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Campomelic Dysplasia

Synonyms: Camptomelic Dysplasia, *SOX9*-Related Campomelic Dysplasia

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Summary

Clinical characteristics

Campomelic dysplasia (CD) is a skeletal dysplasia characterized by distinctive facies, Pierre Robin sequence with cleft palate, shortening and bowing of long bones, and clubfeet. Other findings include laryngotracheomalacia with respiratory compromise and ambiguous genitalia or normal female external genitalia in most individuals with a 46,XY karyotype. Many affected infants die in the neonatal period; additional findings identified in long-term survivors include short stature, cervical spine instability with cord compression, progressive scoliosis, and hearing impairment.

Diagnosis/testing

The diagnosis of CD is usually based on clinical and radiographic findings. Identification of a heterozygous pathogenic variant in *SOX9* by molecular genetic testing can confirm the diagnosis if clinical and radiographic features are inconclusive.

Management

Treatment of manifestations: Care of children with cleft palate by a craniofacial team using routine measures; in persons with a 46,XY karyotype and undermasculinization of the genitalia, the gonads should be removed because of the increased risk for gonadoblastoma; care of hip subluxation and clubfeet using standard protocols; hearing aids for those with hearing impairment; surgery as needed for cervical vertebral instability and progressive cervicothoracic kyphoscoliosis that compromises lung function.

Prevention of secondary complications: If a cervical spine abnormality is identified, special care should be exercised for any surgical procedure.

Surveillance: Annual monitoring of spinal curvature.

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Genetic counseling

CD is inherited in an autosomal dominant manner. To date, most probands have CD as the result of a *de novo* pathogenic variant in *SOX9*; thus, parents of probands are not typically affected. However, a few adults have been diagnosed with CD following the birth of an affected child. Recurrence in sibs has occurred and somatic and germline mosaicism have been reported. Prenatal testing for a pregnancy at increased risk is possible if the pathogenic variant in the family is known.

GeneReview Scope

Campomelic Dysplasia: Included Phenotypes
• Acampomelic campomelic dysplasia • Campomelic dysplasia

For synonyms and outdated names see Nomenclature.

Diagnosis

No consensus clinical diagnostic criteria for campomelic dysplasia (CD) have been published. The diagnosis of CD (derived from the Greek for "bent limb") can usually be clearly established based on clinical and radiographic findings. Although no single clinical feature is obligatory, the radiographic features are consistent and are the most reliable diagnostic clues.

Suggestive Findings

CD **should be suspected** in individuals with the following clinical and radiographic features.

Clinical features

- Relatively large head
- Pierre Robin sequence with cleft palate
- Midface hypoplasia
- Laryngotracheomalacia
- Respiratory distress
- Eleven pairs of ribs
- Ambiguous genitalia or normal female external genitalia in an individual with a 46,XY karyotype
- Dislocatable hips
- Short bowed limbs (lower limbs more frequently than upper limbs)
- Pretibial skin dimples (Bowing of the lower leg is often associated with a skin dimple over the apex of curve.)
- Clubfeet

Note: Bowing of the limbs, the feature that gave the disorder its name, is neither specific nor an obligatory finding. When the limbs are not bowed, the term "acampomelic campomelic dysplasia" is used. Bowing of the limbs is present in many other skeletal dysplasias (e.g., osteogenesis imperfecta).

Radiographic findings (Figure 1, Figure 2, Figure 3)

- Cervical spine anomalies (variable, often kyphosis) (Figure 1)
- Scapular hypoplasia (Figure 2A, Figure 3)
- Hypoplastic thoracic vertebral pedicles (Figure 3)
- Eleven pairs of ribs
- Scoliosis or kyphoscoliosis

- Vertically oriented narrow iliac wings (Figure 2B)
- Bowed femora and/or tibiae (occasionally upper limb) (Figure 3)

Establishing the Diagnosis

The clinical diagnosis of CD **can be established** in a proband with the clinical and radiographic findings described in Suggestive Findings. Identification of a heterozygous pathogenic (or likely pathogenic) variant in *SOX9* by molecular genetic testing (see Table 1) can establish the diagnosis if clinical and radiographic findings are inconclusive.

The molecular diagnosis of CD **is established** in a proband with suggestive findings who has **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous pathogenic (or likely pathogenic) variant involving *SOX9* (~90% of affected individuals) [Pop et al 2004; G Scherer, unpublished data]
- A heterozygous interstitial deletion or reciprocal translocation of 17q24.3-q25.1 involving *SOX9* or its regulatory region (5% of affected individuals) [G Scherer, unpublished data]

  Note: In rare instances, the translocation may be familial; thus, parental karyotypes should be analyzed when an abnormality is found in the proband.

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 *SOX9* 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), **chromosomal microarray**, **karyotype**, and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with skeletal dysplasia and/or ambiguous genitalia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SOX9* 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 *SOX9*) that cannot be detected by sequence analysis.

Karyotype. If *SOX9* testing is not diagnostic, a karyotype may be considered to evaluate for a reciprocal translocation that involves 17q24.3-q25.1 (*SOX9* locus) but does not result in *SOX9* copy number changes. (See Management for recommendations regarding karyotype in phenotypic females with campomelic dysplasia.)

A skeletal dysplasia multigene panel that includes *SOX9* 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

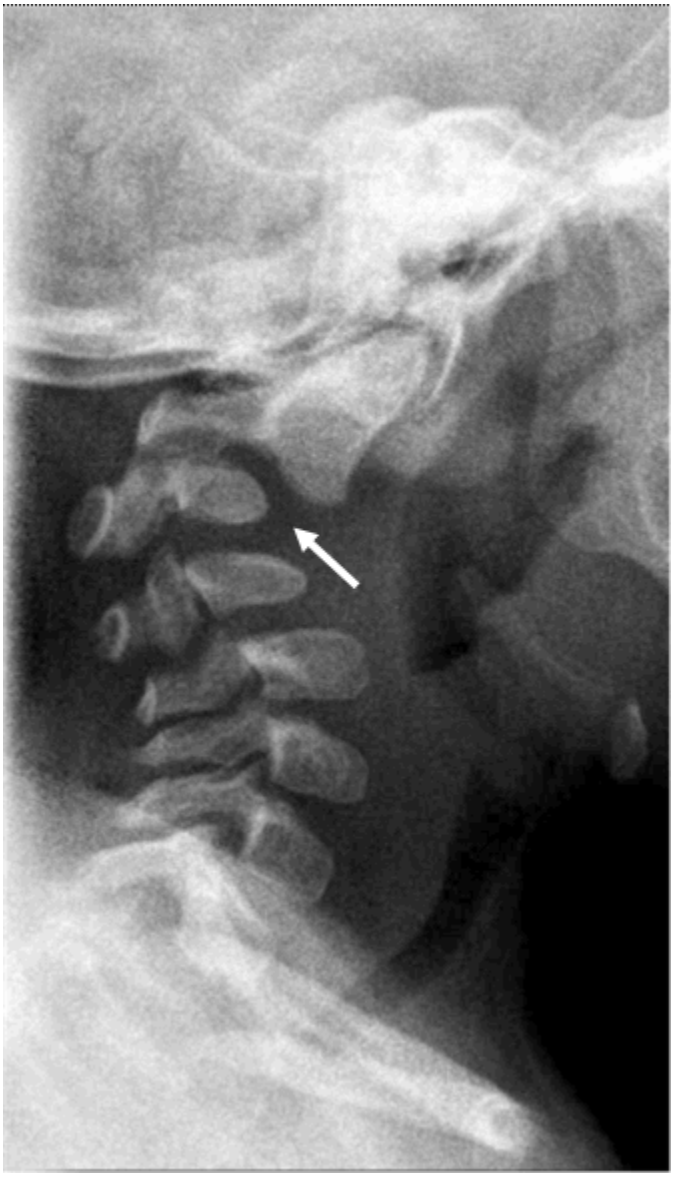

Figure 1. Cervical spine changes (i.e., abnormal AP curvature and anterior dislocation of C2 on C3) (arrow) in a boy age 11 months with classic campomelic dysplasia

significance and pathogenic variants in genes that do not explain the underlying phenotype. The composition of the gene panel is likely to vary depending on presenting feature(s) and age at presentation (e.g., bowed limbs in a fetus, Pierre Robin sequence in a newborn). 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.

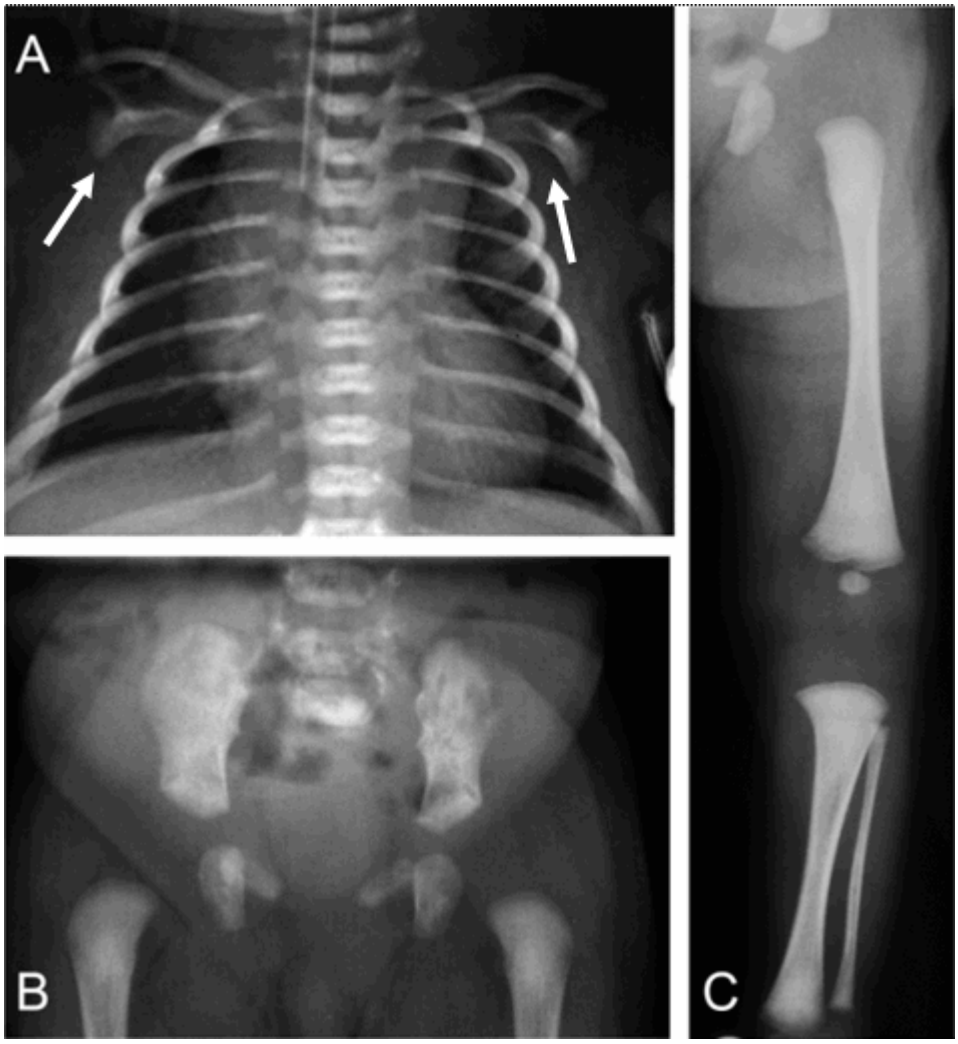

Figure 2. Molecularly confirmed "acampomelic" campomelic dysplasia

A. Tracheostomy tube is in place and the scapulae are markedly hypoplastic (arrows).

B. Vertically oriented narrow iliac wings

C. Straight femora and tibiae

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by skeletal dysplasia, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

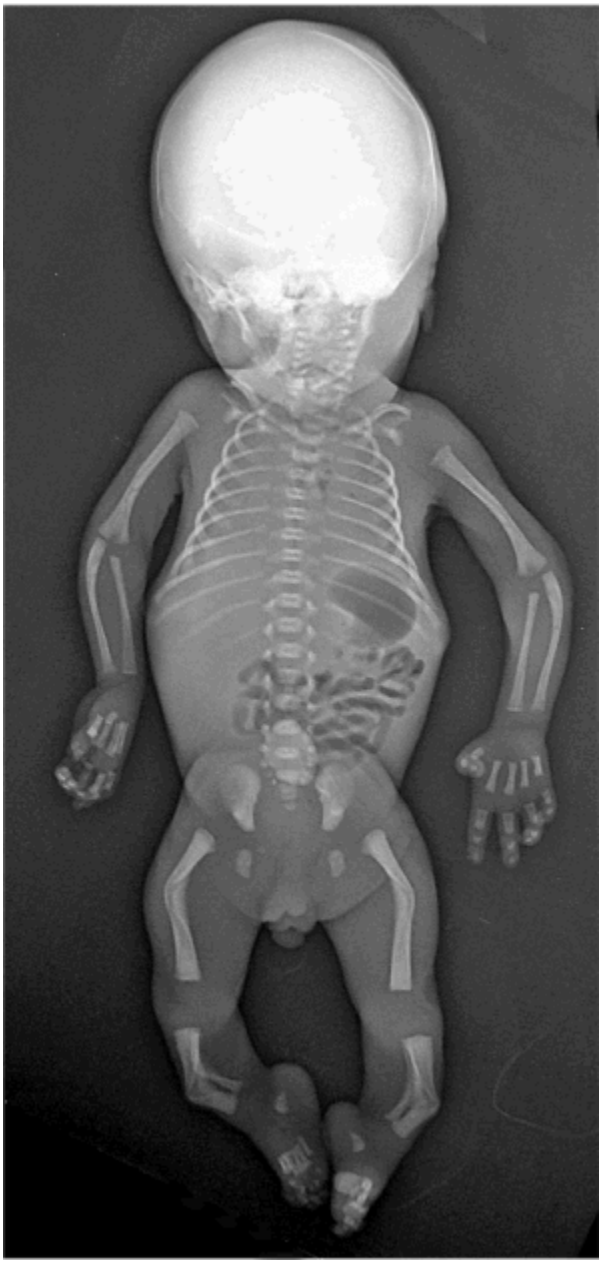

Figure 3. Classic radiographic features of campomelic dysplasia in a 24-week fetus. Note cervical spine abnormalities, hypoplastic thoracic vertebral pedicles, scapular hypoplasia, narrow iliac wings, bowing of the femora and the tibiae, and clubfeet.

Table 1. Molecular Genetic Testing Used in Campomelic Dysplasia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SOX9	Sequence analysis (incl 3' & 5'UTR) [3]	90%-95% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	~2% [7]
	CMA [8]	~1% [9]
	Karyotype	~1% [10]

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020], Pop et al [2004], and von Bohlen et al [2017]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., the family described by Castori et al [2016]) may not be detected by these methods.
6. SOX9 duplication causes XX sex reversal only.
7. Olney et al [1999], Pop et al [2004], Smyk et al [2007]
8. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *SOX9*) 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 17q24.3 region. CMA designs in current clinical use target the 17q24.3 region.
9. Deletions of *SOX9* or upstream regulatory regions cause campomelic dysplasia [Pop et al 2004, Lecointre et al 2009, Kayhan et al 2019].
10. There are multiple reports of individuals with campomelic dysplasia (including the acampomelic form) due to apparently balanced translocations in the vicinity of the *SOX9* locus (breakpoint may be 1 Mb distant, either upstream or downstream) [Ninomiya et al 1995, Pfeifer et al 1999, Fonseca et al 2013, Walters-Sen et al 2014]. Of note, array CGH in at least two of these cases did not detect any imbalance [Fonseca et al 2013].

Clinical Characteristics

Clinical Description

To date, approximately 100 individuals (fetuses included) with a pathogenic variant in *SOX9* have been identified; the data are scattered across many case reports and a few small series [Cameron et al 1996, Pfeifer et al 1999, Mansour et al 2002, Pop et al 2004, Hill-Harfe et al 2005, Smyk et al 2007, Lecointre et al 2009, Gentilin et al 2010, Corbani et al 2011, Fonseca et al 2013, Mattos et al 2015, Castori et al 2016, Csukasi et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Campomelic dysplasia (CD) is sometimes identified on prenatal ultrasound examination but may escape detection until after birth if the limbs are not bowed.

Many newborns with CD die shortly after birth secondary to respiratory insufficiency. In comparison with other lethal skeletal dysplasias, the cause of death in CD is not related to thoracic cage hypoplasia but rather to airway instability (tracheobronchomalacia) or cervical spine instability. Nonetheless, a number of infants with CD have survived the neonatal period [Mansour et al 2002].

The facies in CD resembles the type 2 collagen disorders (e.g., Stickler syndrome), with Pierre Robin sequence (with cleft palate) and flat midface. In the newborn period, the midface is hypoplastic and the eyes are

prominent. Relatively large head size (in comparison to total body length) is common. The limbs are short with body length often below the third percentile. Bowing of the limbs is often present but not obligatory.

Approximately 75% of individuals with CD who have a 46,XY karyotype have either ambiguous external genitalia or normal female external genitalia. The internal genitalia are variable, often with a mixture of müllerian and wolffian duct structures.

Given the relatively small number of survivors described in the literature, it is difficult to generalize about the natural history. The following have been observed:

- Intellect is normal.
- Height is variably affected. Some newborns have significant short stature whereas others are within the normal range.
- When present, scoliosis is usually progressive, contributes to the short stature, and may result in neurologic signs and symptoms.
- Vertebral hypoplasia or malformation, particularly of the cervical spine, may lead to neurologic signs of cord compression unless surgically stabilized and may be the cause of death among those who initially survive the newborn period.
- Hearing impairment/loss in some can be significant enough to require hearing aids.
- A variety of congenital heart defects have been reported in a minority of cases.
- Histologic pancreatic abnormalities have been described in three newborns who died at term from CD; however, pancreatic dysfunction has not been seen in survivors with CD [Piper et al 2002].

Ischiopubic-patella syndrome (IPP). The phenotypic description of IPP is limited to findings in the pelvis and legs including hypoplastic patellae, hypoplastic lesser trochanters, and defective ischiopubic ossification. In several persons with this diagnosis, pathogenic variants of *SOX9* or cytogenetic alterations in the vicinity of *SOX9* have been reported [Mansour et al 2002]. It is now recognized that individuals with IPP have a mild form of campomelic dysplasia with survival to adulthood.

Genotype-Phenotype Correlations

Clear-cut genotype-phenotype correlations are not readily apparent in CD [Meyer et al 1997]. However, correlations of some degree are observed in those with the following two findings.

Chromosomal rearrangements. In long-term survivors with CD and those with acampomelic campomelic dysplasia, d*e novo* translocations or inversions with breakpoints upstream of *SOX9* are more likely to be seen than pathogenic variants in the *SOX9* coding region [Pfeifer et al 1999, Leipoldt et al 2007, Gordon et al 2009, Jakubiczka et al 2010, Fukami et al 2012]. In general, the farther the breakpoint is from *SOX9*, the milder the phenotype, including the effect on male external genitalia [Leipoldt et al 2007] and skeletal findings.

- In two individuals with very distal translocation breakpoints (at 899 kb and 932 kb), the skeletal findings were so mild that they were transmitted through several generations [Hill-Harfe et al 2005, Velagaleti et al 2005].
- Misregulation of *SOX9* has been implicated in individuals with isolated Pierre Robin sequence and translocation breakpoints 1.13 Mb upstream of *SOX9* [Jakobsen et al 2007, Benko et al 2009, Gordon et al 2009, Fukami et al 2012].

Acampomelic campomelic dysplasia (ACD). Mild campomelia and ACD are overrepresented in those with translocations or inversions, accounting for nine of 15 cases with well-defined breakpoints [Leipoldt et al 2007]. In contrast, only approximately 10% of individuals with pathogenic variants in the *SOX9* coding region have ACD. Notably, these are mostly missense variants in the DNA-binding domain [Staffler et al 2010, Corbani et al 2011]. Furthermore, the single missense variant not located in this domain was located in the *SOX9*

dimerization domain in two unrelated individuals with ACD [Bernard et al 2003, Sock et al 2003]. In addition, the few individuals with *SOX9* upstream deletions all had ACD [Pop et al 2004, Lecointre et al 2009, White et al 2011]. Thus, compared to individuals with CD, individuals with ACD have a significantly higher probability of having either a genomic rearrangement with breakpoint upstream of *SOX9*, a *SOX9* upstream deletion, or a *SOX9* missense variant.

Penetrance

Pathogenic variants in the *SOX9* coding region are completely penetrant.

Breakpoints at long distance from *SOX9* may not be completely penetrant.

Nomenclature

The name "campomelic dysplasia," first proposed by Maroteaux in 1971, is derived from the Greek for "bent limb." Other terms used in the past to refer to campomelic dysplasia include campomelic dwarfism, campomelic syndrome, and camptomelic dwarfism.

Although the name "campomelic dysplasia" is well established, it can lead to confusion, as not every child with CD has bowed limbs (ACD) and, conversely, most children with bowed limbs do not have CD but another of the frequent genetic disorders of bone, including osteogenesis imperfecta (OI), hypophosphatasia, cartilage-hair hypoplasia, and others (see Differential Diagnosis).

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], CD is referred to as *SOX9*-related campomelic dysplasia and included in the bent bones dysplasia group.

Prevalence

No reliable data exist regarding the prevalence of CD. The authors estimate it to be in the range of 1:40,000 to 1:80,000.

Genetically Related (Allelic) Disorders

Isolated Pierre Robin sequence. Although it is likely to be rare, chromosomal translocations in the vicinity of *SOX9* may cause isolated Pierre Robin sequence without other obvious findings of CD [Jakobsen et al 2007, Benko et al 2009, Gordon et al 2009].

Isolated sex reversal. There is a report of three adult sibs who were phenotypic females but had male karyotypes. There are no radiographs provided with the report, but the sex reversal is described as isolated. All three sibs had inherited a small 17q24 deletion (not seen in their two phenotypic 46,XX sisters) from their father [Bhagavath et al 2014].

Differential Diagnosis

Differential Diagnosis in the Prenatal Period

Table 2. Disorders with Prenatal Limb Bowing in the Differential Diagnosis of Campomelic Dysplasia

Gene(s)	Differential Disorder	MOI	Comment
ALPL	Hypophosphatasia	AR [1]	
COL1A1 *COL1A2*	Osteogenesis imperfecta (perinatally lethal OI or progressively deforming OI)	AD	OI is more common than CD & thus a more frequent cause of bowed limbs on antenatal US exam.
FGFR3	Thanatophoric dysplasia	AD	Thanatophoric dysplasia type 1 has bowed femurs.

Table 2. continued from previous page.

Gene(s)	Differential Disorder	MOI	Comment
RMRP	Cartilage-hair hypoplasia (See Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders.)	AR	

AD = autosomal dominant; AR = autosomal recessive; CD = campomelic dysplasia; MOI = mode of inheritance; US = ultrasound
1. Perinatal and most infantile cases of hypophosphatasia are inherited in an autosomal recessive manner.

Differential Diagnosis After Birth

After birth, the differential diagnosis is mainly **spondyloepiphyseal dysplasia congenita** (SEDC; see Type 2 Collagen Disorders Overview) because of the facial features, cleft palate, and short limbs. The milder type 2 collagenopathy **Stickler syndrome** may also be considered in the differential diagnosis as the facial features are very similar. Both disorders are caused by pathogenic variants in *COL2A1* and inherited in an autosomal dominant manner. Radiographs differentiate these conditions.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with campomelic dysplasia (CD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended for those infants surviving the neonatal period.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Campomelic Dysplasia

System/Concern	Evaluation	Comment
Respiratory distress due to laryngotracheomalacia or tracheobronchomalacia	Clinical eval	
Cervical spine instability	Lateral radiograph of cervical spine	
Cleft palate	Eval by craniofacial team incl feeding eval	
Risk of gonadoblastoma in 46,XY phenotypic females	Karyotype analysis	In phenotypic females to identify those w/46,XY karyotype
Clubfeet	Referral to orthopedist	
Hearing impairment	Hearing screening	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of CD to facilitate medical & personal decision making

CD = campomelic dysplasia
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Campomelic Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Cleft palate	Care by craniofacial team & surgical closure	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
46,XY karyotype & female genitalia	Gonadectomy because of ↑ risk of gonadoblastoma	No data available re appropriate age for this procedure
Hip dislocation/ luxation	Treatment per orthopedist	
Clubfeet	Surgical correction per orthopedist	
Hearing impairment	Treatment per audiologist incl hearing aids	
Progressive cervicothoracic kyphoscoliosis	Surgical treatment per orthopedist/neurosurgeon	Surgery often required in childhood for those w/ compromised lung function [Thomas et al 1997]; bracing usually not helpful
Cervical spine instability	Surgical treatment per orthopedist/neurosurgeon	

Prevention of Secondary Complications

Risk associated with use of anesthesia prior to imaging or surgery. If a cervical spine abnormality is identified, special care should be exercised for any surgical procedure.

Surveillance

Table 5. Recommended Surveillance for Individuals with Campomelic Dysplasia

System/Concern	Evaluation	Frequency
Kyphoscoliosis	Clinical & radiographic assessment for spinal curvature	Annually in long-term survivors

Agents/Circumstances to Avoid

There are no known circumstances to avoid. However, in long-term survivors with cervical spine malformations, it seems reasonable to limit activities that cause extreme flexion or extension (e.g., somersaults).

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 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

Campomelic dysplasia (CD) is an autosomal dominant disorder typically caused by a *de novo SOX9* pathogenic variant. Rarely, CD is the result of a *de novo* or inherited chromosome rearrangement (e.g., deletion, translocation, or inversion) upstream to or involving *SOX9*.

Risk to Family Members

Parents of a proband

- To date, most probands with campomelic dysplasia (CD) have the disorder as the result of a *de novo SOX9* pathogenic variant; thus, parents of a proband are not typically affected.
- A few adults have been diagnosed with CD following the birth of an affected child [Mansour et al 2002, Savarirayan et al 2003, Lecointre et al 2009].
- Genetic testing capable of detecting the *SOX9* pathogenic variant or chromosome rearrangement identified in the proband is recommended for the parents of a proband to confirm the genetic status of the parents and to allow reliable recurrence risk assessment. (Note: Familial translocations have been reported but are rare.)
- If the *SOX9* pathogenic variant or chromosome rearrangement found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* alteration in the proband or somatic and/or germline mosaicism in a parent.
    - Somatic and germline mosaicism in mildly affected parents of affected sibs has been reported in two families [Higeta et al 2018, Smyk et al 2007].
    - Somatic and/or germline mosaicism for a *SOX9* pathogenic variant has also been reported in unaffected parents [Wagner et al 1994, Cameron et al 1996, Gentilin et al 2010].

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

- If a parent of the proband is heterozygous for a *SOX9* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *SOX9* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 2%-5% because of the possibility of parental mosaicism [Wagner et al 1994, Cameron et al 1996, Smyk et al 2007, Gentilin et al 2010, Higeta et al 2018].
- If a proband has a chromosome rearrangement, the recurrence risk to sibs depends on the chromosome findings in the parents:
    - If neither parent has a chromosome rearrangement, the risk to sibs is negligible.
    - If a parent has a balanced chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement and the possibility of other variables.

Offspring of a proband. Many individuals with CD do not survive infancy; some, however, have reproduced.

- Each child of an individual with a non-mosaic *SOX9* pathogenic variant has a 50% chance of inheriting the pathogenic variant.
- The risk to offspring of an individual with a chromosome rearrangement involving *SOX9* depends on the cytogenetic abnormality.

Other family members. The risk to other family members depends on the status of the proband's parents:

- Because CD typically occurs as a *de novo SOX9* pathogenic variant, risk to other family members is presumed to be low.
- If a parent has a balanced chromosome rearrangement, the parent's family members are at risk and can be offered chromosome analysis.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

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

A priori high-risk pregnancies

- Once a *SOX9* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.
- Similarly, prenatal testing for a pregnancy at increased risk for a familial chromosome rearrangement is possible by chromosome analysis of fetal cells obtained by amniocentesis or chorionic villus sampling.

A priori low-risk pregnancies. Routine prenatal ultrasound examination may identify skeletal findings (e.g., increased nuchal translucency, micrognathia, short bowed limbs, and hypoplastic scapulae) that raise the possibility of CD in a fetus not known to be at increased risk [Schramm et al 2009, Gentilin et al 2010]. Once a skeletal dysplasia is identified prenatally, it is often difficult to establish the diagnosis based on ultrasound findings alone. Consideration of molecular genetic testing for a *SOX9* pathogenic variant in these situations is appropriate; multigene panel testing or exome sequencing may be more efficient in the setting of nonspecific ultrasound signs such as bowed limbs or midface hypoplasia.

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.

- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **Human Growth Foundation**
  www.hgfound.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **Skeletal Dysplasia Group Freiburg**
  University Hospital Freiberg, Centre for Pediatrics and Adolescent Medicine
  Mathildenstrasse 1
  Freiburg 79106
  Germany

Phone: 001-497-6127 0-4363
Email: violetta.volz@uniklinik-freiburg.de

- **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. Campomelic Dysplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SOX9	17q24.3	Transcription factor SOX-9	SOX9 database	SOX9	SOX9

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 Campomelic Dysplasia (View All in OMIM)

114290	CAMPOMELIC DYSPLASIA; CMPD
608160	SRY-BOX 9; SOX9

Molecular Pathogenesis

Pathogenic variants within the *SOX9* coding region lead to an altered SOX9 protein with impaired activity to function as a transcription factor. In contrast, chromosome rearrangements (translocations, inversions) with breakpoints as far as ~1 Mb upstream of *SOX9* as well as *SOX9* upstream deletions leave the *SOX9* coding region intact but most likely lead to reduced expression of *SOX9* by interrupting its extended *cis*-regulatory domain. In either case, SOX9 function as a developmental regulator is compromised.

SOX9 is a proven key regulator at various steps of chondrocyte differentiation, regulating expression of the collagen genes *COL2A1* and *COL11A2* as well as of *CD-RAP* and *ACAN* (also known as *AGGRECAN*) [Akiyama & Lefebvre 2011].

- Regulation of *COL2A1* by *SOX9* may explain some of the phenotypic overlap of campomelic dysplasia (CD) with spondyloepiphyseal dysplasia congenita.
- *SOX9* functions as a testis-determining gene downstream of *SRY*, inducing the formation of Sertoli cells and production of the anti-müllerian hormone AMH (also known as MIS) [Vidal et al 2001]. Of note, duplication or deletion of a common region ~0.5 Mb upstream of *SOX9* causing isolated disorders of sexual development in the absence of any CD symptoms have been reported [Benko et al 2011, Cox et al 2011, Vetro et al 2011].
- Studies in mice provide evidence that the murine ortholog of human *SOX9* also plays a role during formation of the pancreas, heart, gut, and inner ear.

Thus, the wide spectrum of pathologic symptoms seen in CD, including the skeletal defects, XY sex reversal, pancreatic defects (size reduction of islets of Langerhans and reduced insulin secretion), heart defects, and sensorineural and conductive hearing impairment, can be attributed directly to impaired ability of the pleiotropic developmental regulator SOX9 to activate target genes during organogenesis.

Mechanism of disease causation. Pathogenic nonsense and most frameshift variants in *SOX9* predict a prematurely truncated protein resulting in loss-of-function alleles. *SOX9* pathogenic variants that result in a mutated protein retaining the HMG domain (a DNA-binding domain) may function as dominant-negative alleles.

Chapter Notes

Author Notes

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Revision History

- 6 April 2023 (sw) Revision: "*SOX9*-Related Campomelic Dysplasia" added as a synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature
- 18 March 2021 (sw) Comprehensive update posted live
- 9 May 2013 (me) Comprehensive update posted live
- 31 July 2008 (cg) Review posted live
- 14 May 2008 (su) Original submission

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