Management

Treatment: Scoliosis management per orthopedic surgeon; physiotherapy may be helpful for joint contractures; management of oral facial clefts per otolaryngologist; hearing loss is managed by audiology, speech and language therapy, and otolaryngology; vision loss management per ophthalmologist and neurosurgery for nerve compression as indicated; early intervention services and special education as indicated; standard treatments for cardiac, genitourinary, and gastrointestinal anomalies and Wilms tumor or other malignancy.

Surveillance: Annual clinical assessment for skeletal manifestations such as scoliosis, joint contractures, stress fractures, and persistent bone pain. Annual audiology and ophthalmology evaluations for evidence of cranial nerve compression due to sclerotic bone disorder. Consider abdominal ultrasound every three months until age seven years to screen for Wilms tumor.

Genetic counseling

OS-CS is inherited in an X-linked manner. The risk to sibs of a male proband depends on the genetic status of the mother. The risk to sibs of a female proband depends on the genetic status of the mother and the father. If the mother of the proband has an *AMER1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. If the father of the proband has an *AMER1* pathogenic variant, it should be presumed he will transmit the *AMER1* pathogenic variant to all his daughters and none of his sons (to date, paternal transmission has only been reported in mosaic fathers). Females who inherit an *AMER1* pathogenic variant will be heterozygotes and will have variable manifestations of OS-CS. Males who inherit a pathogenic variant will be hemizygotes and will have variable manifestations ranging from mid-late gestation and neonatal lethality to the mild phenotype. Once the *AMER1* pathogenic variant is identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for osteopathia striata with cranial sclerosis (OS-CS) have been published, however the combination of macrocephaly, cranial sclerosis, and longitudinal metaphyseal striations of the long bones are considered highly characteristic of this condition.

Suggestive Findings

OS-CS **should be suspected** in individuals with the following clinical and radiographic findings.

Females and Mosaic and/or Mildly Affected Males

Clinical findings

- Characteristic facial features (e.g., frontal bossing, hypertelorism, epicanthal folds, depressed nasal bridge, prominent jaw)
- Macrocephaly and stature short for mid-parental height
- Orofacial clefting
- Hearing loss (conductive and sensorineural) and progressive hearing loss
- Poor or reduced vision
- Normal intellect or mild developmental delays

Radiographic findings

- Sclerosis of the cranium and skull base
- Sclerosis of lamellar and trabecular bones
- Metaphyseal, longitudinal striations of the long bones and pelvis (Note: Metaphyseal striations are typically absent in mildly affected constitutional males but present in mosaic males.)
- Fibular aplasia or hypoplasia
- Small exostoses

Severely Affected Males

Clinical findings

- Fetal or neonatal death
- Macrocephaly (50%)
- Orofacial clefting (cleft palate or cleft lip and palate)
- Facial features (frontal bossing, hypertelorism, depressed nasal bridge, and micrognathia)
- Multiple congenital malformations:
  - Skeletal anomalies (polysyndactyly, talipes)
  - Genitourinary anomalies (echogenic or enlarged kidneys, nephrogenic rests)
  - Gastrointestinal anomalies (omphalocele, intestinal malrotation)
  - Congenital heart disease (hypoplastic left or right heart, septal defects, patent ductus arteriosus)
  - Brain anomalies (ventriculomegaly, abnormal corpus callosum)

Imaging findings

- Cranial sclerosis
- Sclerosis of pelvis and long bones
- Bilateral absent or hypoplastic fibulae

Establishing the Diagnosis

Female proband. The diagnosis of OS-CS **is established** in a female proband with suggestive findings and can be confirmed with a heterozygous pathogenic (or likely pathogenic) variant in *AMER1* identified by molecular genetic testing (see Table 1).

Male proband. The diagnosis of OS-CS **is established** in a male proband with suggestive findings and can be confirmed with a hemizygous pathogenic (or likely pathogenic) variant in *AMER1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous or hemizygous *AMER1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing**, **chromosomal microarray analysis**, **multigene panel**, and **comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *AMER1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If 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.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *AMER1*) that cannot be detected by sequence analysis.
- **A multigene panel** that includes *AMER1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- When the phenotype is indistinguishable from many other skeletal dysplasias, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **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 Osteopathia Striata with Cranial Sclerosis

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
AMER1	Sequence analysis [3]	~75% [4]
	Gene-targeted deletion/duplication analysis [5]	~25% [4]
	CMA [6]	See footnote 7.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Review of approximately 90 pathogenic variants in the published literature [Author, personal observation], correlation with smaller published case series [Jenkins et al 2009, Perdu et al 2011], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *AMER1*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xq11.2 region. CMA designs in current clinical use target the Xq11.2 region.
7. Several contiguous deletions including *AMER1* have been reported in individuals with features of OS-CS [Chénier et al 2012, Herman et al 2013, Holman et al 2013]. Contiguous gene deletions that include *AMER1* and neighboring genes *ARHGEF9* and *MTMR8* appear to cause OS-CS with intellectual disability in females. Deletions including *AMER1* and *ASB12* only are not reported to be associated with intellectual disability [Holman et al 2013].

Clinical Characteristics

Clinical Description

To date, approximately 90 individuals with a pathogenic variant in *AMER1* have been reported in the medical literature [Jenkins et al 2009; Perdu et al 2011; Author, personal observation]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Osteopathia Striata with Cranial Sclerosis: Frequency of Select Features in Females and Mildly Affected Males

Feature	% of Persons w/Feature [1]	Comment
Cranial sclerosis	100%	
Sclerosis of long bones	100%	
Metaphyseal striations	~95%	In females & mosaic males; not seen in constitutional males
Characteristic facial features	~90%	Frontal bossing, hypertelorism, epicanthal folds, depressed nasal bridge
Macrocephaly	~80%	Absolute or relative macrocephaly
Orofacial clefting	~50%	Cleft palate or cleft lip and palate
Hearing loss	~50%	Conductive &/or sensorineural
Mild developmental delays	~30%	Severe developmental delay is rare.
Congenital heart disease	~25%	
Wilms tumor [2]	~5% [3]	Additional malignancies reported: hepatoblastoma, adult-onset colorectal cancer, adult-onset ovarian cancer

1. Review of approximately 90 individuals reported with OS-CS and an *AMER1* pathogenic variant
2. Association with Wilms tumor (and possibly other cancers) is an emerging feature and a significant departure from what was previously understood about the disorder.
3. Extrapolated from recently published data [Bach et al 2021]

Affected Females

Most females with osteopathia striata with cranial sclerosis (OS-CS) present with macrocephaly and characteristic facial features (frontal bossing, hypertelorism, epicanthal folds, and a depressed nasal bridge). Approximately half have associated features including orofacial clefting and hearing loss, and a minority have some degree of developmental delay (usually mild). Radiographic findings of cranial sclerosis, sclerosis of long bones, and metaphyseal striations (in combination with macrocephaly) can be considered pathognomonic.

- **Cranial sclerosis.** Observed on radiographs of the skull, most notably in the vault. It can be present at birth, and is typically progressive.
- **Sclerosis of the pelvis and long bones.** Best observed on radiographs of the pelvis and diaphyses of the femora and humeri. It can be present at birth, and is typically progressive.
- **Metaphyseal striations.** Best observed on radiographs of the pelvis, proximal and distal femora, proximal tibiae, and humeri. It can be present antenatally, but usually develops during childhood.
- **Characteristic facial features.** Most commonly include frontal bossing, hypertelorism, epicanthal folds, and a depressed nasal bridge. These features can be present at birth, and typically become more exaggerated with age, particularly frontal bossing.
- **Macrocephaly** is usually of postnatal onset and is associated with cranial sclerosis. It is usually absolute (>+2.5 SD), but can be relative to height or weight.
- **Stature.** Unlike in many other skeletal dysplasias, short stature is not commonly associated with OS-CS.
- **Orofacial clefting.** Typically cleft hard palate; bifid uvula has also been observed.

- **Hearing loss.** Both conductive and sensorineural hearing loss have been observed; hearing loss occurs in approximately 50% of females [Jenkins et al 2009, Perdu et al 2011].
- **Cranial nerve palsies.** Rarely, compression of the optic nerve due to bony sclerosis can lead to vision loss, and facial palsies have been reported. This can be progressive, and typically occurs in late adolescence and early adulthood.
- **Cognition.** Most females with OS-CS have normal intellect and a minority (30%) have mild learning delays [Jenkins et al 2009, Perdu et al 2011]. One female with severe learning delays has been reported [Jenkins et al 2009].
- **Congenital heart disease.** Approximately 25% of females with OS-CS have a structural heart defect [Jenkins et al 2009, Perdu et al 2010]. Atrial septal defects, ventricular septal defects, and patent ductus arteriosus are the most commonly described structural anomalies.
- **Association with cancer.** An association of OS-CS with cancer is emerging in the literature. To date, cancer has only been reported in females with OS-CS, including four instances of pediatric-onset **Wilms tumor**: one female with bilateral tumors [Sperotto et al 2017, Bach et al 2021], one with a pediatric-onset hepatoblastoma [Fujita et al 2014], one with an adult-onset colorectal cancer [Jenkins et al 2009], and one with adult-onset ovarian cancer [Perdu et al 2010].

Affected Males

There appear to be two distinct phenotypes in males: mild and severe.

Mild phenotype. Mildly affected males have clinical features similar to affected females, including macrocephaly, characteristic facial features, orofacial clefting, hearing loss, and mild-to-moderate learning delays. Mildly affected males are more likely than females to have congenital or musculoskeletal anomalies. Males with the mild phenotype may have a mosaic or constitutional *AMER1* pathogenic variant, each with distinct radiographic features. Shared radiographic findings include cranial sclerosis and sclerosis of the long bones, however metaphyseal striations are more common in mosaic males.

- **Cranial sclerosis and sclerosis of the pelvis and long bones.** Best observed on radiographs of the skull, pelvis, femora, and humeri. Sclerosis appears to be more marked compared with females, possibly due to the hemizygous nature of the pathogenic variant in males.
- **Metaphyseal striations** have only been observed in one constitutional male [Holman et al 2011], a number of mosaic males [Joseph et al 2010, Perdu et al 2011, Chénier et al 2012], and a male with Klinefelter syndrome [Fradin et al 2017]. They are best observed on radiographs of the pelvis, femora, and humeri (see Pathophysiology).
- **Characteristic facial features** most commonly include frontal bossing, hypertelorism, epicanthal folds, and a depressed nasal bridge.
- **Macrocephaly** is usually of postnatal onset and is associated with cranial sclerosis. It is usually absolute, (>+3 SD), but can be relative to height or weight.
- **Stature.** Proportionate short stature of <−2 SD is commonly associated with OS-CS in males [Holman et al 2011].
- **Orofacial clefting,** typically hard cleft palate, is observed in approximately 66% of mildly affected males [Holman et al 2011, Perdu et al 2011].
- **Hearing loss.** Both conductive and sensorineural hearing loss have been reported. Hearing loss is more common in mildly affected males (~85%) compared with females [Holman et al 2011, Perdu et al 2011].
- **Cranial nerve palsies.** Rarely, compression of the optic nerve due to bony sclerosis can lead to vision loss, and facial palsies have been reported. This can be progressive, and typically occurs in late adolescence and early adulthood.

- **Cognition.** Learning issues are more common in surviving males than females, with approximately 80% of males having mild-to-moderate developmental delays [Holman et al 2011, Perdu et al 2011, Chénier et al 2012, Hague et al 2017].
- **Musculoskeletal.** Scoliosis (which can be progressive) and joint contractures are commonly observed in mildly affected males [Holman et al 2011].
- **Congenital anomalies.** Congenital heart disease is observed in approximately half of mildly affected males [Perdu et al 2011]. Brain malformations including ventriculomegaly and partial agenesis of the corpus callosum are also observed in this cohort [Holman et al 2011].

Severe phenotype. The severe phenotype manifests as a multiple-malformation syndrome, and is lethal in mid-to-late gestation or in the neonatal period [Holman et al 2011, Perdu et al 2011, Quélin et al 2015, Vasiljevic et al 2015]. Severely affected males typically have fewer of the characteristic features described in females, in part due to early mortality. In particular, macrocephaly is not always present, and longitudinal metaphyseal striations have not been observed. Severely affected males typically have multiple congenital malformations including limb patterning and skeletal defects (e.g., polysyndactyly, absent or hypoplastic fibulae), congenital heart disease, and brain, genitourinary, and gastrointestinal anomalies.

- **Pregnancy complications.** Polyhydramnios has been described in two families, and recurred in multiple pregnancies [Quélin et al 2015, Vasiljevic et al 2015].
- **Cranial sclerosis and sclerosis of the pelvis and long bones.** Best observed on radiographs of the skull, pelvis, femora, and humeri. This finding is occasionally not observed [Jenkins et al 2009].
- **Macrocephaly** is observed in approximately 50% of males with the severe phenotype as either absolute or relative macrocephaly.
- **Orofacial clefting.** Approximately 50% of males with a severe phenotype have a cleft palate or cleft lip and palate [Holman et al 2011, Perdu et al 2011, Quélin et al 2015, Vasiljevic et al 2015].
- **Characteristic facial features.** Frontal bossing, hypertelorism, depressed nasal bridge, and micrognathia have been described [Holman et al 2011, Perdu et al 2011, Quélin et al 2015, Vasiljevic et al 2015].
- **Musculoskeletal.** A striking finding in the majority of severely affected males is the bilateral absence or hypoplasia of the fibulae [Holman et al 2011, Quélin et al 2015, Vasiljevic et al 2015, Mi et al 2020]. Polysyndactyly is also common [Holman et al 2011].
- **Brain anomalies.** Ventriculomegaly is common [Holman et al 2011], as are corpus callosal anomalies.
- **Cardiac anomalies.** Approximately 40% of severely affected males have congenital heart disease. Reported anomalies include hypoplastic left heart, hypoplastic right heart, ventricular septal defects, atrial septal defects, and patent ductus arteriosus [Holman et al 2011, Perdu et al 2011].
- **Genitourinary anomalies.** Nonspecific kidney abnormalities including echogenic kidneys, enlarged kidneys, and abnormal collecting systems are common [Holman et al 2011, Vasiljevic et al 2015]. Nephrogenic rests have been identified on postmortem examination in multiple severely affected male fetuses [Fukuzawa et al 2010, Holman et al 2011, Vasiljevic et al 2015], and may play a role in the development of Wilms tumors [Bach et al 2021].
- **Gastrointestinal.** Omphalocele is the most commonly observed gastrointestinal anomaly, followed by intestinal malrotation [Holman et al 2011, Quélin et al 2015, Vasiljevic et al 2015].

Pathophysiology

Metaphyseal striations are hypothesized to be due to the presence of two independently acting osteoblast cell lines [Rott et al 2003]. This can occur either through differential X-chromosome inactivation in a female or mosaicism for an *AMER1* pathogenic variant in a male. This hypothesis would explain why constitutionally affected males with a hemizygous *AMER1* pathogenic variant and only one osteoblast cell line do not have metaphyseal striations on radiographs.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *AMER1* have been confirmed.

Initial reports of truncating variants at the 5' end of *AMER1* predicting a severe phenotype have been disproven [Perdu et al 2010, Perdu et al 2011].

Penetrance

Penetrance appears to be 100%, albeit with variable expressivity and severity of the phenotype, even within families.

Nomenclature

Previous gene names for *AMER1* include *WTX* and *FAM123B*.

OS-CS is also known as hyperostosis generalisata with striations.

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], OS-CS is referred to as *AMER1*-related osteopathia striata with cranial sclerosis and is included in the osteosclerotic disorders group.

Prevalence

Approximately 90 individuals with molecularly confirmed OS-CS have been reported [Author, personal observation].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *AMER1*.

Sporadic tumors (including Wilms tumor) occurring as single tumors in the absence of any other findings of osteopathia striata with cranial sclerosis frequently harbor a somatic pathogenic variant in *AMER1* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Females and mildly affected males. Disorders that may present with sclerotic bone disease similar to that observed in females (and mildly affected males) with osteopathia striata with cranial sclerosis (OS-CS) are summarized in Table 3. See also the Nosology of Genetic Skeletal Disorders: 2023 Revision, Group 24 – Osteopetrosis and related osteoclast disorders and Group 25 – Osteosclerotic disorders [Unger et al 2023] for a review of additional disorders that may be considered in the differential diagnosis of OS-CS.

Males with a severe phenotype present with a multiple-malformation syndrome, usually without metaphyseal striations, making the differential diagnosis very broad. *AMER1* should be included within the gene list for any fetal or neonatal multiple-malformation presentation.

Table 3. Genes of Interest in the Differential Diagnosis of Osteopathia Striata with Cranial Sclerosis

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/OS-CS	Distinguishing from OS-CS
ANKH	Craniometaphyseal dysplasia, autosomal dominant	AD	Bony sclerosis of cranial bones	• Metaphyseal flaring • Absence of metaphyseal striations

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/OS-CS	Distinguishing from OS-CS
CA2 *CLCN7* *LRP5* *OSTM1* *PLEKHM1* *SNX10* *TCIRG1* *TNFRSF11A* *TNFSF11*	Osteopetrosis [1] (OMIM PS259700 & PS607634)	AR AD	Bony sclerosis of cranial and long bones	• Absence of dysmorphic features • More diffuse sclerosis of long bones • Absence of metaphyseal striations
GJA1	Craniometaphyseal dysplasia, autosomal recessive (OMIM 218400)	AR	Bony sclerosis of cranial bones	• Metaphyseal widening • Absence of metaphyseal striations
LRP4	Sclerosteosis 2 (OMIM 614305)	AD AR	Bony sclerosis	• Absence of dysmorphic features • Absence of metaphyseal striations
PORCN	Focal dermal hypoplasia (Goltz syndrome)	XL	Metaphyseal striations	• Ectodermal manifestations • Limb malformations • Ocular manifestations
SOST	Endosteal hyperostosis, van Buchem type (van Buchem disease) (See *SOST*-Related Sclerosing Bone Dysplasias.)	AR	Bony sclerosis	• Absence of metaphyseal striations • Progressive skeletal overgrowth • Hyperphosphatasemia
	Craniodiaphyseal dysplasia (OMIM 122860)	AD	Bony sclerosis; progressive overgrowth of craniofacial bones w/ cranial nerve entrapment	• Absence of metaphyseal striations • Diaphyses of long bones expanded within the cortices • Choanal stenosis a common complication
	Sclerosteosis (See *SOST*-Related Sclerosing Bone Dysplasias.)	AR	Bony sclerosis	• Absence of metaphyseal striations • 2-3 finger syndactyly, nail dysplasia
TGFB1	Camurati-Engelmann disease (progressive diaphyseal dysplasia)	AD	Bony sclerosis of cranial and long bones	• Absence of metaphyseal striations • Pronounced diaphyseal hyperostosis of long bones • Proximal muscle weakness & wide-based waddling gait
TONSL	Spondyloepimetaphyseal dysplasia, sponastrime type (OMIM 271510)	AR	Metaphyseal striations	• Spondylar changes • Absence of OS-CS facial characteristics • Absence of sclerosis

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

1. See also the Nosology of Genetic Skeletal Disorders: 2023 Revision, Group 24 – Osteopetrosis and related osteoclast disorders and Group 25 – Osteosclerotic disorders [Unger et al 2023].

Voorhoeve disease (osteopathia striata) is characterized by isolated metaphyseal striations. Unlike OS-CS, Voorhoeve disease is not associated with cranial sclerosis or macrocephaly. Voorhoeve disease may be inherited in an autosomal dominant manner or occur in a single family member; the genetic cause(s) of the disorder are unknown.

Management

No consensus clinical diagnostic criteria for osteopathia striata with cranial sclerosis (OS-CS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with OS-CS, 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 Osteopathia Striata with Cranial Sclerosis

System/Concern	Evaluation	Comment
Musculoskeletal	Skeletal survey – long bones & skull	To assess for sclerosis &/or metaphyseal striations
	Clinical assessment for scoliosis & joint contractures	
ENT	ENT assessment	To assess for orofacial clefting
Hearing	Hearing assessment	To evaluate hearing loss
Eyes	Ophthalmology assessment	To evaluate for optic nerve compression
Constitutional	Growth assessment	To assess for short stature in surviving males (less common in females)
Cognition	Developmental assessment	
Cardiac	Cardiology assessment incl echocardiography	To assess for structural heart defects in females & surviving males
Renal	Renal ultrasound exam	• To assess for renal anomalies in surviving males • To evaluate for nephrogenic rests &/or Wilms tumor in females & males
Neurology	Neurology assessment incl brain MRI	To assess for CNS anomalies in surviving males
Gastroenterology	Imaging for malrotation performed as clinically indicated	
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of OS-CS in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CNS = central nervous system; MOI = mode of inheritance; OS-CS = osteopathia striata with cranial sclerosis
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists, including pediatrician, clinical geneticist, orthopedic surgeon, ENT specialist, and, in the presence of congenital malformations, relevant additional subspecialists, is recommended.

Table 5. Treatment of Manifestations in Individuals with Osteopathia Striata with Cranial Sclerosis

Manifestation/ Concern	Treatment	Considerations/Other
Scoliosis	Management per orthopedic surgeon	
Joint contractures	PT may be helpful.	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Orofacial clefting	Management per ENT surgeon	
Hearing loss	• Management per audiologist • Speech-language therapy • Surgical management per otolaryngologist should be considered on a case-by-case basis if underlying pathology involves foraminal compression.	• Community & support groups for hearing loss • Sclerotic bone poses surgical challenges [Katsevman et al 2016], and the success of surgical decompression of cranial nerve foramina in OS-CS is not established.
Vision loss	Management per ophthalmologist	Community & support groups for vision loss
	Surgical management per neurosurgeon should be decided on a case-by-case basis.	Sclerotic bone poses surgical challenges [Katsevman et al 2016], and the success of surgical decompression of cranial nerve foramina in OS-CS is not established.
Cognition	Early intervention services & special education services as indicated	
Cardiac anomalies	Treatment per cardiologist	
Genitourinary anomalies	Treatment per urologist &/or nephrologist	
Gastrointestinal anomalies	Treatment per gastroenterologist &/or surgery	
Wilms tumor &/or other malignancy	Standard treatment	

PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with Osteopathia Striata with Cranial Sclerosis

System/Concern	Evaluation	Frequency
Musculoskeletal	Clinical assessment for scoliosis & joint contractures	Annually or as indicated
Hearing	Audiology eval	
Vision	Ophthalmology eval	
Cognition	Developmental assessment	
Wilms tumor	Abdominal ultrasound	Every 3 mos until age 7 yrs as per Beckwith-Wiedemann syndrome guidelines until OS-CS specific guidelines are established [1]

1. The association of OS-CS with Wilms tumor has only recently been established [Bach et al 2021]. Until there is an evidentiary base for OS-CS-specific surveillance guidelines, surveillance based on Beckwith Wiedemann syndrome guidelines is recommended [Brioude et al 2018; Bach et al 2021; Author, personal communication with Professor Stephen Robertson].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early diagnosis and treatment of hearing and/or vision loss and congenital heart disease, from cancer surveillance, and from review for congenital anomalies (males).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

No specific OS-CS pregnancy management is described, but guidelines for management of pregnant individuals with a skeletal dysplasia should be consulted [Savarirayan et al 2018].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Osteopathia striata with cranial sclerosis (OS-CS) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *AMER1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *AMER1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case):
  - The mother may be a heterozygote.
  - The affected male may have a *de novo AMER1* pathogenic variant (in which case the mother is not a heterozygote). About 25% of affected males have the disorder as the result of a *de novo* pathogenic variant.
  - Note: If a male proband is found to be mosaic for the *AMER1* pathogenic variant, this is presumed to be due to a *de novo* postzygotic change in the proband, and is not inherited from either parent.
  - The mother may have germline mosaicism.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *AMER1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Females who inherit the pathogenic variant will be heterozygotes and will have variable manifestations of OS-CS (see Clinical Description, Affected Females)

- Males who inherit the pathogenic variant will be hemizygotes and will have variable manifestations ranging from mid-late gestation and neonatal lethality to the mild phenotype (see Clinical Description, Affected Males).

  Of the males reported in the literature, approximately half died in mid-late gestation or the neonatal period. However, the incidence of lethality is likely to be under-reported, due to the nonspecific multiple-malformation presentation of males, increasing the likelihood of a missed diagnosis. The low number of reported males suggests that early fetal loss is also possible.

- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *AMER1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.

Parents of a female proband

- A female proband may have inherited the *AMER1* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*. About 45% of affected females have the disorder as the result of a *de novo* pathogenic variant.
- Note: Paternal inheritance has only been reported in mosaic fathers [Ciceri et al 2013, Mi et al 2020].
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and subsequently the father) can help to determine if the pathogenic variant was inherited.

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has an *AMER1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.

  - Females who inherit the pathogenic variant will be heterozygotes and will have variable manifestations of OS-CS (see Clinical Description).

  - Males who inherit the pathogenic variant will be hemizygotes and will have variable manifestations ranging from mid-late gestation and neonatal lethality to the mild phenotype (see Clinical Description).

    Of the males reported in the literature, approximately half died in mid-late gestation or the neonatal period. However, the incidence of lethality is likely to be under-reported, due to the nonspecific multiple-malformation presentation of males, increasing the likelihood of a missed diagnosis. The low number of reported males suggests that early fetal loss is also possible.

- If the father of the proband has an *AMER1* pathogenic variant, it should be presumed he will transmit the *AMER1* pathogenic variant to all his daughters and none of his sons. Only two instances of paternal vertical transmission have been reported; in both families the fathers were mosaic [Ciceri et al 2013, Mi et al 2020].

- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *AMER1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a male proband. Men with an *AMER1* pathogenic variant will transmit the *AMER1* pathogenic variant to all of their daughters and none of their sons.

Offspring of a female proband. Women with an *AMER1* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:

Other family members. If the mother of the proband is heterozygous for an *AMER1* pathogenic variant (or, theoretically, the father is hemizygous for the *AMER1* pathogenic variant), her (or his) family members may be at risk of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended 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 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, heterozygous, or at increased risk of being affected or heterozygous.

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *AMER1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.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
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

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. Osteopathia Striata with Cranial Sclerosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AMER1	Xq11.2	APC membrane recruitment protein 1	FAM123B @ LOVD	AMER1	AMER1

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 Osteopathia Striata with Cranial Sclerosis (View All in OMIM)

300373	OSTEOPATHIA STRIATA WITH CRANIAL SCLEROSIS; OSCS
300647	APC MEMBRANE RECRUITMENT PROTEIN 1; AMER1

Molecular Pathogenesis

AMER1 (also known as *FAM123B* or *WTX*) encodes adenomatous polyposis coli membrane recruitment protein 1.

The *AMER1* protein acts as an inhibitor of the canonic WNT signaling pathway, through the ubiquitination and degradation of beta-catenin [Tanneberger et al 2011]. The WNT signaling pathway acts on a range of cellular processes including body axis patterning and bone morphogenesis. Up- or downregulation of this pathway can have a broad range of phenotypic effects [Huybrechts et al 2020].

Reduced expression of *AMER1* (e.g., through a loss-of-function variant) leads to an accumulation of beta catenin in the nucleus. This in turn causes upregulation of the WNT pathway and osteoblastic function, leading to bony sclerosis [Mi et al 2020].

Metaphyseal striations are hypothesized to be due to the presence of two independently acting osteoblast-cell lines [Rott et al 2003]. This can occur either through differential X-chromosome inactivation in a female or mosaicism for an *AMER1* pathogenic variant in a male. This hypothesis would explain why constitutionally affected males with a hemizygous *AMER1* pathogenic variant and only one osteoblast cell line do not have metaphyseal striations on radiographs.

Mechanism of disease causation. Loss of function

***AMER1*-specific laboratory technical considerations.** *AMER1* contains two exons, the first of which is noncoding. To date, almost all reported pathogenic variants causing osteopathia striata with cranial sclerosis (OS-CS) are germline truncating variants in exon 2 or whole-gene deletions [Author, personal observation].

However, two pathogenic variants in the noncoding exon 1 of *AMER1* have been reported, which may not be captured by traditional sequencing methods [Mi et al 2020].

Mosaicism has also been reported in several males [Joseph et al 2010, Holman et al 2011, Perdu et al 2011, Chénier et al 2012, Hague et al 2017], and in a male with Klinefelter syndrome [Fradin et al 2017]. Alternative cell lines, alternative technologies, or an increased depth of sequencing should be considered to identify suspected mosaic pathogenic variants.

Cancer and Benign Tumors

Somatic *AMER1* variants are found in 15%-30% of Wilms tumors, evenly divided between mesenchymal- and epithelial-derived tumors [Fukuzawa et al 2009].

Early studies suggested that germline *AMER1* variants did not predispose to Wilms tumors; however, a recent association has been reported in four individuals including one with bilateral Wilms tumors [Bach et al 2021].

Chapter Notes

Author Notes

www.mcri.edu.au/users/professor-ravi-savarirayan

www.skeletaldysplasia.org

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Revision History

- 30 March 2023 (sw) Revision: "*AMER1*-Related Osteopathia Striata with Cranial Sclerosis" added as synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature and Differential Diagnosis
- 15 April 2021 (sw) Review posted live
- 4 February 2021 (rs) Original submission

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