



## July: Question 5



- 1 January 09
- 2 February 09
- 3 March 09
- 4 April 09
- 5 May 09
- 6 June 09
- 7 July 09
- 8 August 09
- 9 September 09
- 10 October 09
- 11 November 09
- 12 December 09

A 23-year-old primigravida presents in labor at 37 weeks' gestation. She has had prenatal care, and her fetus has been diagnosed with a lethal skeletal dysplasia. Amniotic fluid volume is normal. There is no history of consanguinity. Both parents are of normal stature. After delivery, the infant develops severe respiratory failure. Physical examination reveals a female infant with symmetrical short limbs, marked bowing of long bones, and redundant skin folds. The head is disproportionately large with wide open fontanelles. Frontal bossing, depressed nasal bridge, and midfacial hypoplasia are also present. The trunk appears normal in length. The thorax is narrow, and the abdomen is markedly protuberant (Figure 1). A skeletal survey is obtained (Figures 2 through 5).

Figure 1



Figure 2



Figure 3

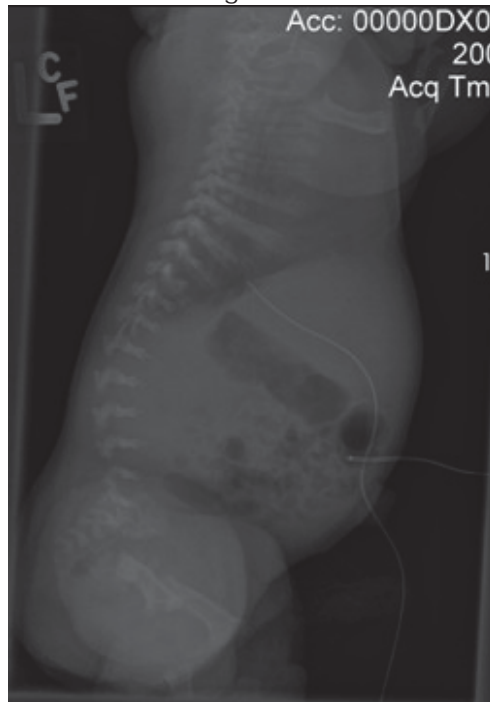


Figure 4

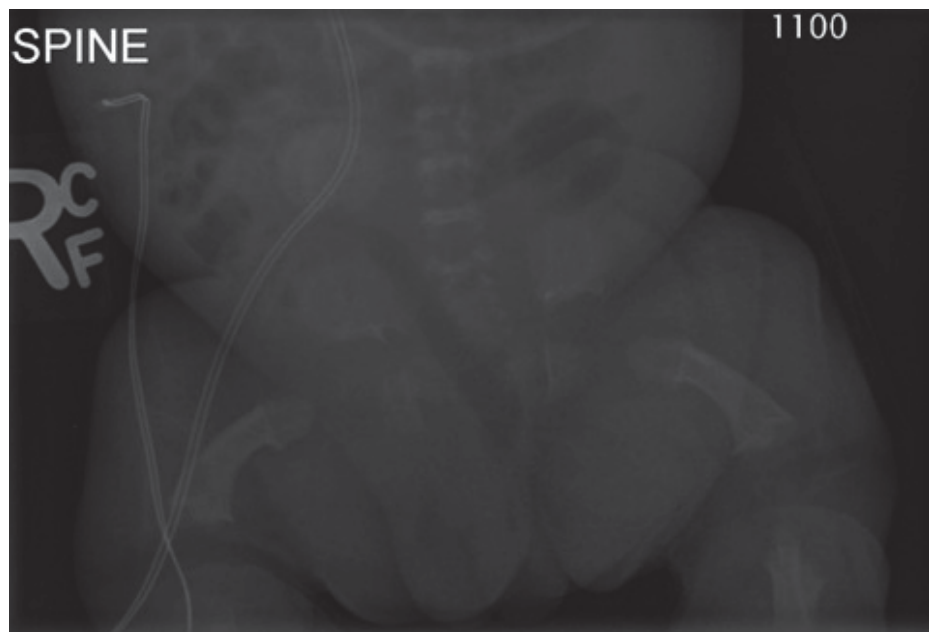
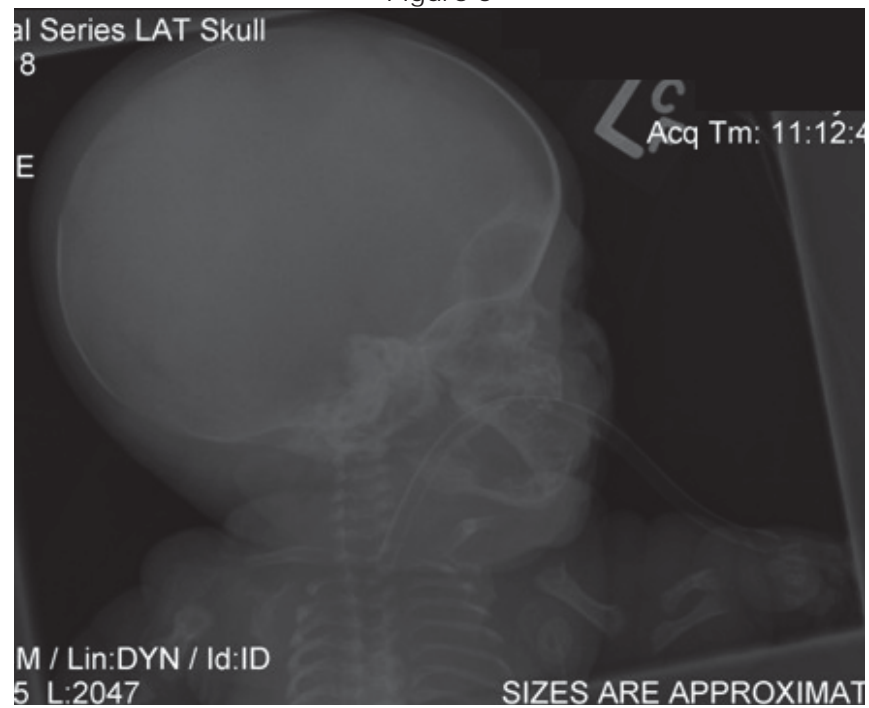


Figure 5



Of the following, the MOST likely diagnosis in this infant is:

- |                                  |   |                           |
|----------------------------------|---|---------------------------|
| <input type="radio"/>            | 1 | achondrogenesis           |
| <input type="radio"/>            | 2 | campomelic dysplasia      |
| <input checked="" type="radio"/> | 3 | chondrodysplasia punctata |
| <input type="radio"/>            | 4 | hypophosphatasia          |
| <input type="radio"/>            | 5 | thanatophoric dysplasia   |

You selected **3**, the correct answer is **5**.

**Do you want to add anything to your Learning Plan?**

*(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)*



The infant in this vignette has classic clinical and radiographic features of thanatophoric dysplasia (TD), the most common lethal skeletal dysplasia (Figures 2 through 5).

Figure 2: Classic radiologic features of thanatophoric dysplasia type I. Radiographs demonstrate thin flattened vertebrae (platyspondyly), short ribs, flaring ilia, extremely short long tubular bones, and markedly short and curved femora (telephone receiver-like appearance) and relatively normal looking skull.



Figure 3: Radiologic features of thanatophoric dysplasia type I

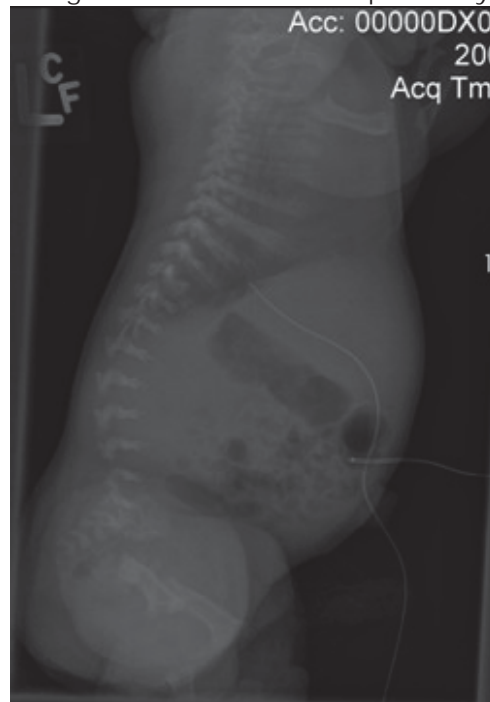


Figure 4: Thanatophoric dysplasia type I

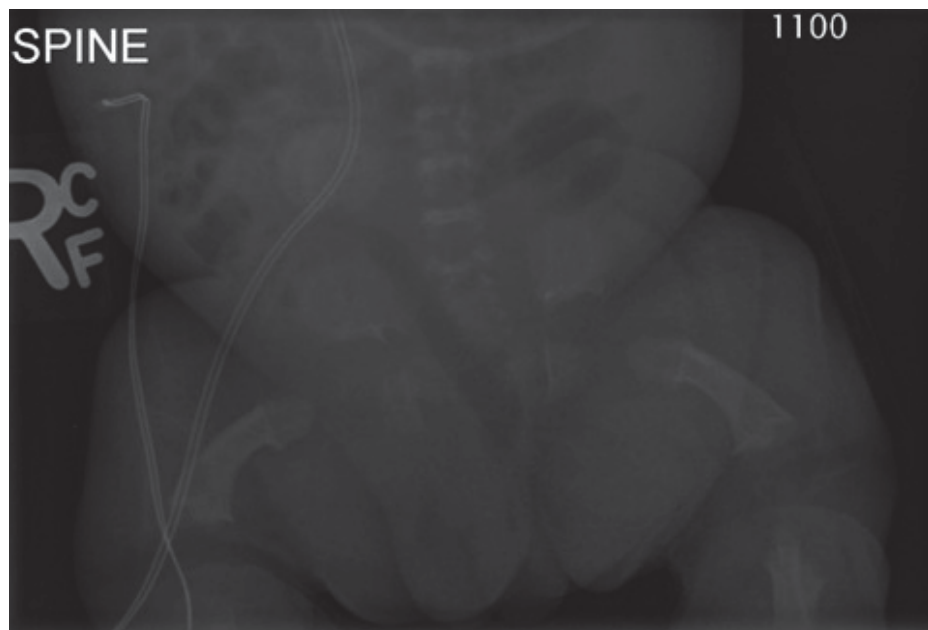
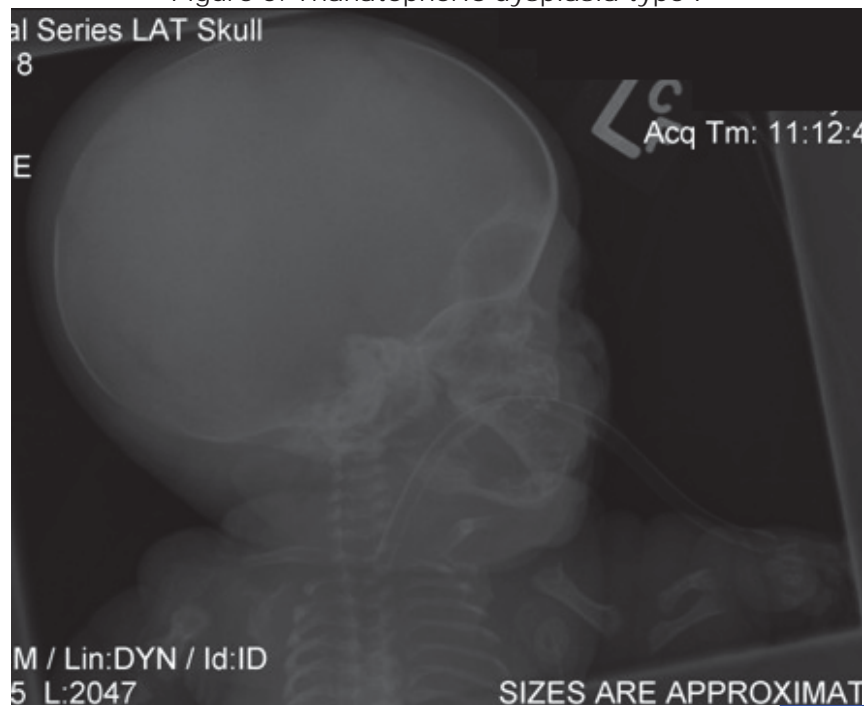


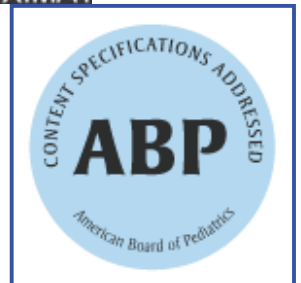
Figure 5: Thanatophoric dysplasia type I



Skeletal dysplasias are a heterogeneous group of disorders characterized by abnormalities of cartilage and bone growth, resulting in abnormal shape and size of the skeleton and disproportionate long bones, spine, and head. The overall incidence of skeletal dysplasias is approximately 1 in 4,000 to 5,000 births. The four most common skeletal dysplasias are thanatophoric dysplasia, achondroplasia, osteogenesis imperfecta, and achondrogenesis. Thanatophoric dysplasia and achondrogenesis account for 62% of all lethal skeletal dysplasias. Achondroplasia is the most common nonlethal skeletal dysplasia.

Among infants with skeletal dysplasias detected at birth, approximately 13% are stillborn and 44% die during the perinatal period. The overall frequency of skeletal dysplasias in infants who die in the perinatal period is 9.1 per 1,000 births.

Skeletal dysplasias can be classified based on morphologic, clinical, and radiographic criteria. This system takes into consideration the region of bone involved (epiphysis, metaphysis, or diaphysis), spinal involvement, and the relative proportion of limbs to trunk. Disproportionate short stature can result from a short limb or a short trunk. Short limbs can be further classified according to the location as rhizomelic (proximal), mesomelic (middle), or acromelic (distal) segment shortening. Descriptive terms are also used in relation to the appearance of the



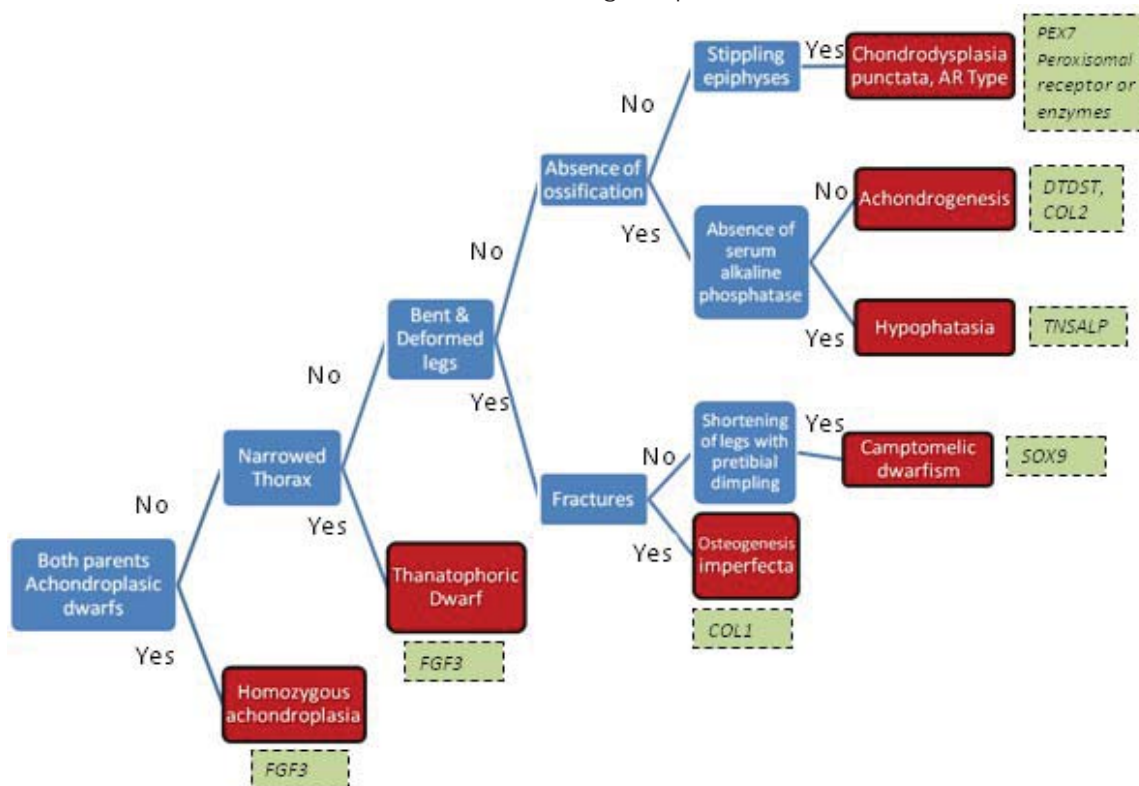
bones such as diastrophic (twisted), campomelic (curved or bent limb), metatropic (changing), or thanatophoric (death bringing).

The evaluation of patients with skeletal dysplasias includes a careful clinical examination, detailed radiographic examination, history (length at birth, growth curves, etc) and pedigree analysis, followed by anthropometric measurements with special emphasis on body proportions. Skeletal dysplasias that may manifest at birth can be classified as lethal or nonlethal (Table). An algorithm for the differential diagnosis of lethal skeletal dysplasias is presented in Figure 6.

Table: Lethal and Nonlethal Types of Skeletal Dysplasias

Lethal	Nonlethal
Thanatophoric dysplasia	Achondroplasia
Achondrogenesis	Asphyxiating thoracic dystrophy of DeJeune
Chondrodysplasi punctata	Chondrodysplasia punctata
Homozygous achondroplasia	Chondroectodermal dysplasia
Hypophosphatasia	Diastrophic dwarfism
Osteogenesis imperfecta type II	Hypochondroplasia
Campomelic dysplasia	Hypophosphatasia tarda
	Mesomelic dwarfism
	Metatropic dwarfism
	Spondyloepiphyseal dysplasia congenita

Figure 6: Algorithm for lethal types of neonatal dwarfism (adapted from Clark [1990]). Blue boxes indicate clinical/laboratory characteristic; red boxes, skeletal dysplasia; and green boxes, abnormal gene product.



Thanatophoric dysplasia is divided into type I, characterized by micromelia with bowed femurs (“telephone receiver” femurs); and type II, characterized by micromelia with straight femurs and uniform presence of moderate-to-severe cloverleaf skull deformity (kleeblattschaedel) (Figure 7). Other features common to type I and type II include short ribs, narrow thorax, macrocephaly, frontal bossing, depressed nasal bridge, midfacial hypoplasia, proptotic eyes, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die shortly after birth.

Figure 7: Cloverleaf skull deformity (kleeblattschaedel) in thanatophoric dysplasia type II



Prenatal diagnosis is possible with ultrasonographic examination and molecular genetic testing. Shortening of the long bones may be visible as early as 12 to 14 weeks' gestation. Several other skeletal disorders may give rise to prenatal ultrasonographic findings similar to those of TD. Therefore, the diagnosis of TD is based on postnatal physical examination, radiographic studies, and genetic testing. **FGFR3** is the only gene associated with TD. Up to 99% of mutations causing TD type I and more than 99% of mutations causing TD type II can be identified through molecular genetic testing of **FGFR3**, which is available on a clinical basis.

Achondrogenesis is a lethal skeletal dysplasia characterized by severe micromelia, macrocephaly, narrow thorax, protuberant abdomen, short trunk, and pseudohydrops. The hydropic fetal appearance is caused by the abundance of soft tissue relative to the short skeleton.

Infants with achondrogenesis are frequently born preterm. Death occurs prenatally or shortly after birth. Two types are recognized.

- Achondrogenesis type I (autosomal recessive): Characterized by poor mineralization of both the skull and vertebral bodies as well as rib fractures.
- Achondrogenesis type II (sporadic, new autosomal dominant mutations): Characterized by hypomineralization of the vertebral bodies but normal mineralization of the skull, and absence of rib fractures.

Campomelic dysplasia (CD) is a skeletal dysplasia characterized by cleft palate with Pierre Robin sequence, shortening and bowing of long bones, pretibial skin dimples, and club feet (Figure 8). Other findings include laryngotracheomalacia with respiratory compromise and ambiguous genitalia or normal female external genitalia in most individuals with a 46,XY karyotype. 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.

Figure 8: Radiographs showing bowing of the long bones in campomelic dysplasia



Chondrodysplasia punctata, also known as rhizomelic chondrodysplasia punctata type 1 (RCDP1), an autosomal recessive inheritance, is a peroxisome biogenesis disorder (PBD) characterized by proximal shortening of the humerus and to a lesser degree of the femur (rhizomelia), enlarged joints, contractures, punctate calcifications in cartilage with epiphyseal and metaphyseal abnormalities, coronal clefts of the vertebral bodies, and cataracts that are usually present at birth or appear in the first few months after birth (Figure 9). The diagnosis of RCDP1 is based on clinical findings and confirmed with clinically available biochemical or molecular genetic tests. Biochemical tests of peroxisome function include red blood cell concentration of plasmalogens, plasma concentration of phytanic acid, and plasma concentration of very-long-chain fatty acids. **PEX7**, which encodes the receptor for a subset of peroxisomal matrix enzymes, is the only gene known to be associated with RCDP1.

Figure 9: Punctate calcifications in the epiphyses at the knee joint in chondrodysplasia punctata





Hypophosphatasia is characterized by defective bone mineralization and a deficiency of tissue nonspecific alkaline phosphatase activity because of mutations in the liver/bone/kidney alkaline phosphatase gene. Clinical expression ranges from stillbirth without mineralized bone to pathological fractures developing late in adulthood. Six clinical forms are currently recognized, depending on the age at diagnosis and the severity of the symptoms: perinatal lethal; infantile; childhood; adult; odontohypophosphatasia; and, more recently described, perinatal benign. In the perinatal lethal form of hypophosphatasia, patients show markedly impaired mineralization in utero. They have skin-covered osteochondral spurs protruding from the forearms or legs that are often diagnostic for hypophosphatasia. In the perinatal benign form of hypophosphatasia, despite prenatal symptoms, skeletal defects spontaneously improve. The patients manifest limb shortening and bowing, and often have dimples overlying the long bone anomalies.

**Do you want to add anything to your Learning Plan?**

(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)



#### References:

Braverman N, Moser AB, Steinberg SJ. Rhizomelic chondrodysplasia punctata type 1. Accessed February 26, 2009, at: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=rcdp>

Chen H 2007 Skeletal dysplasia. eMedicine.com Web site. Accessed November 10, 2008, at: <http://www.emedicine.com/PED/topic625.htm>

Clark RN Congenital dysplasias and dwarfism. *Pediatr Rev.* 1990;12:149-159

Hurst JA, Firth HV, Smithson S. Skeletal dysplasias. *Semin Fetal Neonatal Med.* 2005;10:233-241

Karczeski B, Cutting GR. Thanatophoric dysplasia. Accessed November 10, 2008, at: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=td>

Mornet E. Hypophosphatasia. *Best Pract Res Clin Rheumatol.* 2008;22(1):113-127

Pilu G, Nicolaidis K, Ximenes R, Jeanty P. Skeleton: diagnosis of fetal abnormalities—the 18-23 weeks scan. Accessed November 10, 2008, at: <http://www.centrus.com.br/DiplomaFMF/>

[SeriesFMF/18-23-weeks/chapter-09/skeleton.html](#)

Unger S, Scherer G, Superti-Furga A. Campomelic dysplasia. Accessed January 21, 2009, at: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=campo-dysp>

American Board of Pediatrics Content Specification(s):

Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc

◀ PREVIOUS    NEXT ▶

## October: Question 6



- 1 January 09
- 2 February 09
- 3 March 09
- 4 April 09
- 5 May 09
- 6 June 09
- 7 July 09
- 8 August 09
- 9 September 09
- 10 October 09
- 11 November 09
- 12 December 09

A 4-day-old female infant, who weighed 3,410 g at birth at an estimated gestational age of 40 weeks, has an anterior chest wall abnormality (Figure 1).

Figure 1: Anterior chest wall abnormality. Note the sternal defect, the abdominal raphe connecting the defect and the umbilicus, and the surgical marker placed prior to surgery (arrow).

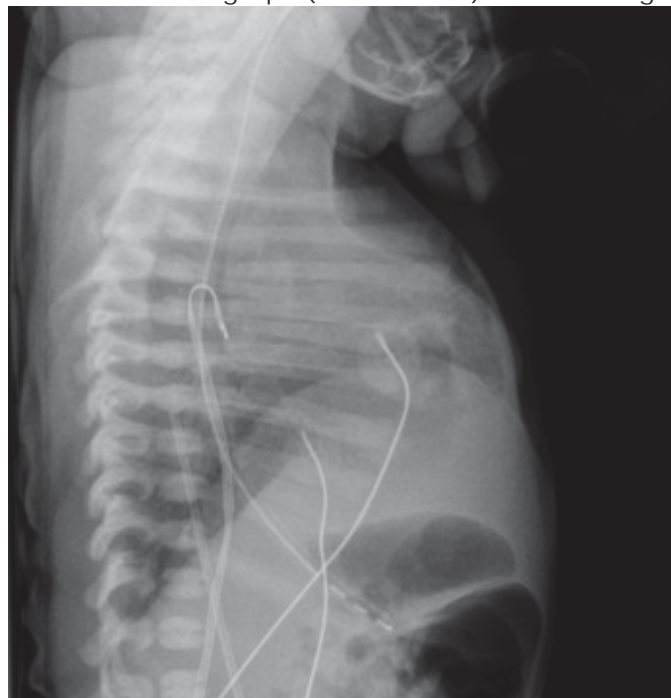


A pulsating heart covered with thin skin is visible through the thoracic midline defect. A midline abdominal raphe extends from the thoracic defect to the umbilicus (Figure 1). Chest radiographs (Figures 2 and 3) reveal superior mediastinal widening with an increased distance between the sternal ends of the clavicles, indicative of complete absence of the sternum.

Figure 2: Chest radiograph (anteroposterior view) of sternal agenesis



Figure 3: Chest radiograph (lateral view) of sternal agenesis



No other congenital anomalies or dysmorphic features are apparent. The infant is breathing spontaneously in room air without distress and is receiving full enteral feeds of breast milk by mouth. You review with the parents the type of the sternal defect and its implications for their infant.

Of the following, the MOST common sternal defect reported in cleft sternum is:

<input type="radio"/> 1	complete cleft
<input type="radio"/> 2	inferior cleft
<input type="radio"/> 3	minimal cleft with skin ulceration
<input checked="" type="radio"/> 4	superior partial U-shaped cleft
<input type="radio"/> 5	superior total V-shaped cleft

You selected **5**, the correct answer is **4**.

**Do you want to add anything to your Learning Plan?**

(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)



Cleft sternum, also called **bifid sternum**, is a congenital anomaly of the sternum typically characterized by the presence of a normally placed heart, normal skin coverage, an intact pericardium, and a sternal defect of variable degree and location. Normally, the sternum consists of three parts: the manubrium, the body, and the xiphoid process (<http://www.nlm.nih.gov/medlineplus/ency/imagepages/1740.htm>). The manubrium at each of its borders has the clavicular notch and the first costal notch for articulation with the clavicle and the first rib. The junction between the manubrium and the body has the second costal notch for articulation with the second rib. The body of the sternum at each of its borders has the costal notches three through seven for articulation with the remainder of the ribs. To understand the congenital anomalies of the sternum, it is important to review the development of the sternum during fetal life.

The sternum and pectoral muscles originate from the lateral plate mesoderm. The earliest embryologic evidence of the sternum can be found at 6 weeks of gestation, when the sternum is detected as two parallel lateral mesenchymal bands in the anterior thoracic wall. By 10 weeks of gestation, the sternal bands fuse craniocaudally in the midline to form the manubrium and the body of the sternum. At 20 to 24 weeks of gestation, the sternum begins to lay cartilage (chondrification), including the formation of the mostly cartilaginous xiphoid process, and then deposit bone (ossification). This ossification begins as a single center in the manubrium and proceeds in a cephalocaudal direction. In the body of the sternum, the ossification centers typically are observed in pairs. This process of ossification usually is complete within the first year after birth. Most isolated sternal defects result from a failure of the lateral mesenchymal bands to fuse during the eighth week of gestation.



Sternal defects are classified depending on their location and extent as superior, inferior, and complete. The most common sternal defect, seen in approximately 40% of cases of cleft sternum, is the superior partial U-shaped cleft that involves the manubrium and the upper half of the body of the sternum up to the level of the fourth costal notch. The second most common sternal defect (30% of cases) is the superior total V-shaped cleft that involves the manubrium and the whole body of the sternum extending to the xiphoid process. The third most common sternal defect (20% of cases) is the complete cleft, identified as absence or agenesis of the sternum, as in the infant in this vignette. The fourth most common sternal defect (8% of cases) is the inferior cleft that involves the xiphoid process and the lower half of the body of the sternum below the level of the fourth costal notch. The least common sternal defect (2% of cases) is the midline, barely perceptible cleft with a breach in the overlying skin.

Most superior sternal clefts are isolated abnormalities with no intrinsic cardiac or other defects. Often associated are abdominal raphes (bandlike scars) that extend from the inferior aspect of the sternal defect to the umbilicus, as seen in the infant in this vignette. Conversely, most inferior sternal clefts are often accompanied by other severe anomalies, notably ectopia cordis and the pentalogy of Cantrell. The latter consists of a midline supraumbilical abdominal wall defect, a defect of the lower sternum, a deficiency of the diaphragmatic pericardium, a deficiency of the anterior diaphragm, and intracardiac anomalies.

Although most cases of sternal clefts are sporadic in occurrence, an autosomal recessive familial association has been reported. Female infants outnumber male infants in most reported case series. Sternal clefts can be a part of the PHACES syndrome, a disorder included in the sternal malformation-vascular dysplasia spectrum. The PHACES syndrome is a term applied to the association of **p**osterior fossa brain malformations, **h**emangiomas (especially facial), **a**rterial anomalies in the cranial vasculature, **c**oarctation of the aorta/**c**ardiac defects, **e**ye abnormalities, and **s**ternal clefting.

The optimal time for surgical repair of the sternal defect is during the neonatal period, when the chest wall is most compliant for achieving complete closure. Corrective surgery often improves respiratory function, provides protection to the heart and great vessels, and improves physical appearance of the infant. The infant in this vignette underwent successful

primary closure of the sternal defect and has remained in a healthy condition.

[Do you want to add anything to your Learning Plan?](#)

(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)



References:

Jones KL. Sternal malformation-vascular dysplasia spectrum. In: **Smith's Recognizable Patterns of Human Malformation**. 6<sup>th</sup> ed. Philadelphia, Pa: Elsevier Saunders; 2006:746-747

Mazzie JP, Lepore J, Price AP, et al. Superior sternal cleft associated with PHACES syndrome. **J Ultrasound Med**. 2003;22:315-319

Shamberger RC. Congenital chest wall abnormalities. In: O'Neill JA, Rowe MI, Grosfeld JL, Fonkalsrud EW, Coran AG, eds. **Pediatric Surgery**. 5<sup>th</sup> ed. St. Louis, Mo: Mosby; 1998:787-817

American Board of Pediatrics Content Specification(s):

Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc

Recognize the clinical features of extrapulmonary causes of respiratory distress, including diaphragmatic hernia, diaphragmatic paralysis, and cord transection

Recognize the radiographic features of extrapulmonary causes of respiratory distress, including diaphragmatic hernia, diaphragmatic paralysis, and cord transection

[◀ PREVIOUS](#) [NEXT ▶](#)



## October: Question 2

- 1 January 09
- 2 February 09
- 3 March 09
- 4 April 09
- 5 May 09
- 6 June 09
- 7 July 09
- 8 August 09
- 9 September 09
- 10 October 09
- 11 November 09
- 12 December 09

A 23-year-old primigravida presents in labor at 37 weeks' gestation. She has had prenatal care and her fetus has been diagnosed with a lethal skeletal dysplasia. Amniotic fluid volume is normal. There is no history of consanguinity. Both parents are of normal stature. After delivery, the infant develops severe respiratory failure. Physical examination reveals a female infant with symmetrical short limbs, marked bowing of long bones, and redundant skin folds. The head is disproportionately large with wide open fontanelles. Frontal bossing, depressed nasal bridge, and midfacial hypoplasia are also present. The trunk appears normal in length. The thorax is narrow and the abdomen is markedly protuberant. A skeletal survey is obtained (Figures 1 through 4).

Figures 1 through 4: Radiograph demonstrating thin flattened vertebrae (platyspondyly), short ribs, flaring ilia, extremely short long tubular bones, and markedly short and curved femora (telephone receiver-like appearance) and relatively normal looking skull

Figure 1



Figure 2



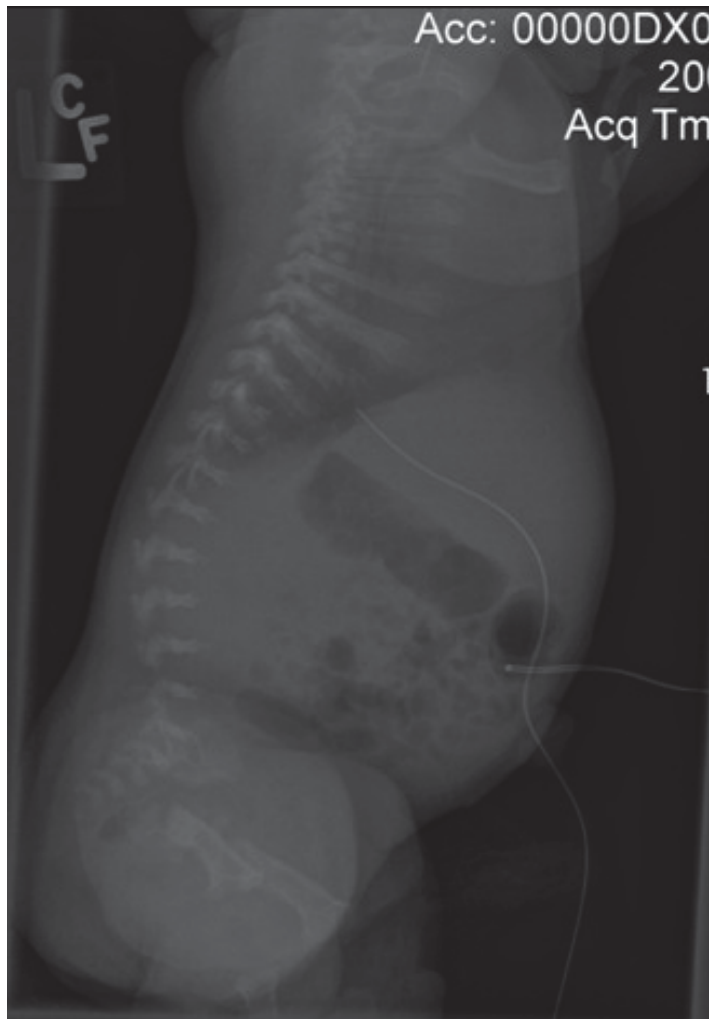


Figure 3

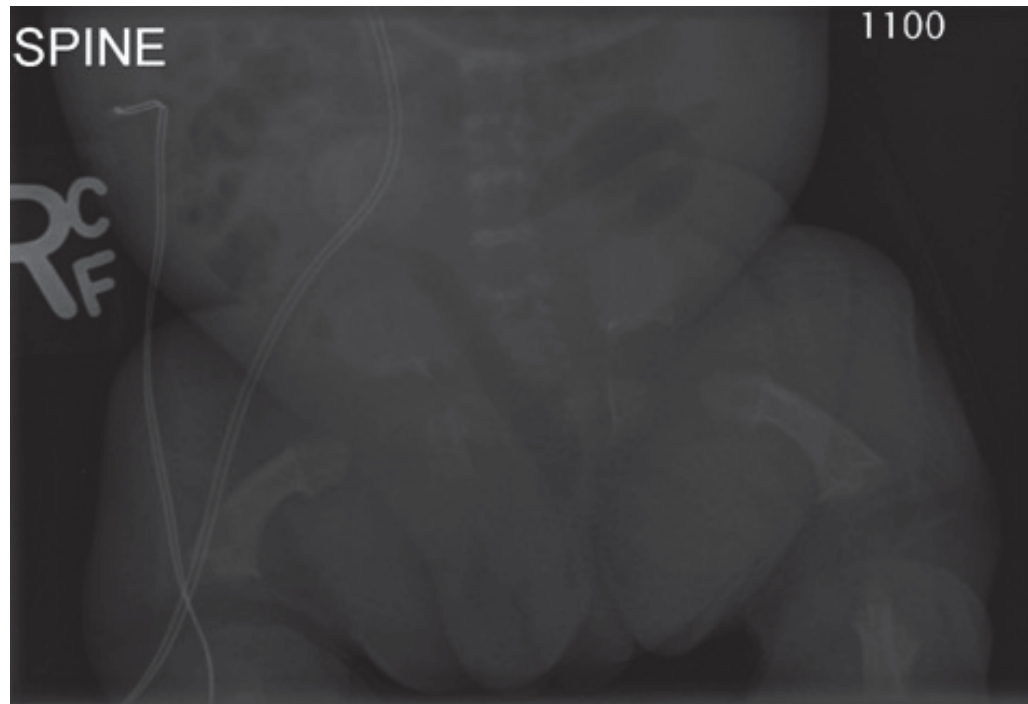
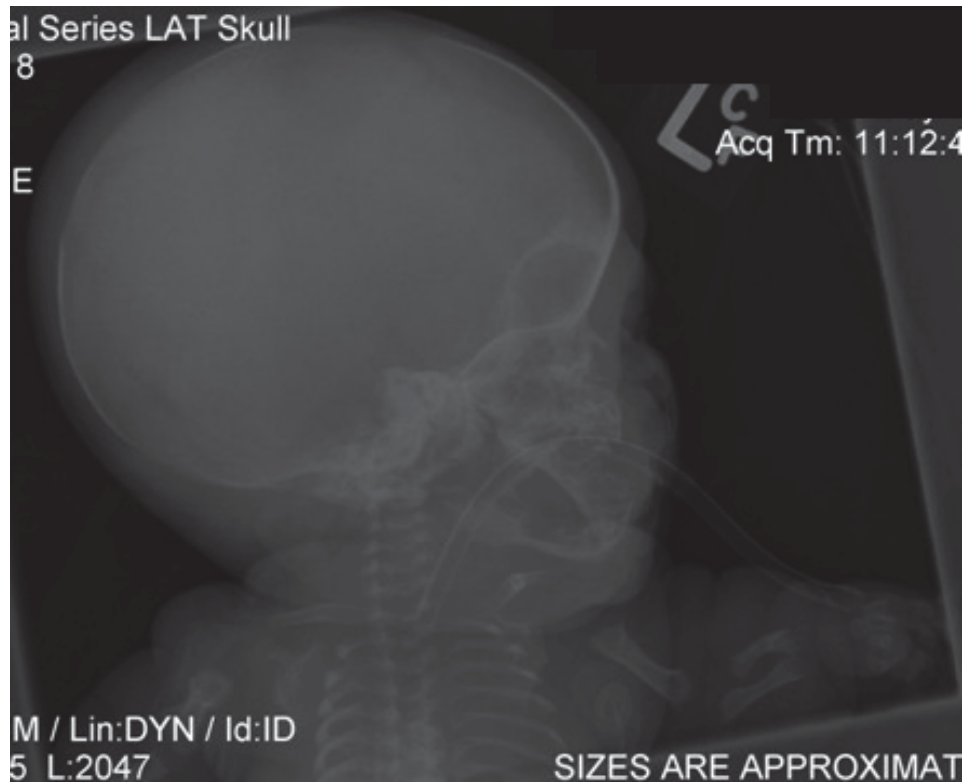


Figure 4



Of the following, the gene product MOST likely to be abnormal in this infant is:

<b>1</b>	alkaline phosphatase
<b>2</b>	fibroblast growth factor receptor
<b>3</b>	peroxisomal receptor
<b>4</b>	SOX9 DNA binding protein
 <b>5</b>	type I collagen

You selected **5**, the correct answer is **2**.

### Do you want to add anything to your Learning Plan?

(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)



The infant in this vignette has classic clinical and radiographic features of thanatophoric dysplasia (TD), the most common lethal skeletal dysplasia presenting in neonates. The genetic mutation associated with this disorder involves the fibroblast growth factor receptor 3 gene (**FGFR3**).

Skeletal dysplasias are a heterogeneous group of disorders characterized by abnormalities of cartilage and bone growth, resulting in abnormal shape and size of the skeleton and disproportion of the long bones, spine, and head. The overall incidence of skeletal dysplasias is approximately 1 per 4,000 to 5,000 births. The true incidence may be twice as high because many skeletal dysplasias present later during childhood. Lethal skeletal dysplasias are estimated to occur in 0.95 per 10,000 deliveries. The four most common skeletal dysplasias are TD, achondroplasia, osteogenesis imperfecta, and achondrogenesis. TD and achondrogenesis account for 62% of all lethal skeletal dysplasias. Achondroplasia is the most common nonlethal skeletal dysplasia. Among infants with skeletal dysplasias detected at birth, approximately 13% are stillborn, and 44% die during the perinatal period.



The evaluation of patients with skeletal dysplasias warrants a multidisciplinary approach involving clinical geneticists, radiologists, molecular biologists, and a host of surgical specialists. A careful clinical examination and detailed radiographic evaluation of the skeleton are the first steps toward an accurate diagnosis. A detailed history (length at birth, growth curves, etc) and pedigree analysis, followed by anthropometric measurements with special emphasis on body proportions are important. A skeletal survey is important and includes plain radiographs of the skull, spine, pelvis, one leg, and one arm. Skeletal dysplasias that manifest at birth can be classified as lethal or nonlethal.

Thanatophoric dysplasia is the most common short-limb dwarfism syndrome that is lethal in the perinatal period. TD is divided into type I, characterized by micromelia with bowed femurs ("telephone receiver" femurs); and type II, characterized by micromelia with straight femurs and uniform presence of moderate-to-severe cloverleaf skull deformity (*kleiblattschaedel*). Other features common to type I and type II include short ribs, narrow thorax, macrocephaly, frontal bossing, depressed nasal bridge, midfacial hypoplasia, proptotic eyes, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die soon after birth. Death is often secondary to pulmonary hypoplasia caused by the small thoracic cavity, or to foramen magnum stenosis and resultant failure of respiratory control. Rare long-term survivors have been reported.

Up to 99% of mutations causing TD type I and more than 99% of mutations causing TD type II can be identified through molecular genetic testing of **FGFR3**, the only gene known to cause TD. Mutations for TD type I have been described in **FGFR3** exons 7, 10, 15, and 19; and for TD type II

on **FGFR3** exon 15. The **FGFR3** mutation p.Lys650Glu has been identified in all individuals with TD type II. Targeted mutation analysis of **FGFR3** is available clinically. TD is inherited in an autosomal dominant manner; the majority of probands have a **de novo** mutation in **FGFR3**. Risk of recurrence for parents who have had one affected child is not significantly increased over that of the general population.

Thus the gene product most likely to be abnormal in the infant in this vignette with classic features of TD is fibroblast growth factor. Abnormalities in alkaline phosphatase, peroxisomal receptor, SOX9 DNA binding protein, and type I collagen are responsible for other less common lethal skeletal dysplasias. Mutations in the alkaline phosphatase gene cause perinatal lethal and infantile forms of hypophosphatasia. Abnormalities in genes that encode the peroxisomal biogenesis factors (PEX) are responsible for rhizomelic chondrodysplasia punctata and Zellweger syndrome. Mutations in the gene coding for the SRY-box 9 protein (**SOX9**) cause camptomelic dysplasia. Mutations in the procollagen I genes (**COL1A1**, **COL1A2**) cause various types of osteogenesis imperfecta.

The clinical, radiographic, laboratory, and genetic characteristics of other less common lethal skeletal dysplasias are summarized in the Table. An algorithm for the differential diagnosis of lethal skeletal dysplasias is presented in Figure 5.

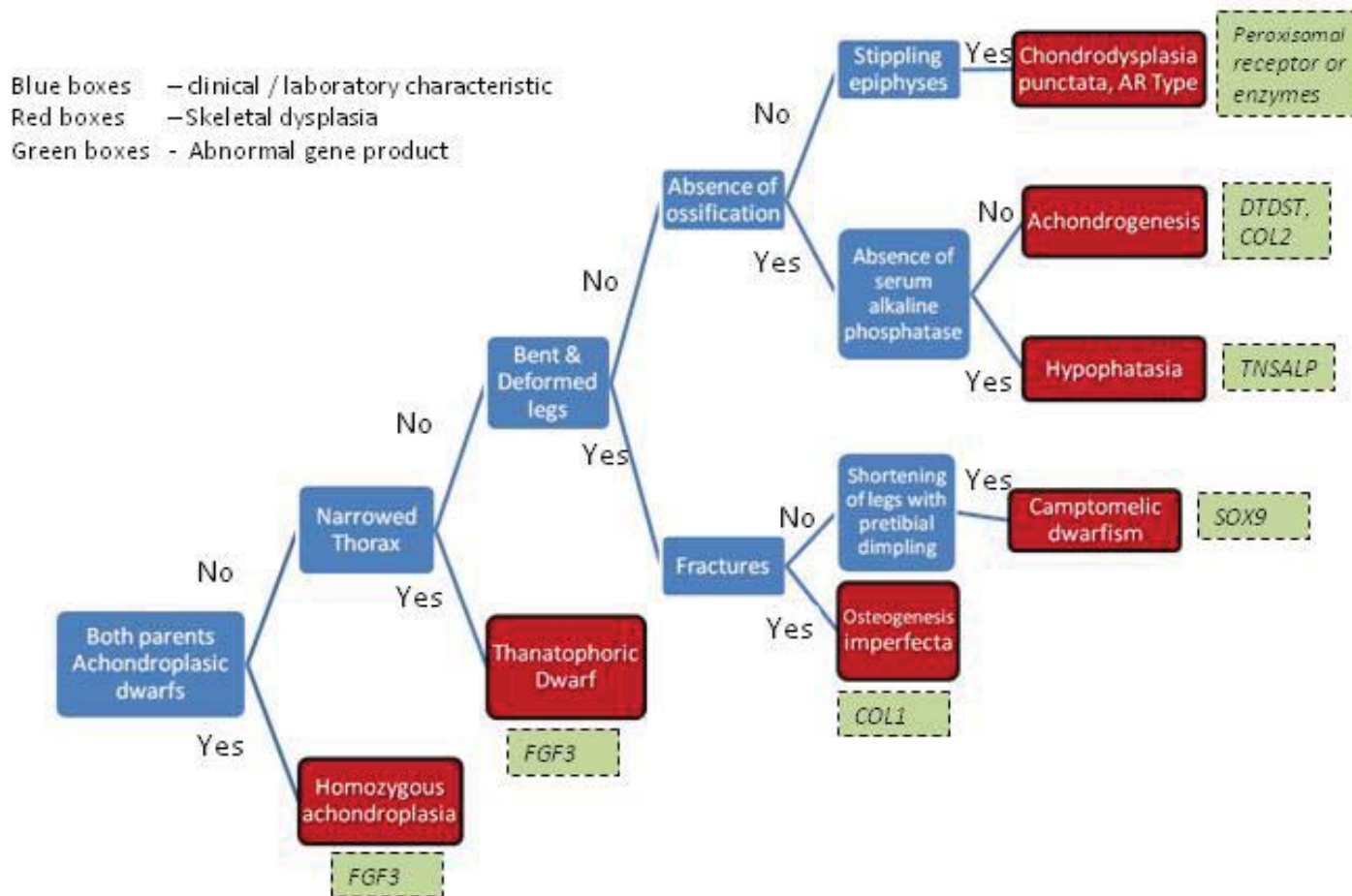
Table: Characteristics of Lethal Skeletal Dysplasias

Disorder	Major Clinical Manifestations	Laboratory/X-ray	Inheritance	Gene Product
Thanatophoric dysplasia type I	Short ribs, narrow thorax, macrocephaly, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs	Marked platyspondyly, short ilia, bowed femur with broad metaphyses	AD	FGFR3, fibroblast growth factor receptor 3
Thanatophoric dysplasia type II	Short ribs, narrow thorax, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs, macrocephaly, clover leaf skull anomaly	Platyspondyly, straight femur	AD	FGFR3, fibroblast growth factor receptor 3
Achondrogenesis type I	Flat nose, short limbs, hydrops, narrow thorax, short trunk, large head	Short tubular bones, poor mineralization of vertebral bodies and skull, rib fractures present	AR	DTDST/SLC26A2 (diastrophic dysplasia sulfate transporter)
Achondrogenesis type II	Flat nose, short limbs, hydrops, narrow thorax, short trunk, large head	Short tubular bones, hypomineralization of vertebrae, normal mineralization of skull, no rib fractures	AD	COL2A1 (Collagen 2 $\alpha$ 1 chain)
Camptomelic dwarfism	Shortening and bowing of the long bones of the legs, dimples over tibia, clubfeet, narrow chest, hypoplastic scapulae, large	Short bowed femur and tibia; narrowed ilia, hypoplastic scapulae	AD	SOX9 (HMG-type DNA binding protein/transcription factor)

	hypoplastic scapulae, large calvarium with disproportionately small face, flat nose, cleft palate, genetically male individuals may show a female phenotype			factor)
Chondrodysplasia punctata (AR)	Rhizomelic shortening of limbs, disproportionate short stature, enlarged joints, contractures	Epiphyseal stipplings on the proximal humerus, both ends of the femora, and lower spine	AR	PEX7 (peroxisomal receptor/importer) and other peroxisomal enzymes
Homozygous achondroplasia	Relatively normal-sized trunk, narrow thorax, large head, rhizomelic shortening of limbs, lumbar lordosis, and trident hands	Abnormal pelvis with small square iliac wings, horizontal acetabular roofs, and narrowing of the greater sciatic notch, an oval translucent area at the proximal ends of the femora, caudal narrowing of the interpedicular distances in the lumbar region, short pedicles, and lumbar lordosis	AD	FGFR3, fibroblast growth factor receptor 3
Severe hypophosphatasia	Severe shortening of the long bones, small thorax, hypomineralization of the skull and long bones	Very short underossified long bones with spikes; absence of liver and bone isoenzymes of alkaline phosphatase	AR, AD	TNSALP (Tissue non-specific alkaline phosphatase)
Osteogenesis imperfecta type II	Early prenatal onset of severe bone shortening	Multiple fractures affecting all long bones and ribs, poor mineralization of the skull	AD	COL1A1, COL1A2 (collagen 1 $\alpha$ 1, $\alpha$ 2 chains)

AD = autosomal dominant; AR = autosomal recessive.

Figure 5: Algorithm for lethal types of neonatal dwarfism (adapted from Clark [1990])



**Do you want to add anything to your Learning Plan?**

(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)



#### References:

Chen H 2007 Skeletal dysplasia. eMedicine.com Web site. Accessed November 10, 2008, at:

<http://www.emedicine.com/PED/topic625.htm>

Clark RN Congenital dysplasias and dwarfism. *Pediatr Rev.* 1990;12:149-159

Hurst JA, Firth HV, Smithson S. Skeletal dysplasias. *Semin Fetal Neonatal Med.* 2005;10:233-241

Karczeski B, Cutting GR 2008 Thanatophoric dysplasia. Accessed November 10, 2008, at: <http://>

[www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=td](http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=td)

Pilu G, Nicolaides K, Ximenes R, Jeanty P. Skeleton: diagnosis of fetal abnormalities—the 18-23 weeks scan. Accessed November 10, 2008, at: <http://www.centrus.com.br/DiplomaFMF/SeriesFMF/18-23-weeks/chapter-09/skeleton.html>

Rimoin DL, Cohn D, Krakow D, Wilcox W, Lachman RS, Alanay Y. The skeletal dysplasias: clinical-molecular correlations. *Ann N Y Acad Sci.* 2007;1117:302-309

Superti-Furga A, Bonafe L, Rimoin DL. Molecular-pathogenetic classification of genetic disorders of the skeleton. *Am J Med Genet.* 2001;106:282-293

American Board of Pediatrics Content Specification(s):

Know the clinical features and know how to manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodermal dysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc

[◀ PREVIOUS](#) [NEXT ▶](#)