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CHST3-Related Skeletal Dysplasia

Synonyms: Chondrodysplasia with Congenital Joint Dislocations, CHST3 Type; CHST3 Deficiency; *CHST3*-Related Dysplasia; Recessive Larsen Syndrome

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Summary

Clinical characteristics

CHST3-related skeletal dysplasia is characterized by short stature of prenatal onset, joint dislocations (knees, hips, radial heads), clubfeet, and limitation of range of motion that can involve all large joints. Kyphosis and occasionally scoliosis with slight shortening of the trunk develop in childhood. Minor heart valve dysplasia has been described in several persons. Intellect and vision are normal.

Diagnosis/testing

The diagnosis is based on the radiographic features of progressive spondyloepiphyseal dysplasia with joint anomalies, spinal abnormalities, normal thumbs (not spatulate), and normal bone age. *CHST3* is the only gene in which pathogenic variants are known to cause *CHST3*-related skeletal dysplasia.

Management

Treatment of manifestations: Surgical correction of the abnormal joints is the only treatment modality; however, surgical correction is often only partially successful and multiple procedures are needed. Physical therapy has not been effective.

Surveillance: If normal at the time of diagnosis, echocardiogram should probably be repeated every five years.

Agents/circumstances to avoid: Activities with a high impact on joints (e.g., jogging) and obesity.

Genetic counseling

CHST3-related skeletal dysplasia is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a

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25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for a prengancy at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

The diagnosis of *CHST3*-related skeletal dysplasia is based on the combination of characteristic clinical and radiographic signs and confirmation by molecular genetic testing.

Suggestive Findings

CHST3-related skeletal dysplasia **should be suspected** in individuals with the following clinical and radiographic features.

Clinical features

- Joint dislocations at birth (knees, hips, radial heads) with short stature (Figure 1)
- Clubfeet
- Limitation of range of motion that can involve all large joints
- Development of kyphosis and occasionally scoliosis with slight shortening of the trunk in childhood

Radiographic features

- Progressive spondyloepiphyseal dysplasia with joint anomalies
  - Generalized mild epiphyseal dysplasia (small epiphyses)
  - Delayed ossification of the capital femoral epiphyses and femoral necks
  - Coxa valga (increase in the angle formed between the head and neck of the femur and the shaft of the femur)
- Spinal abnormalities
  - Conspicuous increase in interpediculate distance from T12 to L1 or L2 (Figure 2)
  - Notching of the vertebral bodies, similar in appearance to coronal clefts (Figure 3)
- Normal thumbs (not spatulate)
- Normal or (more rarely) slightly advanced bone age (especially carpal)

Establishing the Diagnosis

The diagnosis of *CHST3*-related skeletal dysplasia **is established** in a proband by identification of biallelic pathogenic variants in *CHST3* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

- **Single-gene testing.** Sequence analysis of *CHST3* is performed first. If no pathogenic variants or only a single pathogenic variant have been identified and the clinical-radiographic index of suspicion is high for a *CHST3*-related skeletal dysplasia, consider doing gene-targeted deletion/duplication analysis. However, no individuals with a deletion/duplication have been reported.

- **A multigene panel** that includes *CHST3* and other genes of interest (see Differential Diagnosis) may also be considered. Laboratories may offer a general "skeletal dysplasia" panel or a more targeted "skeletal dysplasia with multiple dislocations" panel. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the

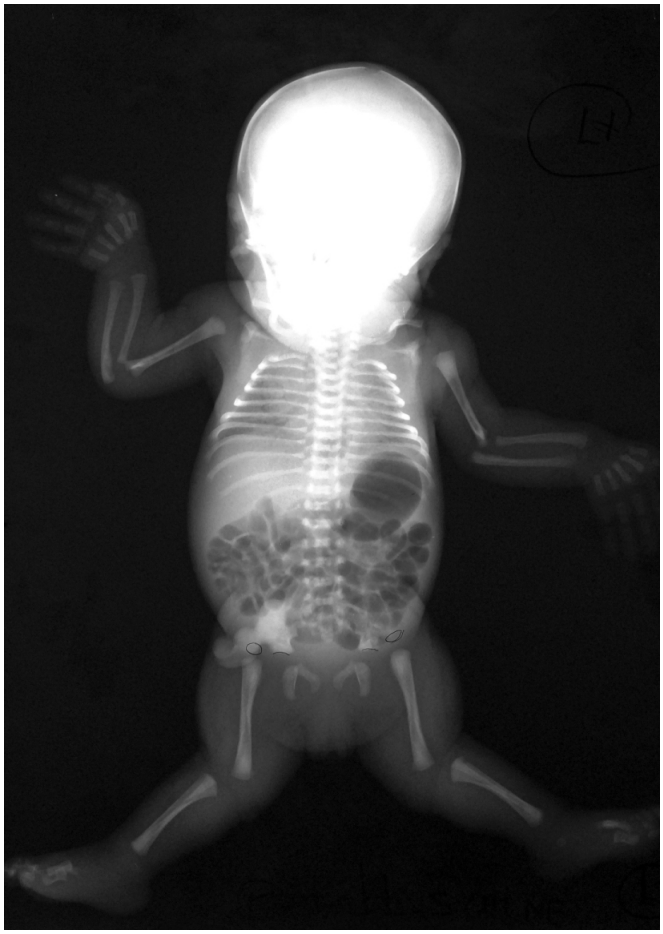

Figure 1. A newborn with molecularly confirmed *CHST3*-related skeletal dysplasia. Note the bilateral dislocation of the knees and radial heads.

condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) 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.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

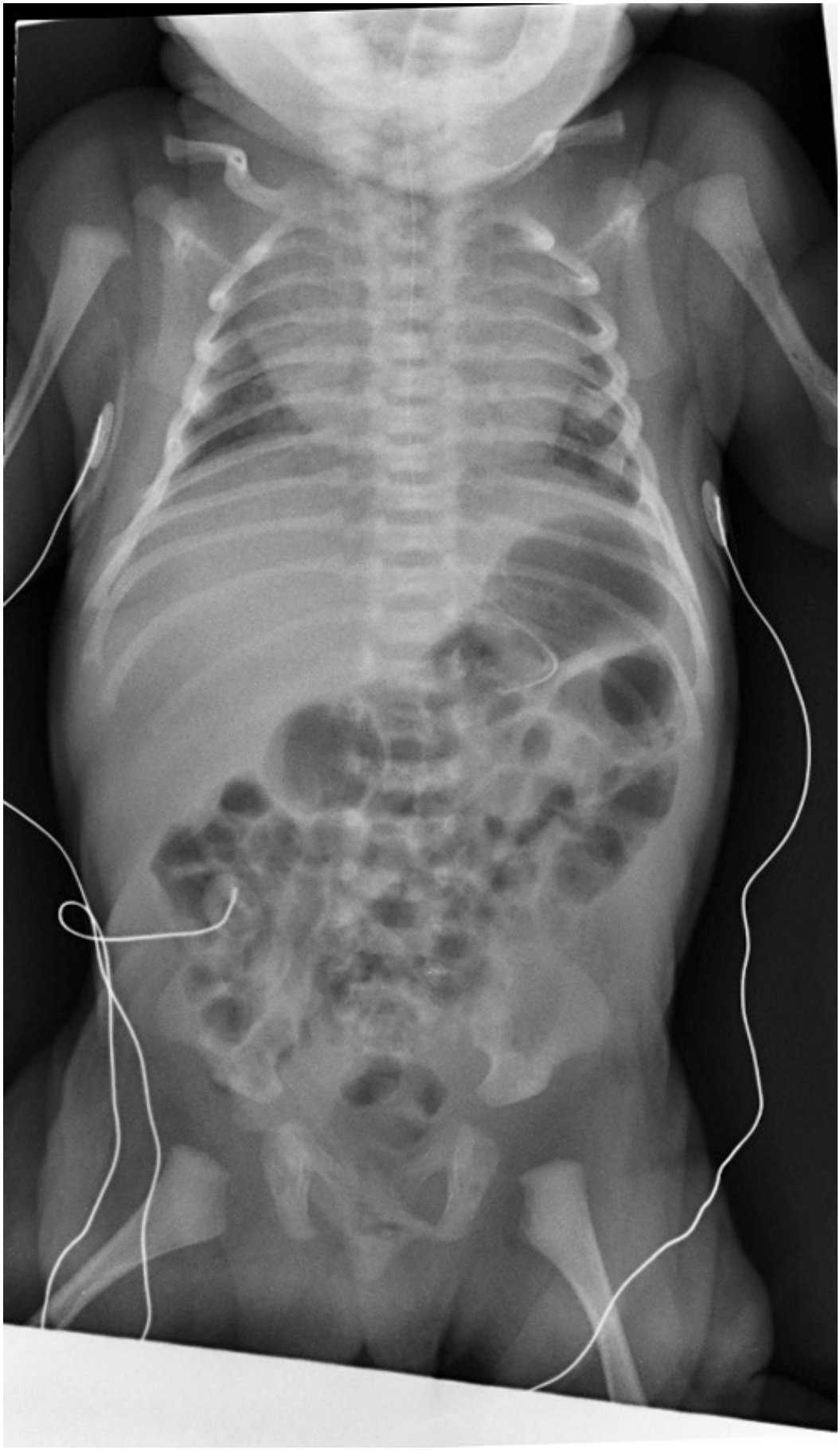

Figure 2. Note the conspicuous increase in interpediculate distance from T12 to L1. Also appreciable is the bilateral hip subluxation.

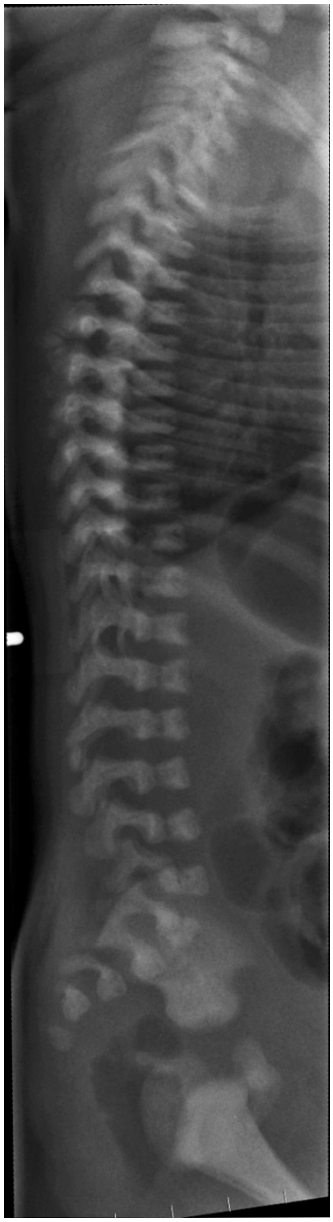

Figure 3. Mild platyspondyly is observed. Note also the coronal clefts throughout the lumbar region.

Table 1. Molecular Genetic Testing Used in *CHST3*-Related Skeletal Dysplasia

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
CHST3	Sequence analysis [3]	>90% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	1 reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
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. Hermanns et al [2008], Unger et al [2010]
5. The high detection rate applies only to those individuals with clear clinical and radiographic changes consistent with CHST3 deficiency and not to an unselected population of children with joint dislocations.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Ranza et al [2017]

Biochemical testing. Cultured fibroblasts can be used to determine proteoglycan sulfation (i.e., sulfotransferase activity). The fibroblasts are incubated with radioactive sulfate [^{35}S] and chondroitin. In all patients with CHST3 deficiency studied thus far, the incorporation of sulfate at the C6 position was dramatically decreased while incorporation at the C4 position was within normal levels [Hermanns et al 2008, van Roij et al 2008]. This test requires a skin biopsy and thus is more invasive and less widely available than molecular genetic testing. Biochemical testing can be useful in those cases in which pathogenic variants are not identified or variants of uncertain significance have been detected. The diminished sulfation at carbon 6 of proteoglycans offers unambiguous evidence of CHST3 deficiency.

Clinical Characteristics

Clinical Description

Most children with *CHST3*-related skeletal dysplasia are identified at birth as having a generalized skeletal disorder. The features of this disorder are generally limited to the skeleton and joints and are progressive in nature.

Occasionally, short stature and knee dislocations are seen on prenatal ultrasound examination [Unger et al 2010]. The prenatal presentation may be that of arthrogryposis [Muys et al 2017].

At birth, affected infants are noted to have short stature (birth length: 39 to 44 cm) and joint dislocations: the large majority have bilateral knee luxation or subluxation. The radial heads and hips are the next most commonly affected joints. Clubfeet are also frequently seen. Despite the congenital joint dislocations, the overall phenotype is one of restricted movement and many children undergo multiple corrective procedures with only limited success [Rajab et al 2004, Unger et al 2010, Searle et al 2014].

In the large family reported from Oman, the adult heights ranged from 110 cm to 130 cm [Rajab et al 2004], while in a large Pakistani family the mean adult height was 84 cm [Waryah et al 2016]. A review article included information on three adults with heights of 117 cm, 121 cm, and 134.5 cm [Unger et al 2010]. Adult height appears to be severely affected in all individuals with *CHST3*-related skeletal dysplasia but with some intrafamilial variability and large interfamilial variability.

Many adults develop arthritic-type changes. They also develop spinal kyphosis, frequently in the cervical spine, and (rarely) scoliosis.

Other findings include:

- Minor heart valve dysplasia with valvular insufficiency in several persons, including one in the kindred from Oman [Hall 1997, Rajab et al 2004, Tuysuz et al 2009];
- Nonskeletal complications: inguinal hernia and gastric volvulus;
- Tooth anomalies (microdontia, delayed eruption), reported in the large Omani kindred though not observed in others [Rajab et al 2004];
- Normal intellect, vision, and hearing [Unger et al 2010]. However, in a large Pakistani kindred, at least six affected individuals also had mixed hearing loss; thus, this may be an associated feature [Waryah et al 2016];
- Sagittal craniosynostosis has been reported in a single individual [Searle et al 2014] while "sclerosis of sutures" was reported in three unrelated patients [Srivastava et al 2017].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed. The phenotype reported thus far has been strikingly homogeneous regardless of type of *CHST3* variant [Unger et al 2010]. Persons with homozygous pathogenic missense variants are no less severely affected than those with nonsense variants.

Nomenclature

In 1950, Dr LJ Larsen described autosomal dominant Larsen syndrome, now known to be caused by pathogenic variants in *FLNB*, the gene encoding filamin B [Bicknell et al 2007]. Larsen syndrome is characterized by multiple joint dislocations, dysmorphic facial features, spatulate thumbs, and accelerated carpal ossification (see *FLNB*-Related Disorders).

Following the delineation of autosomal dominant Larsen syndrome, several reports of "autosomal recessive Larsen syndrome" and other similar disorders were published. By careful reevaluation of patients and through recruitment of cases with autosomal recessive Larsen syndrome, several investigators showed that, in fact, all the various reports of autosomal recessive Larsen syndrome, humerospinal dysostosis, and spondyloepiphyseal dysplasia (SED), Omani type could be attributed to CHST3 deficiency and that the different names had arisen from the part of the phenotype the various authors had emphasized [Hermanns et al 2008, Unger et al 2010]; that is, they were describing the same condition from different viewpoints:

- Humerospinal dysostosis was described by Kozlowski et al [1974] in two brothers with joint dislocations and radiographic abnormalities (bifid humeri and coronal clefts). Because the brothers were reported to be half-sibs, autosomal dominant inheritance was suspected and no link was made to autosomal recessive Larsen syndrome.
- Mégarbané and Ghanem [2004] described "a newly recognized chondrodysplasia with joint dislocations." Although they made the link to humero-spinal dysostosis, they rejected that diagnosis because the evidence strongly suggested autosomal recessive inheritance.
- Rajab et al [2004] described a large family originating from Oman with what they termed "a new recessive type of SED with progressive spinal involvement." The same group went on to demonstrate that the disorder was caused by CHST3 deficiency and renamed the disorder SED, Omani type [Thiele et al 2004].

The name "*CHST3*-related skeletal dysplasia" has been proposed as an unbiased and inclusive designation for this disorder. However, an argument could also be made for retaining the name "autosomal recessive Larsen syndrome," as the joint dislocations are the presenting feature and "Larsen syndrome" is usually the first diagnosis considered; thus, the continued use of this designation is open to debate. The term "recessive Larsen

syndrome" is more appropriate for *CHST3*-related skeletal dysplasia than for the *B4GALT7*-associated linkeropathy, as bilateral knee dislocation at birth is much more common in CHST3 deficiency than in B4GALT7 deficiency.

Prevalence

No firm data regarding the prevalence of *CHST3*-related skeletal dysplasia are available. More than 40 cases (including familial recurrences) have been reported.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with pathogenic variants in *CHST3*.

Differential Diagnosis

A summary of key differentiating clinical and radiographic features for chondrodysplasias with multiple dislocations is available in Ranza et al [2017].

Table 2. Disorders to Consider in the Differential Diagnosis of *CHST3*-Related Skeletal Dysplasia

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/*CHST3* Skeletal Dysplasia	Distinguishing from *CHST3* Skeletal Dysplasia
Larsen syndrome (See *FLNB*-Related Disorders.)	*FLNB*	AD	Multiple dislocations	• Normal birth length in Larsen syndrome; ↓ in *CHST3* skeletal dysplasia • Distinctive facial features in Larsen syndrome, w/↑ incidence of cleft palate; normal facies in *CHST3* skeletal dysplasia • Advanced bone age in Larsen syndrome; normal or delayed bone age in *CHST3* skeletal dysplasia
Diastrophic dysplasia	*SLC26A2*	AR	• Short limbs • Clubfeet • Joint stiffness / limited mobility	• Hitchhiker thumb • Lacks characteristic *CHST3* skeletal dysplasia spine findings
Desbuquois dysplasia (OMIM 251450, 615777)	*CANT1* *XYLT1*	AR	• Prenatal-onset short stature • Joint dislocations • Multiple coronal clefts on lateral spine x-ray	• Distinctive facial features in Desbuquois dysplasia (marked midface hypoplasia, prominent eyes) • Advanced bone age
B4GALT7 deficiency [1] (OMIM 604327)	*B4GALT7*	AR	• Prenatal-onset short stature • Joint dislocations	• Advanced bone age • Lacks characteristic *CHST3* skeletal dysplasia spine findings
***B3GALT6* linkeropathy** (OMIM 61521)	*B3GALT6*	AR	• Prenatal-onset short stature • Joint dislocations	• Advanced bone age • Lacks characteristic *CHST3* skeletal dysplasia spine findings

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

1. The La Reunion variant of recessive Larsen syndrome is caused by a specific *B4GALT7* pathogenic variant [Cartault et al 2015].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *CHST3*-related skeletal dysplasia, the following evaluations are recommended if they have not already been completed:

- Orthopedic referral
- Referral to a specialized skeletal dysplasia clinic if available
- Echocardiogram
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The focus of treatment has thus far been surgical correction of the abnormal joints. Presumably because of the basic defect present in *CHST3*-related skeletal dysplasia, surgical correction is often only partially successful and most patients have had multiple procedures by adulthood [Unger et al 2010].

Of note, physical therapy has not been demonstrated to be effective in this disorder.

Surveillance

Thus far, heart valve dysplasia has not required correction; thus, no firm guidelines for appropriate surveillance have been developed. Echocardiogram is suggested at time of diagnosis and, if normal, should probably be repeated at intervals of five years.

Agents/Circumstances to Avoid

Activities with a high impact on joints (e.g., jogging) should be avoided.

Obesity, which places an excessive load on the large weight-bearing joints, should be avoided.

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

CHST3-related skeletal dysplasia is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *CHST3* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic. There is no evidence that they are at increased risk for degenerative joint disease.
- To date, neither *de novo* pathogenic variants nor germline mosaicism in parents has been reported.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *CHST3*-related skeletal dysplasia are obligate heterozygotes (carriers) for a *CHST3* pathogenic variant.

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of a *CHST3* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CHST3* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

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).

Prenatal Testing and Preimplantation Genetic Testing

Once the *CHST3* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *CHST3*-related skeletal dysplasia are possible.

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.

- **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. CHST3-Related Skeletal Dysplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CHST3	10q22.1	Carbohydrate sulfotransferase 3	CHST3 @ LOVD	CHST3	CHST3

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 CHST3-Related Skeletal Dysplasia (View All in OMIM)

143095	SPONDYLOEPIPHYSEAL DYSPLASIA WITH CONGENITAL JOINT DISLOCATIONS; SEDCJD
603799	CARBOHYDRATE SULFOTRANSFERASE 3; CHST3

Gene structure. *CHST3* is a relatively small gene, comprising three exons. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Several recurrent pathogenic variants have been identified in families of similar ethnic background and, thus, may represent founder variants [Unger et al 2010]. No hot spots have been identified, but the majority of known pathogenic variants are clustered in the sulfotransferase domain.

Normal gene product. Carbohydrate sulfotransferase 3 is the enzyme responsible for the transfer of sulfate from PAPS to position 6 of N-acetyl galactosamine. Proper sulfation of the chondroitin sulfate proteoglycans is essential for normal cartilage structure.

Abnormal gene product. Sulfation studies as well as the nature of the known pathogenic variants and the mode of inheritance suggest that the pathogenesis of the disorder results from decreased/absent catalytic activity of the enzyme.

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Chapter Notes

Revision History

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