GENEReviews

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Campomelic Dysplasia

[*Campomelic Dwarfism, Campomelic Syndrome, Camptomelic Dwarfism, Camptomelic Dysplasia. Includes: Acampomelic Campomelic Dysplasia*]

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Summary

Disease 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 club feet. 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 problems 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. Molecular genetic testing of *SOX9*, the only gene known to be associated with CD, is available in clinical laboratories and detects mutations or chromosome rearrangements in approximately 95% of affected individuals.

Management. *Treatment of manifestations:* care of children with cleft palate by a craniofacial team using routine measures; care of club feet and hip subluxation using standard protocols; surgery as needed for cervical vertebral instability and progressive cervico-thoracic kyphoscoliosis that compromises lung function. In persons with a 46,XY karyotype and undermasculinization of the genitalia, the gonads should be removed because of the increased

risk of gonadoblastoma. Hearing aids for those with hearing impairment. *Surveillance:* annual monitoring of growth and spinal curvature.

Genetic counseling. CD is inherited in an autosomal dominant manner. To date, most probands have CD as the result of a *de novo* mutation in *SOX;* 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 diagnosis for pregnancies at increased risk is possible if the disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

The diagnosis of campomelic dysplasia (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.

Clinical features

- Relatively large head
- Pierre Robin sequence with cleft palate
- Flat face
- 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)
- Club feet

Note: Bowing of the limbs, the feature that gave the disorder its name, is not an obligatory finding. When the limbs are not bowed, the term "acampomelic campomelic dysplasia" is used.

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)
- 11 pairs of ribs
- Scoliosis or kyphoscoliosis
- Vertically oriented narrow iliac wings
- Bowed femora and/or tibiae (occasionally upper limb) (Figure 3)

Testing

Cytogenetic testing. In approximately 5% of individuals with CD, routine karyotype analysis may identify one of the following:

- A *de novo* reciprocal translocation with one breakpoint in chromosome region 17q24.3-q25.1 where *SOX9* is located
- A *de novo* interstitial deletion of 17q

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

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *SOX9* is the only gene currently known to be associated with CD [Meyer et al 1997, Pfeifer et al 1999, Leipoldt et al 2007].

Clinical testing

- **Sequence analysis**. Sequence analysis of the coding regions of the three-exon *SOX9* gene and of its exon/intron boundaries identifies mutations in approximately 90% of individuals with the clinical diagnosis of CD.
- **Deletion analysis**. Deletion analysis by a variety of methods such as quantitative PCR, real-time PCR, or multiplex ligation-dependent probe amplification (MLPA) of amplicons for all three exons of *SOX9* detects partial and whole-gene *SOX9* deletions in approximately 5% of individuals with CD and a normal karyotype [Leipoldt et al 2007; G Scherer, unpublished].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Campomelic Dysplasia

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method[1]	Test Availability
SOX9	Sequence analysis	Coding regions and splice mutations	~90%	Clinical Testing
	Deletion analysis	Partial or whole-gene deletions [2]	~5%	

1. Percent of disease alleles detected in individuals with typical clinical and radiologic features of CD and with a normal karyotype
2. Depending on the method employed by the laboratory, the extent of the deletion can be more or less precisely defined.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband

- Clinical and radiologic features can strongly suggest the diagnosis of CD.
- In probands with a clinical diagnosis of CD, molecular genetic testing allows a precise diagnosis in the great majority of cases.

- It is appropriate to initiate karyotype and sequence analysis at the time of clinical and radiographic diagnosis, followed by deletion testing if the first two analyses are negative.

Prenatal diagnosis. Prenatal diagnosis for pregnancies at risk as a result of a mildly affected parent or potential somatic or germline mosaicism requires prior identification of the disease-causing mutation in a previously affected child or the mildly affected parent.

Genetically Related (Allelic) Disorders

Isolated 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].

Ischio-pubic-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, mutations of *SOX9* or cytogenetic alterations in the vicinity of *SOX9* have been reported [Mansour et al 2002].

Clinical Description

Natural History

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 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, such as Stickler syndrome, with marked micrognathia. 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 obligate.

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 make generalizations about the natural history. The following have been observed:

- Intellectual abilities are 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.
- 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].

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 (ACD), d*e novo* translocations or inversions with breakpoints upstream of *SOX9* are more likely to be seen than mutations in the *SOX9* coding region [Pfeifer et al 1999, Leipoldt et al 2007]. 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 the two individuals with the most 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* and/or of its 5′ flanking gene *KCNJ2* has been implicated in an individual with isolated Pierre Robin sequence and a translocation breakpoint 1.13 Mb upstream of *SOX9* and 800 kb downstream of *KCNJ2* [Jakobsen et al 2007].
- **Acampomelic campomelic dysplasia (ACD)**. Mild campomelia and ACD are over-represented 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 *SOX9* coding region mutations have ACD. Notably, these are mostly missense mutations; of 20 individuals with ACD with mutations in the *SOX9* coding region, 16 had missense mutations in the DNA-binding domain [Thong et al 2000; Moog et al 2001; G. Scherer, unpublished]. Furthermore, the single missense mutation not located in this domain was located in the *SOX9* dimerization domain in an individual with ACD [Bernard et al 2003, Sock et al 2003]. 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* or a *SOX9* missense mutation.

Penetrance

SOX9 coding region mutations 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.”

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).

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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

In the prenatal period, the most common error is to confuse osteogenesis imperfecta (OI) types 2 or 3 with campomelic dysplasia (CD). As OI is more common than CD, it is a more frequent cause of bowed limbs on antenatal ultrasound examination.

Other genetic disorders of the skeleton with prenatal limb bowing to consider include hypophosphatasia, cartilage hair hypoplasia, and even thanatophoric dysplasia.

After birth, the differential diagnosis is mainly spondyloepiphyseal dysplasia congenita (SEDC; *COL2A1* mutations) because of the facial features, cleft palate, and short limbs. Radiographs distinguish between the two conditions.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with campomelic dysplasia (CD), the following investigations are recommended:

- Karyotype analysis to identify abnormalities involving the *SOX9* locus on 17q24.3-q25.1 and especially in phenotypic females to identify those with a 46,XY karyotype
- Full skeletal survey including views of the cervical spine to identify cervical vertebral abnormalities
- Hearing screening

Treatment of Manifestations

In children with CD and cleft palate, care by a craniofacial team and surgical closure are recommended.

In individuals with a 46,XY karyotype and female genitalia, gonadectomy is recommended because of the increased risk of gonadoblastoma. (No data regarding the appropriate age for this procedure are available.)

Most survivors with CD require orthopedic care. Club feet require surgical correction. The hips should be checked for luxation.

Cervical fusion surgery is sometimes needed for cervical vertebral instability resulting from vertebral malformations.

Surgery is often required in childhood for progressive cervico-thoracic kyphoscoliosis that compromises lung function [Thomas et al 1997]. Bracing is usually not helpful.

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

Most long-term survivors require annual monitoring of growth and spinal curvature by clinical and radiographic measurements.

Testing 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 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Campomelic dysplasia (CD) is inherited in an autosomal dominant manner but is most commonly the result of a *de novo* dominant mutation. Rarely, CD is the result of a chromosome rearrangement (e.g., deletion, *de novo* translocation, or inversion) upstream to or involving *SOX9*.

Risk To Family Members

Parents of a proband

- To date, most probands with CD have the disorder as the result of a *de novo* mutation; thus, parents of probands 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].
- Parents of a proband with a chromosome translocation or deletion are at risk of having the chromosome rearrangement themselves and should be offered chromosome analysis. Familial translocations have been reported but are rare. One family has been reported with somatic mosaicism for a small deletion encompassing *SOX9*; this seems to be a very rare occurrence [Smyk et al 2007].

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a non-mosaic parent of the proband is affected, the risk to the sibs is 50%.
- Somatic mosaicism for the *SOX9* mutation in an unaffected mother [Wagner et al 1994] and for a *SOX9* deletion in a mildly/minimally affected father of two affected children has been reported [Smyk et al 2007]. An unaffected father of three affected children had germline, but not somatic, mosaicism [Cameron et al 1996].
- Because parental mosaicism has been documented, the sibs of a proband are at an estimated 2%-5% risk even if the disease-causing mutation found in the proband cannot be detected in the DNA of either parent.
- The risk to sibs of a proband with an unbalanced chromosome constitution 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. The risks to offspring of a proband:

- **Offspring with a non-mosaic *SOX9* mutation**. 50%
- **Offspring with a chromosome rearrangement involving *SOX9*.** Depends on the cytogenetic abnormality

Other family members of a proband. Because CD typically occurs as a *de novo* mutation, other family members of a proband are not at increased risk. If a parent is found to have a balanced chromosome rearrangement, his or her 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methods and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

A priori high-risk pregnancies. Prenatal diagnosis for pregnancies at increased risk as a result of parental mosaicism or the presence of a *SOX9* mutation in a parent is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis at approximately 16-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to12 weeks' gestation. The disease-causing allele of an affected family member should be identified before prenatal testing can be performed.

Similarly, prenatal diagnosis for pregnancies at increased risk for a familial chromosome rearrangement is possible by chromosome analysis of fetal cells obtained by amniocentesis or CVS.

A priori low-risk pregnancies. Routine prenatal ultrasound examination may identify skeletal findings such as 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. 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* mutation in these situations is appropriate only when specific features of CD have been identified; however, such testing is usually best deferred until after pregnancy termination or delivery when a diagnosis can be confirmed by radiographs.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation or familial chromosome rearrangement has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Campomelic Dysplasia

Gene Symbol	Chromosomal Locus	Protein Name
SOX9	17q24.3-q25.1	Transcription factor SOX-9

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Campomelic Dysplasia

114290	CAMPOMELIC DYSPLASIA
608160	SRY-BOX 9; SOX9

Table C. Genomic Databases for Campomelic Dysplasia

Gene Symbol	Entrez Gene	HGMD
SOX9	6662 (MIM No. 608160)	SOX9

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Mutations within the *SOX9* coding region lead to an altered SOX-9 protein with impaired activity to function as a transcription factor. In contrast, chromosomal rearrangements (translocations, inversions) with breakpoints as far as approximately 1 Mb upstream of *SOX9* 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, SOX-9 function as a developmental regulator is compromised.

SOX-9 is a proven key regulator at various steps of chondrocyte differentiation [Akiyama et al 2002]: regulation of expression of the collagen genes *COL2A1* and *COL11A2* as well as of *ACAN* (also known as *AGGRECAN*).

- 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].
- Studies in the mouse 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 SOX-9 to activate target genes during organogenesis.

Normal allelic variants: The coding sequence of the 5.4-kb *SOX9* gene is distributed over three exons separated by introns of 0.9 kb and 0.6 kb. There are no known normal allelic variants at the amino acid level. At the nucleotide level, one frequent synonymous variant within codon 169 leaves the encoded amino acid histidine unchanged (see Table 2).

Table 2. *SOX9* Allelic Variants Discussed in This *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change (Alias [1])	Reference Sequence
Normal	c.507C>T (879C>T)	p.(=) [2] (His169His)	NM_000346.3 NP_000337.1
Pathologic	c.1320C>A (1692C>A)	p.Tyr440X	
	c.1320C>G (1692C>G)	p.Tyr440X	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).
1. Variant designation that does not conform to current naming conventions. For *SOX9* these numbers correspond to the first base position of the reference sequence NM_000346.3.
2. The designation p.(=) means that protein has not been analyzed but no change is expected.

Pathologic allelic variants: Numerous pathogenic nonsense and frameshift mutations of *SOX9* are distributed over the entire coding region; there is no mutation hot spot with the exception of the recurrent nonsense mutation p.Tyr440X [Pop et al 2005]. Missense mutations cluster in the HMG domain (a DNA-binding domain) or in the dimerization domain and are occasionally recurrent. A few splice mutations and deletions of part of *SOX9* or the entire *SOX9* gene and of flanking genes have been described [Olney et al 1999; Pop et al 2004; Smyk et al 2007; G Scherer, unpublished]. Translocation and inversion breakpoints that interrupt the 1-Mb *cis*-regulatory domain upstream of *SOX9* are all unique but concentrate within a proximal and a distal breakpoint cluster [Leipoldt et al 2007]. Approximately 90% of the pathogenic mutations are found in the *SOX9* coding region and approximately 5% are *SOX9* deletions, translocations, or inversions upstream of *SOX9*.

Normal gene product: The SOX-9 protein consists of 509 amino acids and functions as a transcription factor. Like all SOX proteins, it contains a DNA-binding domain (the HMG

domain) encompassing 79 amino acids (residues 103-181) by which it binds to regulatory sites at target genes. The activation of these target genes is mediated by a C-terminal transactivation (TA) domain (residues 402-509) and an adjacent auxiliary TA domain (residues 339-379) [McDowall et al 1999]. A fourth functionally relevant domain is a dimerization domain, located N terminal to the HMG domain [Bernard et al 2003, Sock et al 2003].

Abnormal gene product: Nonsense and most frameshift mutations in *SOX9* predict a prematurely truncated protein that misses all or part of the TA domain and, when the mutation is located toward the N terminus, all or part of the HMG domain as well. Resultant mutant proteins missing both domains constitute loss-of-function alleles, whereas mutant proteins retaining the HMG domain may function as dominant-negative alleles. More C-terminally located frameshift mutations are predicted to encode an extended SOX-9 protein with a mutant C terminus in place of the TA domain. Missense mutations are exclusively located in the HMG domain, affecting the DNA-binding capacity of SOX-9 [Meyer et al 1997, McDowall et al 1999], or in the dimerization domain, causing loss of SOX-9 dimer formation [Bernard et al 2003, Sock et al 2003].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

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Revision History

- 31 July 2008 (cg) Review posted live

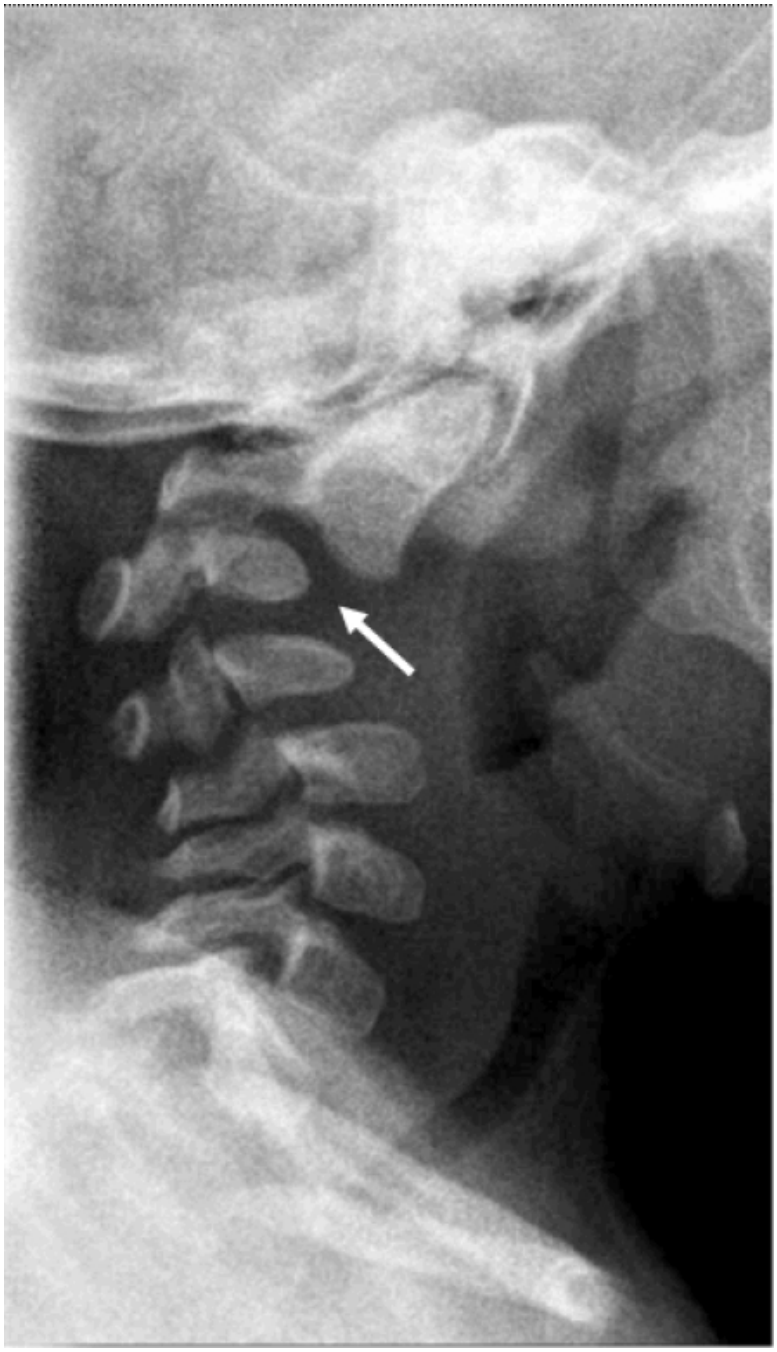

Figure 1. Cervical spine changes (i.e., abnormal AP curvature and anterior dislocation of C2 on C3) (arrow) in an 11-month-old boy with classic campomelic dysplasia

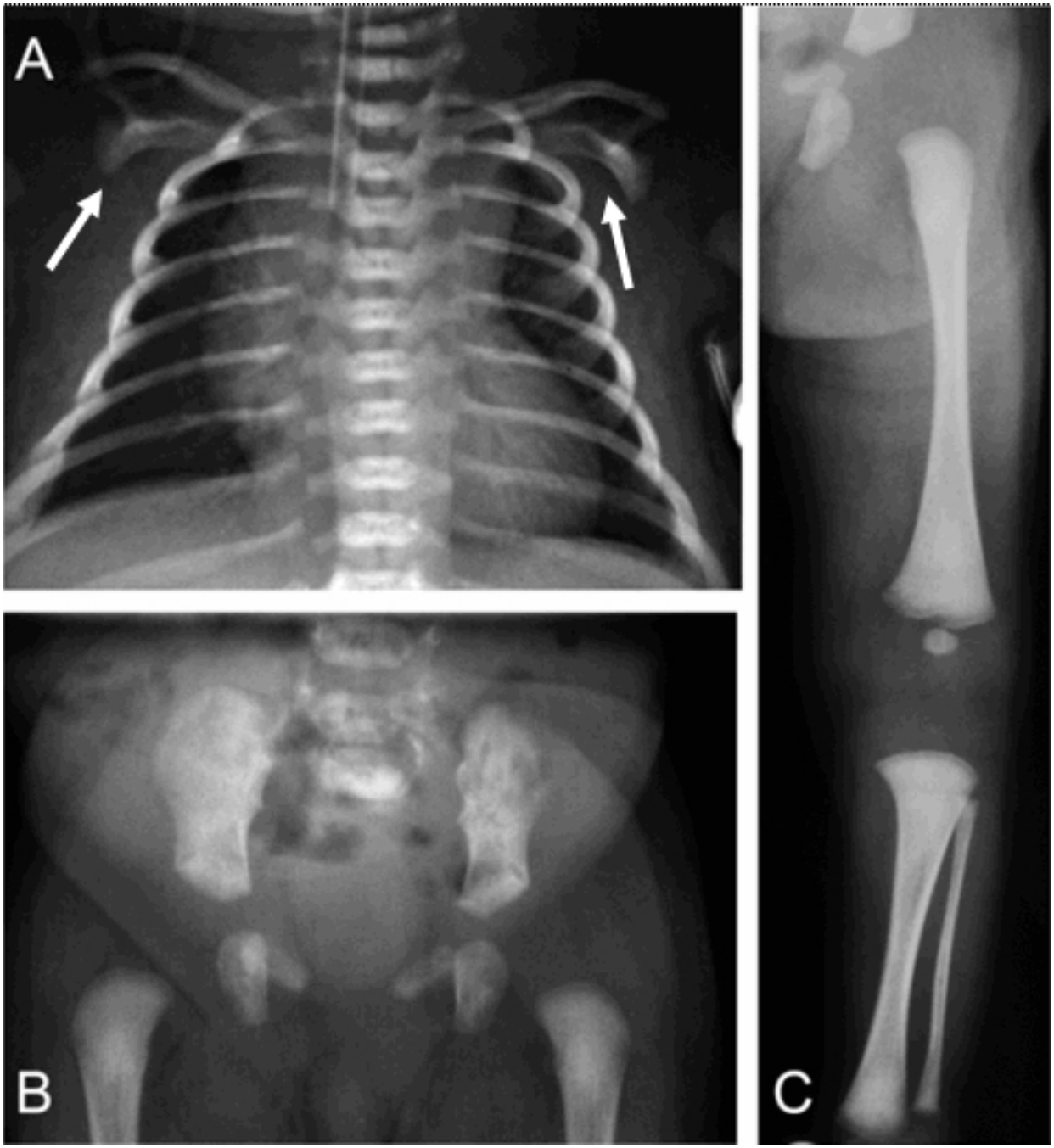

Figure 2. Mutation-proven "acampomelic" campomelic dysplasia
A. Tracheostomy tube is in place and the scapulae are markedly hypoplastic (arrows).
B. Vertically oriented narrow iliac wings
C. Straight femora and tibiae

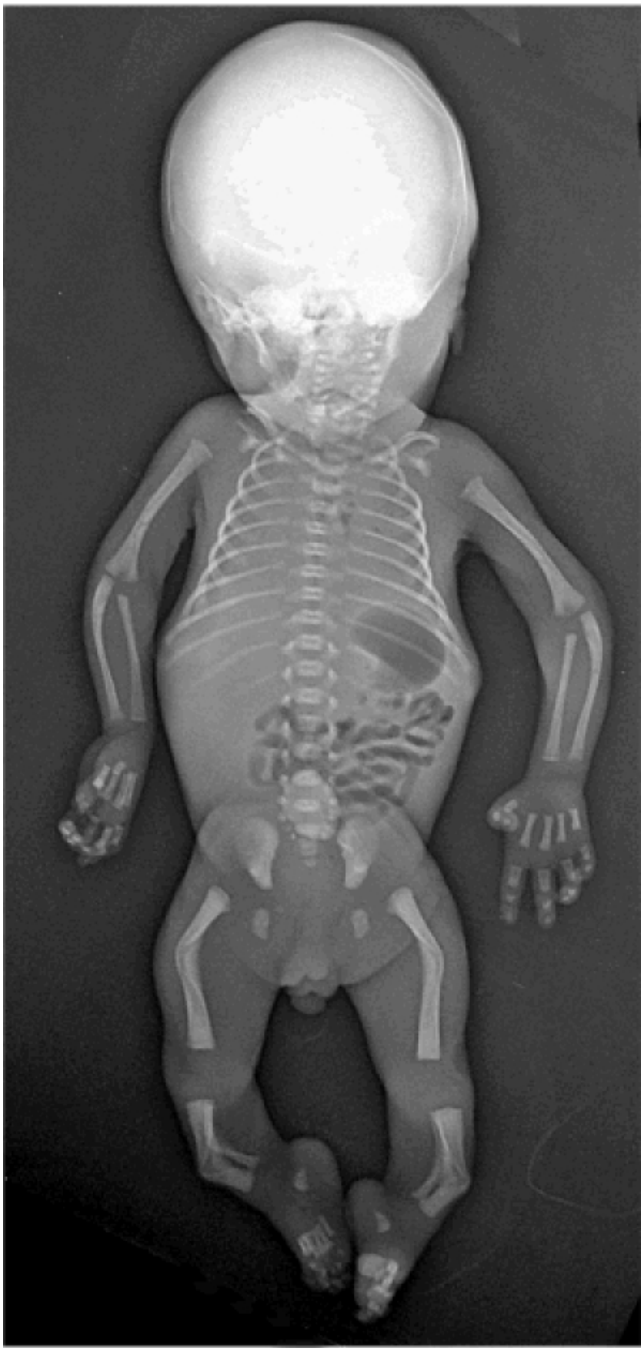

Figure 3. Classic radiographic features of campomelic dysplasia in a 24 week fetus. Note cervical spine abnormalities, scapular hypoplasia, narrow iliac wings, bowing of the femora and the tibiae, and club feet.