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# Skeletal Dysplasias of the Human Fetus: Postmortem Diagnosis

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## 1. Introduction

Congenital skeletal disorders comprise a heterogeneous group of abnormalities of the bones related to their shape, growth and integrity. They are present at birth or become manifest during gestation causing abnormal development of the fetal skeleton that can be prenatally detected by ultrasonography. They make part of a large group of genetic skeletal disorders, formerly called constitutional disorders of bone. They all refer to abnormal skeletal development on the basis of a defective genetic background. Excluding chromosomal abnormalities affecting the skeleton, the large and heterogeneous family of genetic skeletal disorders comprise (1) disorders with significant skeletal involvement corresponding to the definition of skeletal dysplasias (alternatively called osteochondrodysplasias), (2) metabolic and molecular bone disorders, (3) dysostoses, (4) skeletal malformation and/or reduction syndromes and (5) multiple congenital malformation syndromes with a prominent skeletal involvement. . The genetic skeletal disorders, although individually rare, are not uncommon as a whole group. The latest 2010 Revision of the Nosology and Classification of Genetic Skeletal Disorders (Warman et al., 2011) includes 456 entities. Some 50 of them are perinatally lethal and can be diagnosed at birth (Nikkels, 2009), while some others, non lethal and compatible with short or long term survival, may present with abnormal phenotypic findings at birth or with abnormal ultrasonographic findings in utero and raise a prenatal diagnostic dilemma, as pertains to the possible lethality or morbidity of the affected fetus. With the advent of prenatal ultrasonographic examination, many of the affected fetuses are aborted at an early gestational age. A correct diagnosis and typing of the skeletal disorder is essential for the prognosis and genetic counselling of the family, as well as for the possibility of prenatal diagnosis in subsequent pregnancies. The molecular defects underlying the genetic skeletal disorders are increasingly being identified and have shed some light on the pathogenesis of these conditions. One important example is that of the fibroblast growth factor receptor (FGFR3) defects underlying skeletal dysplasias such as Thanatophoric dysplasia, Achondroplasia etc. Nevertheless, in only a restricted subgroup of fetal skeletal dysplasias is the molecular genetic analysis part of a routine prenatal control able to provide an accurate diagnosis. In most instances, the responsibility of the final diagnosis of a fetal skeletal dysplasia lies on the post-mortem examination and in many institutions it is largely or uniquely the task of the pathologist.

The objective of this chapter is to provide an overview on the role of the pathologist in the handling of the congenital skeletal disorders and enable the postmortem diagnostic

approach. The chapter will summarize the principal postnatal diagnostic features of the more common subgroups of fetal genetic skeletal disorders to be used as diagnostic tools by the fetal pathologist at autopsy.

## 2. Current knowledge

General information on the definitions, frequency, classification, as well as the possibilities and restrictions of prenatal sonographic and genetic molecular diagnosis is given below.

### 2.1 Definitions

All the entities included in the latest classification of genetic skeletal disorders present a significant skeletal involvement corresponding to the definition of osteochondrodysplasias, dysostoses, metabolic bone disorders, and skeletal malformation and/or reduction syndromes.

The osteochondrodysplasias are disorders in the development and/or growth of cartilage and/or bone. The long bones are affected in a generalized manner with or without involvement of the membranous bone of the skull. The abnormalities are usually symmetric, and dwarfism is common and often disproportionate (Kornak & Mundlos, 2003).

A dysostosis is a disturbance in the pattern of the chondroid anlage as an organ. A dysostosis affects one or a few skeletal elements while the other bones remain normal. Dysostoses are caused by defects in signalling during organogenesis. These disorders can be asymmetric, there is usually no dwarfism and chondro-osseous histology is often normal.

### 2.2 Incidence – Frequency

The overall incidence of genetic skeletal disorders has been estimated to approximately 2 in 10,000 births (range according to the literature 2-5/10,000) (Rasmussen et al., 1996). Of those, the frequency of lethal skeletal dysplasias among stillborn and liveborn infants is 1 in 4,000 - 6,000 (Nikkels, 2009). A percentage of 23% of affected fetuses are stillborn, while a 32% die during the first week of life. The perinatal mortality rate due to skeletal dysplasias is estimated to 0.9% (Goncalves & Jeanty, 1994). The frequency among perinatal autopsies ranges from 1 in 50 to 1 in 100 (Konstantinidou, 2009; Nikkels, 2009). Overall, the skeletal dysplasias that are more frequently encountered are Thanatophoric dysplasia, Achondroplasia, Osteogenesis Imperfecta, Achondrogenesis, and the Short-Rib with or without Polydactyly syndromes (Jeanty et al., 2003, Konstantinidou et al., 2009). Thanatophoric dysplasia, Osteogenesis Imperfecta and Achondrogenesis constitute the majority of lethal skeletal dysplasias (Konstantinidou et al., 2009). Achondroplasia is the more frequent nonlethal skeletal dysplasia.

### 2.3 Classification

Since the mid-1960s the knowledge of skeletal dysplasias has significantly expanded and numerous new entities have been identified (Gilbert-Barness, 2007). Before then, a disproportionately short stature was called without any distinction by clinicians as “achondroplasia” (attributed to short limbs) or “Morquio disease” (attributed to a short trunk). The lack of knowledge and the scarcity of individual skeletal dysplasias, in

association with the large heterogeneity, phenotypic variability and overlapping features of skeletal dysplasias led to a significant diagnostic controversy surrounding the skeletal dysplasias. The terminology has been basically descriptive, based on the clinical evolution (e.g. thanatophoric dysplasia - greek thanatos = death, phero = to bear: the dysplasia that bears death), the clinical description (e.g. campomelic dysplasia - greek campsis = curving, bending / meli = limbs: the dysplasia with curved or bent limbs), the assumed pathogenesis (e.g. osteogenesis imperfecta, achondrogenesis), or the name of investigators that first described the disease (e.g. Ellis-van Creveld syndrome).

With time, acquired knowledge in the field of molecular and clinical genetics has significantly contributed to the distinction and classification of skeletal disorders. A first significant classification was created in 1970 in Paris, and was subsequently revised in 1978 and 1983, while a substantial classification took place in 1998 and was revised in 2002, 2006 and 2010 (INCO, 1998; Hall, 2002; Superti-Furga & Unger, 2007; Warman et al., 2011). However, in the recent years, the number of recognized genetic disorders with a significant skeletal component is growing and the distinction between dysplasias, metabolic bone disorders, dysostoses and malformation syndromes is blurring. Molecular evidence leads to confirmation of individual entities and to the constitution of new groups but also allows for delineation of related but distinct entities and indicates a previously unexpected heterogeneity of molecular mechanisms. Thus, accumulating molecular evidence does not necessarily simplify the Nosology, and a further increase in the number of entities and growing complexity is expected. For classification purposes, in the latest revision, the 456 genetic skeletal disorders included are placed in 40 groups defined by molecular, biochemical and/or radiographic criteria. For classification purposes, pathogenetic and molecular criteria are integrating with morphological ones, but disorders are still identified by clinical and radiographic criteria (Warman et al., 2011).

According to our experience in diagnosing fetal skeletal dysplasias, the latest Revisions of the Nosology and Classification placing the genetic skeletal disorders in groups, have proved most useful in providing a list of conditions entering the differential diagnosis, once the main group has been recognized. In our cases of fetal autopsy, the diagnostic approach is still based on morphological features, radiographic appearance, pathological and histological findings.

## **2.4 Prenatal ultrasonography in skeletal dysplasias**

Prenatal diagnosis is initially based on the sonographic detection, most commonly during the second gestational trimester. Several previously published series have emphasized on the diagnostic and prognostic implications of prenatal ultrasonography in fetal skeletal disorders (Doray et al., 2000; Parilla et al., 2003; Krakow et al., 2008; Witters et al., 2008). Two-dimensional ultrasonography may detect the majority of skeletal dysplasias, however, difficulties in the diagnosis as well as in the differential diagnosis are frequently arising. The use of further imaging modalities or invasive procedures is sometimes necessary in order to detect or exclude an underlying chromosomal or single gene disorder. An accurate diagnosis is essential to allow adequate genetic counseling as well as further management of the case. For this approach, the three-dimensional ultrasonography and three-dimensional computed tomography may provide more detailed imaging results, whereas the role of fetal MRI may prove to be useful in the future. Despite the indisputable progress that has been achieved in the last years, in some cases the antenatal detection delays and is feasible only at the late

second or even at the third gestational trimester. This may generate serious bioethical concern as well as difficulties in the management and the genetic counseling, particularly in cases of lethal skeletal dysplasias.

Prenatal ultrasound can detect cases of dwarfism and several other skeletal malformations, while there are sonographic measurements that serve as good predictors of lethality (Parilla et al., 2003). Lethality is usually due to thoracic underdevelopment and lung hypoplasia. Sonographic markers of lethality are mainly based on the assessment of lung biometry, measurements of chest circumference (CC) and its relation to the abdominal circumference (AC), femur length (FL), and finally assessment of the pulmonary arteries by Doppler ultrasonography. Thus, measurements of CC lower than the 5<sup>th</sup> centile, CC/AC <5<sup>th</sup> centile, chest/trunk length ratio <0.32, lung area <5<sup>th</sup> centile, right lung area/thoracic area ratio <0.11, and FL/AC <0.16, are considered as markers of lethality of high predictive value (Parilla et al., 2003). The presence of curved or bent femora should be taken into consideration when estimating the femur length in order to assess lethality, as in such conditions the bone may be longer than it appears. In the lethal skeletal dysplasias, the femur length is shorter with a deviation of 6.7 weeks from the 50<sup>th</sup> centile during the second trimester of gestation, whereas in those compatible with life the deviation is of 4.2 weeks (Parilla et al., 2003). The discordance between lethal and non lethal dysplasias is raised with advancing gestation. In achondrogenesis, the femur length is 30% of the normal mean, in osteogenesis imperfecta type 2 and thanatophoric dysplasia type 1 it measures 40-60% of the normal mean, while in the nonlethal achondroplasia and hypochondroplasia is as high as 80% (Goncalves et al., 1994).

Despite the accuracy in predicting lethality, however, in cases of skeletal malformations, as in all cases of fetal malformations, a specific diagnosis is necessary not only for the prognosis of the current pregnancy, but also to assess recurrence risk in subsequent pregnancies and enable genetic counseling and future prenatal diagnosis. Given that prenatal ultrasound accuracy in the final diagnosis of genetic skeletal disorders remains relatively low, ranging from 18% to 65% in published series (Doray et al., 2000; Parilla et al., 2003; Krakow et al., 2008; Witters et al., 2008; Konstantinidou et al., 2009; Hatzaki, et al., 2011), the impact of the specific diagnosis is still dependent on the molecular genetic or postmortem examination.

## 2.5 Prenatal molecular genetic control in skeletal dysplasias

Out of 456 entities included in the latest Revision of the Nosology (Warman et al., 2011), 215 are associated with one or more of 226 different genes. The nosologic status has been classified as final (mutations or locus identified), probable (pedigree evidence), or bona fide (multiple observations and clear diagnostic criteria, but no pedigree or locus evidence yet). Among the skeletal dysplasias that can be encountered in the fetus at autopsy, several have a known underlying molecular defect. Examples include type 1 collagenopathies (e.g. osteogenesis imperfecta type 1, 2 and 3 with *COL1A* defects), type 2 collagenopathies (e.g. achondrogenesis type 2 and hypochondrogenesis with *COL2A* defects) and the group of fibroblast growth factor receptor defects (e.g. thanatophoric dysplasia, achondroplasia and hypochondroplasia with *FGFR3* mutations). This last group comprises practically the vast majority of the cases that are prenatally diagnosed by molecular genetic method (Hatzaki et al., 2011). The possibility of molecular analysis for mutations in selected exons of the *FGFR3*



gene by PCR amplification of fetal DNA extracted from amniotic fluid cells has led to an increased demand for *FGFR3* testing. This has become part of a routine prenatal control when a preliminary diagnosis of “skeletal dysplasia” is set by ultrasonography, regardless of the phenotypic relevance to the *FGFR3* group of skeletal disorders. Thus, in many instances, the prenatal *FGFR3* molecular control proves to be irrelevant with the case, and should be substituted by molecular confirmation of other underlying defects, as indicated by the postmortem diagnosis.

### 3. Postmortem examination: The role of the pathologist

More than 50 skeletal dysplasias are identifiable at birth, the list being rapidly expanding (Krakow et al., 2008). Fetuses with skeletal disorders are frequently subjected to postmortem examination following prenatal ultrasonographic pathological findings and interruption of pregnancy or after intrauterine fetal demise.

Despite the scarcity of individual skeletal dysplasias, our experience is that the fetopathologist frequently deals with this group of disorders at fetal or perinatal autopsy and is responsible, in everyday practice, for the correct identification of such conditions. In the department of Pathology of Athens University, where consult cases of fetal autopsies are received from central and district hospitals in Greece, the frequency of fetal/perinatal skeletal dysplasias has raised to 1 in 40 over a 15-year period. Affected fetuses of the second trimester of gestation form the majority in the series of our patients. Liveborn infants affected with perinatally lethal skeletal dysplasias on the other hand are only a small minority, usually the offspring of families with a low socio-economic background that have not received prenatal follow-up. Increasing expertise in prenatal ultrasound has led to increased and more accurate early identification of fetal skeletal dysplasias. Prenatal identification of a presumably lethal skeletal dysplasia raises the option of termination of the pregnancy. Molecular characterization is often carried out prenatally, particularly for the family of *FGFR3* gene mutations. In the case of positive results for a *FGFR3* gene mutation, termination of pregnancy is often decided by the parents and the fetus is sent for autopsy. Postmortem examination in the context of a known molecular defect, apart from the confirmation of the diagnosis, may also be of scientific interest: the pathologist may observe and record phenotypic variability under the same molecularly defined entity with a single mutation, or contribute to a phenotype-genotype correlation in entities with mutational variability. When there is no molecular diagnosis preceding autopsy, the fetopathologist is responsible for the diagnostic approach, given that the prenatal ultrasonographic evaluation can usually predict lethality, but very often fails to identify the particular type of skeletal dysplasia, which is necessary for genetic counseling and future prenatal diagnosis. Significant phenotypic overlapping and relatively limited knowledge of the genetic background are the main sources of controversy in the diagnosis of these disorders. Thus, in everyday practice, the diagnosis and prognosis still depend on the postmortem radiographical, pathological and histopathological findings.

Although the assistance of an experienced paediatric radiologist or clinical geneticist in the interpretation of the postmortem radiography is desirable, this is not always feasible in many countries, because of lack of expertise. Under these circumstances, the fetopathologist should be able to deal with the radiographic interpretation of, at least, the more common among skeletal dysplasias and refer the remaining cases to specialized referral centers. Radiological

diagnosis in very young fetuses may occasionally be very difficult, as some bones are not yet mineralized and only the chondroid anlage is present. Genetic metabolic diseases and malformation syndromes involving the skeleton are also difficult to diagnose at autopsy, demanding from the pathologist knowledge and skills of clinical dysmorphology and clinical genetics. The diagnostic difficulties are obvious, such as the restricted or incomplete phenotype at an early gestational age and the eventual lack of typical morphological or clinical hallmarks of the syndrome in utero (e.g. mental retardation, hearing deficit, hair loss etc). Despite these restrictions, however, there are many examples where an alert and experienced fetopathologist has first provided the affected family with a correct diagnosis of a genetic syndrome, based on the postmortem examination of an affected fetus.

#### **4. Methods**

In a combined retrospective and prospective study, we have gathered radiological, physical, gross pathological and histopathological data on 50 cases of genetic skeletal disorders diagnosed among 2250 fetal and perinatal autopsies carried out at the Department of Pathology of the University of Athens over a 12-year period.

The methodology for postmortem examination of the fetus with skeletal dysplasia included radiographic control, photographs, external inspection, gross inspection of all organs including the brain, organ dissection and sampling for microscopical examination, and, finally, sampling from the bones and cartilage for histological, histochemical and occasionally immunohistochemical staining.

##### **4.1 Radiography**

X-rays/babygram both anteroposterior and lateral, using a Faxitron Cabinet X-Ray System, were taken in the following instances: in all cases identified as possible “skeletal dysplasias” on prenatal ultrasonographic examination; in cases suspect of skeletal dysplasia on external inspection; in cases of external deformities. Measurements of the length of the long bones and spine on the X-ray were compared to normal values of fetal long bone growth and spine (van der Harten, 1990).

##### **4.2 Autopsy - Histopathology**

Detailed autopsy with histological sampling from various organs was performed in all cases. Bone samples included the head of the femur or humerus with the metaphysis and part of the diaphysis in all cases. A midsagittal section of lumbar vertebral bodies and the costochondral junction of the ribs were occasionally available. After fixation in 10% formalin and decalcification in 0,5M EDTA, paraffin sections were stained with Hematoxylin-Eosin, Periodic-acid-Schiff (PAS) and PAS after diastase predigestion, and occasionally additional Alcian blue and Masson trichrome stains were used. The bones were cut longitudinally to include the resting cartilage, growth plate, and primary spongiosa of the metaphysis .

##### **4.3 Molecular genetic analysis**

Molecular genetic control was available and confirmed the diagnosis in 12 cases. Of those, 6 referred to mutations of the FGFR3 gene, prenatally or postnatally tested by PCR amplification analysis. The mutations tested included R248C and S249C for Thanatophoric

dysplasia, G380R for Achondroplasia and N540K for Hypochondroplasia, as previously published (Konstantinidou et al., 2009; Hatzaki et al., 2011). Molecular genetic control was also available in selective cases of Osteogenesis Imperfecta, Greenberg dysplasia and Cranioectodermal dysplasia (Konstantinidou et al., 2009).

## 5. Results

In our series of 2250 autopsied fetuses and infants, 50 cases could be identified as genetic skeletal disorders and were grouped under 13 of the 40 groups included in the 2010 Revision of the Nosology (Warman et al., 2011). The various types of skeletal dysplasias included in our series are shown in Table 1.

Among the overall group of fetal genetic skeletal disorders, the skeletal dysplasias (osteochondrodysplasias) were the more common (87.5%), followed by the limb hypoplasia/reduction group (12%) and the dysostoses (10%). The larger group of osteochondrodysplasias was the group of FGFR3 defects (20%). The more common types of osteochondrodysplasia were Thanatophoric dysplasia (16%), Osteogenesis Imperfecta (14%), and the group of Short-Rib dysplasia - with or without polydactyly (14%). Achondrogenesis/Hypochondrogenesis cases, although perinatally lethal, were not common in our series of autopsies (4%), in contrast with other published autopsy series (Nikkels et al., 2009). Fetal age at autopsy ranged from 12 to 37.4 weeks with a mean of 20.5 weeks. There was a predilection for male gender among skeletal disorders (male to female ratio 3:1). Lethal osteochondrodysplasias represented a majority of 58% among the diagnosed genetic skeletal disorders. The remaining 42% belonged to groups that are known to be non lethal or not always lethal, presenting, however, severe morbidity in most cases. Lethality could be accurately predicted by prenatal ultrasonography, based on the identification of thoracic underdevelopment and severe limb shortening.

The main ultrasonographic findings that led to a presumptive prenatal diagnosis of "skeletal dysplasia" were short limbs, curved femora, narrow thorax, fractures and acrania (lack of skull ossification). At postmortem examination, several cases of short femora were attributed to intrauterine growth restriction (IUGR), with no signs of a genetic skeletal disorder. Short and/or curved limbs were seen in a variety of skeletal dysplasias other than thanatophoric dysplasia. Fractures were seen in the context of osteogenesis imperfecta, achondrogenesis type 1A, hypophosphatasia and gracile bone dysplasia (osteocraniostenosis, osteocraniosplenic syndrome). Acrania was a feature of osteogenesis imperfecta type 2A, achondrogenesis type 2A and osteocraniostenosis.

Correct typing coinciding with the final postmortem diagnosis was achieved in only 25% of cases by ultrasonography. Lack of knowledge of the large variety of the less common skeletal dysplasias was the main reason of prenatal ultrasonographic diagnostic failure. Curved or angular bent femora were occasionally mistaken for fractured limbs, misleading the presumptive prenatal diagnosis towards the conditions that appear with fractures, such as osteogenesis imperfecta.

## 6. Description of the more common genetic skeletal disorders

The more common among the fetal skeletal disorders encountered in our series will be presented briefly below. The group number refers to the order of the 2010 Revision of the Nosology and Classification of Genetic Disorders of Bone (Warman et al., 2011).



1. <i>FGFR3</i> group	21. <i>Chondrodysplasia punctata (CDP)</i> group
Thanatophoric dysplasia type 1	Chondrodysplasia punctata (CDPX2)
Achondroplasia heterozygous	HEM (Greenberg) dysplasia
Hypochondroplasia	25. <i>Dysplasias with decreased bone density</i>
2. <i>Type 2 collagen</i> group	Osteogenesis Imperfecta type 2a
Achondrogenesis type 2	Osteogenesis Imperfecta type 2b
Spondyloepiphyseal dysplasia	Osteogenesis Imperfecta type 2c
7. <i>Filamin</i> group	26. <i>Abnormal mineralization</i> group
Atelosteogenesis type 1	Hypophosphatasia
9. <i>Short-rib dysplasia (with or without polydactyly)</i> group:SR(P)	27. <i>Lysosomal storage diseases with skeletal involvement (dysostosis multiplex group)</i>
SR(P) 2 (Majewski)	Mucopolysaccharidosis
SR(P) 1/3 (Saldino-Noonan/Verma-Naumoff)	35. <i>Dysostoses with predominant vertebral involvement, with and without costal involvement</i>
Chondroectodermal dysplasia (Ellis-van Creveld)	Spondylocostal dysostosis / Jarcho-Levin syndrome
15. <i>Acromelic dysplasias</i>	38. <i>Limb hypoplasia-reduction defects</i> group
Cranioectodermal dysplasia (Sensenbrenner)	Roberts syndrome
18. <i>Bent-bone dysplasia</i> group	De Lange syndrome
Campomelic dysplasia	Ectrodactyly-radial defect
19. <i>Slender bone dysplasia</i> group	Split Hand-Foot malformation with tibial hypoplasia
Gracile bone dysplasia (Osteocraniostenosis)	Femoral hypoplasia – Unusual facies
IMAGE syndrome	

Table 1. The various types of genetic skeletal disorders in our series

6.1 Group 1: FGFR3 mutations group

Index cases: Thanatophoric dysplasia type 1, Achondroplasia

6.1.1 Thanatophoric dysplasia type 1 (TD1)

This type of congenital skeletal dysplasia was the most common in our series (8/50 cases, 16%). Prenatal ultrasonography detected all these cases as “skeletal dysplasias”, but the correct labelling of *thanatophoric dysplasia* was suggested by the ultrasonographic findings in four of them, all belonging to the latest chronological period of our series. As the name suggests, the condition is invariably lethal in the perinatal period. It is attributed to mutations in the gene encoding the Fibroblast Growth Factor Receptor (FGFR3). Most cases occur sporadically as a result of a *de novo* autosomal dominant mutation. Three of our cases were molecularly confirmed to host the 742C>T mutation, resulting in aminoacid change R248C within exon 7 of the FGFR3 gene (Konstantinidou et al., 2009; Hatzaki et al., 2011). The mean age at autopsy was 21.3 weeks, ranging from 20 to 24 weeks of gestation.



Fig. 1. Fetuses with Thanatophoric Dysplasia type 1 at 20 weeks (left) and 22.5 weeks (right)



Fig. 2. Thanatophoric dysplasia type 1 at 20 and 32 weeks: Platyspondyly, short ribs, short tubular bones, curved femora with metaphyseal spikes, horizontally shortened ilia

All cases presented the following constant typical characteristics (Fig. 1): At external inspection the head was large with an increased fronto-occipital diameter. A flat nasal bridge and protruding tongue were typical facial characteristics. The thorax was narrow and bell-shaped and the abdomen distended. The upper and lower limbs were short in all respects (rhizomelic, mesomelic and acromelic shortening). All the linear somatometric measurements were affected in thanatophoric dysplasia, particularly the crown-heel and toe-heel lengths, as well as the cranial perimeter, chest and abdominal circumferences.

**X-rays** (Fig. 2) show severe platyspondyly with H-shaped or U-shaped vertebral bodies, relatively short ribs, small horizontally shortened iliac bones with sacrosciatic notches and markedly shortened upper and lower limb bones. Short and curved “telephone receiver-like” femora are a hallmark of type 1 thanatophoric dysplasia, but curving may be less pronounced in the younger fetuses. The femora show small metaphyseal spikes.

**At autopsy**, fetuses with thanatophoric dysplasia type 1 have a large head with small cranial sutures and megalencephaly. The brain is heavy, the temporal lobe is enlarged and there are multiple transverse grooves along the inferomedial surface of the temporal and occipital lobes (Fig. 3). Hippocampal dysplasia is also part of the temporal lobe dysplasia in this condition.

Temporal dysplasia was present in all the examined fetal brains in our sample of fetuses with thanatophoric dysplasia type 1. The finding could not be confirmed in severely macerated brains.

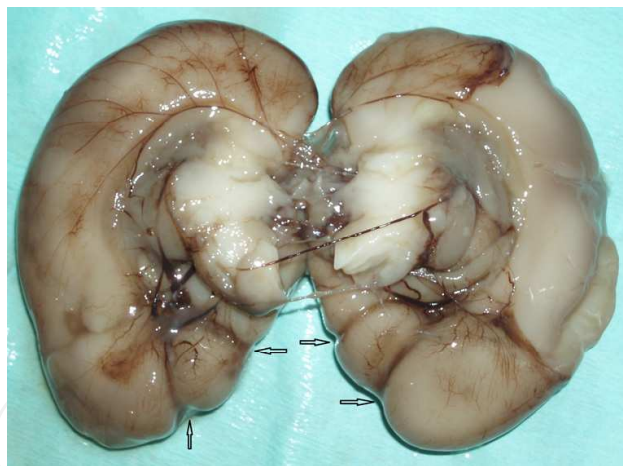


Fig. 3. The brain in Thanatophoric dysplasia at 22 weeks: transverse sulci along the inferomedial surface of the temporal and occipital lobes (arrows)

In one unique case of a fetus with otherwise typical TD1 findings, organ inspection and dissection revealed intestinal malrotation, renal tubular cysts and persisting ductal plate of the liver. These findings are frequent in other forms of skeletal dysplasias, particularly in the family of Short-Rib-Polydactyly dysplasias (referred to later in this chapter). The findings are unique in that they have never been reported in cases of TD1 to our knowledge. Molecular analysis in that case confirmed the presence of a typical R248C mutation in the *FGFR3* gene. A possible explanation for this unusual association of abnormal findings could be the presence of a second mutation or microdeletion in a different part of the genome.



**Histopathologic examination** of the epiphyseal growth plate in TD1 shows retardation and disorganization of the growth plate with irregular borders of the periphysis. There is fibrous extension of the ossification groove of Ranvier and periosteal expansion of bone formation at this site. These alterations correspond to the metaphyseal spikes seen on radiography (Fig. 4).

*FGFR3* molecular genetic analysis showed the R248C mutation in four examined cases, while in the remaining cases the diagnosis of TD1 was based on the typical external, radiographic and histopathologic findings provided by the postmortem examination.

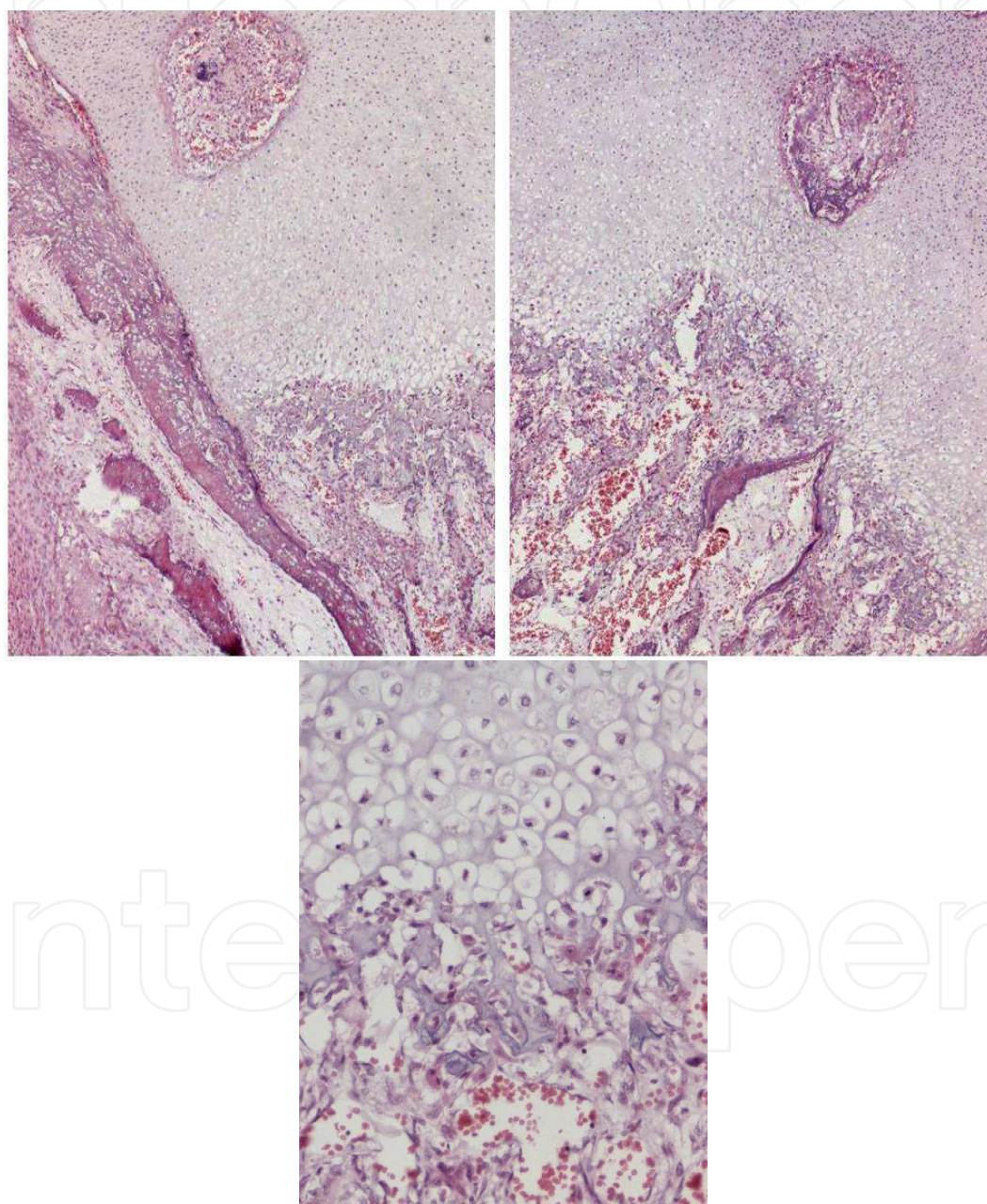


Fig. 4. Epiphyseal growth plate from the femoral head of a fetus with Thanatophoric dysplasia type 1. TOP: The borders between the cartilage and the primary spongiosa are irregular. Extension of the ossification groove of Ranvier (corresponding to the metaphyseal spikes seen on radiography) are seen on the left. BOTTOM: The growth plate is disorganized, without column formation.

### 6.1.2 Achondroplasia

This condition is the most common nonlethal osteochondroplasia. It is autosomal dominant due to mutations in the FGFR3 gene. In our case, there was a *de novo* heterozygous G380R mutation. The facial appearance is typical with a prominent forehead, small maxillary area and flat nasal bridge. The trunk is of almost normal length and there is rhizomelic shortening of limbs.

**Radiographic features** include platyspondyly, short ribs, squared iliac wings with horizontal acetabular roofs and spurs (trident appearance), splayed upper femoral metaphyses, metaphyseal flaring and short metacarpals (Fig. 5).



Fig. 5. Achondroplasia at 37 weeks: narrow thorax, rhizomelic limb shortening, splayed upper femoral metaphyses and trident appearance of iliac bones.



## 6.2 Group 2: Type II collagen group

### *Index case: Achondrogenesis type II*

Achondrogenesis is the most severe lethal form of osteochondrodysplasia. This condition, commonly encountered in European published series of lethal skeletal dysplasias (Nikkels et al., 2009), was uncommon in our Greek series (1/50 cases). Achondrogenesis type II, as all type II collagenopathies, is an autosomal dominant disorder caused by mutations in the *COL2A1* gene.

**Major radiographic features** and clinical presentation are similar in achondrogenesis type I and type II (Fig. 6). Deficient skull ossification and rib fractures are present only in type Ia.

**Histologically**, the growth plate is severely disorganized. The resting cartilage is cellular with many prominent blood vessels and perivascular fibrosis. The chondrocytes may appear ballooned.

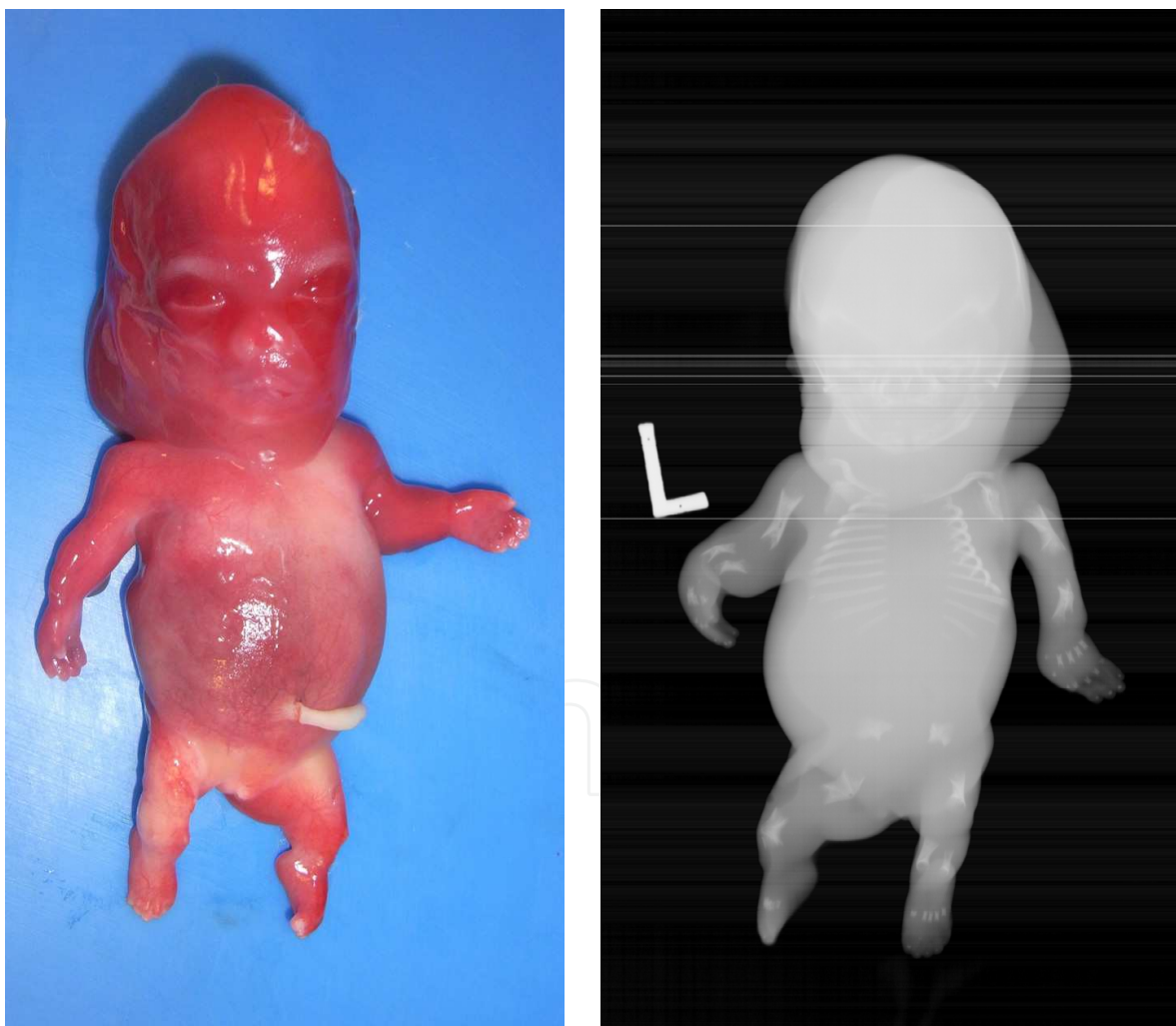


Fig. 6. Achondrogenesis: The trunk and extremities are extremely short. Hydrops is present. There is complete absence of ossification in the vertebrae, sacrum and pubis in the young fetus. The limb bones are extremely short and there are metaphyseal spike-like spurs. (Images kindly ceded by Dr. I. Scheimberg; Barts and The London NHS Trust)

### 6.3 Group 25: Osteogenesis Imperfecta and dysplasias with decreased bone density

#### *Index cases: Osteogenesis Imperfecta type IIa and type IIb*

##### 6.3.1 Osteogenesis Imperfecta (O.I.) type II

The lethal type 2 is the most commonly met in the fetus. It is mostly a dominantly inherited condition due to mutations in the *COL1A1* and *COL1A2* genes. Some severe cases of O.I. are caused by compound heterozygote mutations in the *CRTAP* and *LERPE* genes and follow recessive inheritance. Based on morphological features radiology or histology, it is not yet possible to discriminate between the O.I. cases caused by mutations in the collagen I gene and the autosomal recessive cases (Nikkels et al., 2009).

Two index cases of Osteogenesis Imperfecta type IIa and IIb are shown below (Figure 7). Both cases had dominant mutations in the *COL1A1* gene. The fetus with O.I. type IIa has a large membranous skull (acrania) (Figure 7, left). There is deficient ossification of the skull but not complete acrania in type IIb (Figure 7, right). The femora are bent and shortened as a result of multiple recurrent fractures. The characteristic “blue sclera” recognised in infancy or later are not a feature of the fetus at autopsy. Brain heterotopias have been described in O.I. and were present in both of these index cases with O.I type IIa and IIb.

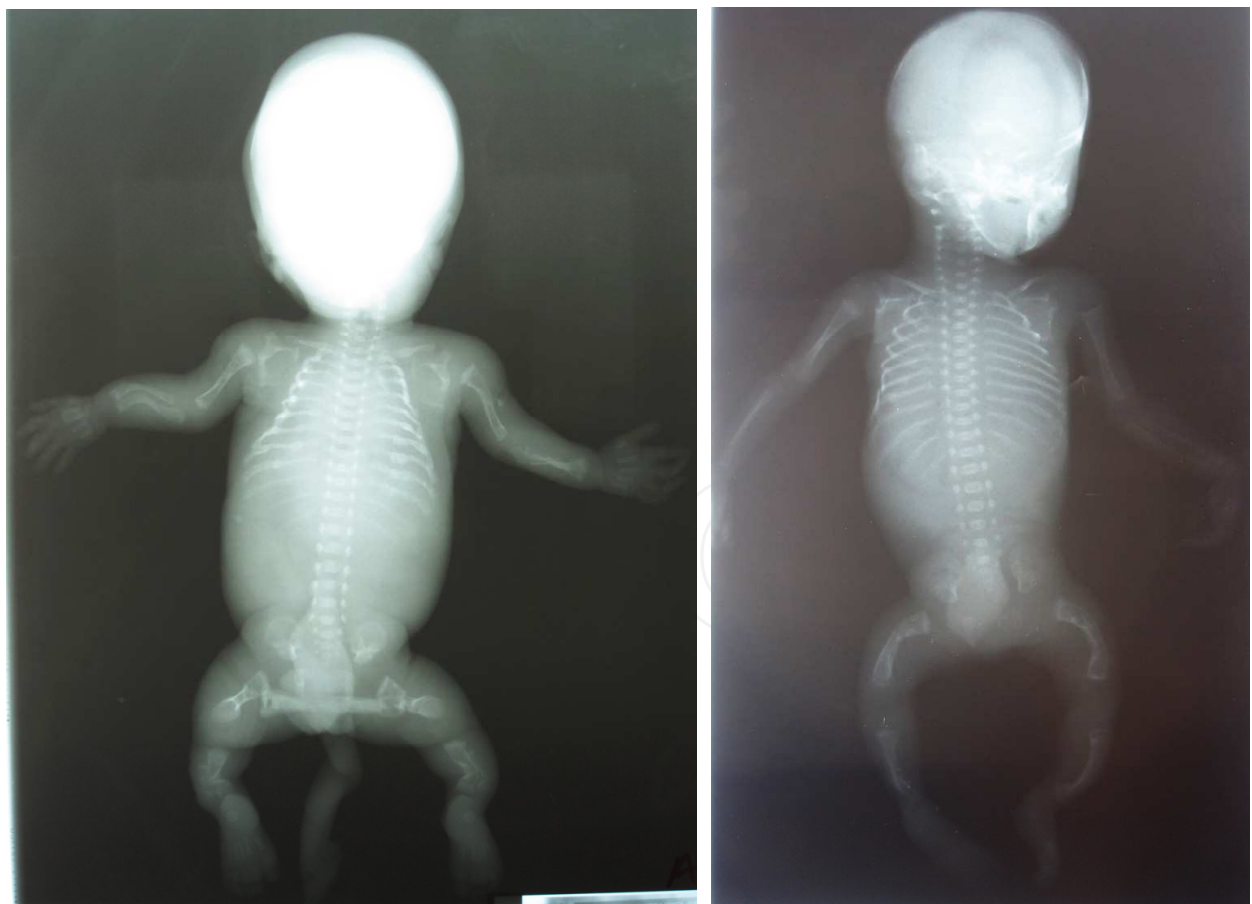


Fig. 7. Osteogenesis Imperfecta type IIa at 26 weeks (left) and type IIb at 20 weeks (right) Rib fractures are present in type IIa but there are hardly any in type IIb. The femora are deformed. The spine is normal.

**Radiography** (Fig. 7) of the 2<sup>nd</sup> trimester fetus shows multiple fractures with beaded ribs and crumbled femora in the more severe O.I. type IIa (Fig. 7, left) or bowed femora with fewer or no rib fractures in the less severe type IIb (Fig. 7, right). The humeri are usually straight without fractures, but they may appear bowed in severe forms of O.I. later in pregnancy. The spine is normal in the fetus.

**Histopathology** of the bone and cartilage is comparable in types IIa and IIb of Osteogenesis Imperfecta (Fig. 8, 9). The bony spicules in the metaphysis are narrow, hypercellular, and covered by basophilic meager primitive woven bone. They are markedly reduced in number and size in the diaphysis. The osteocytes are closely arranged around the bony trabeculae and in the subperiosteal area (Fig. 9). The growth plate is normal.

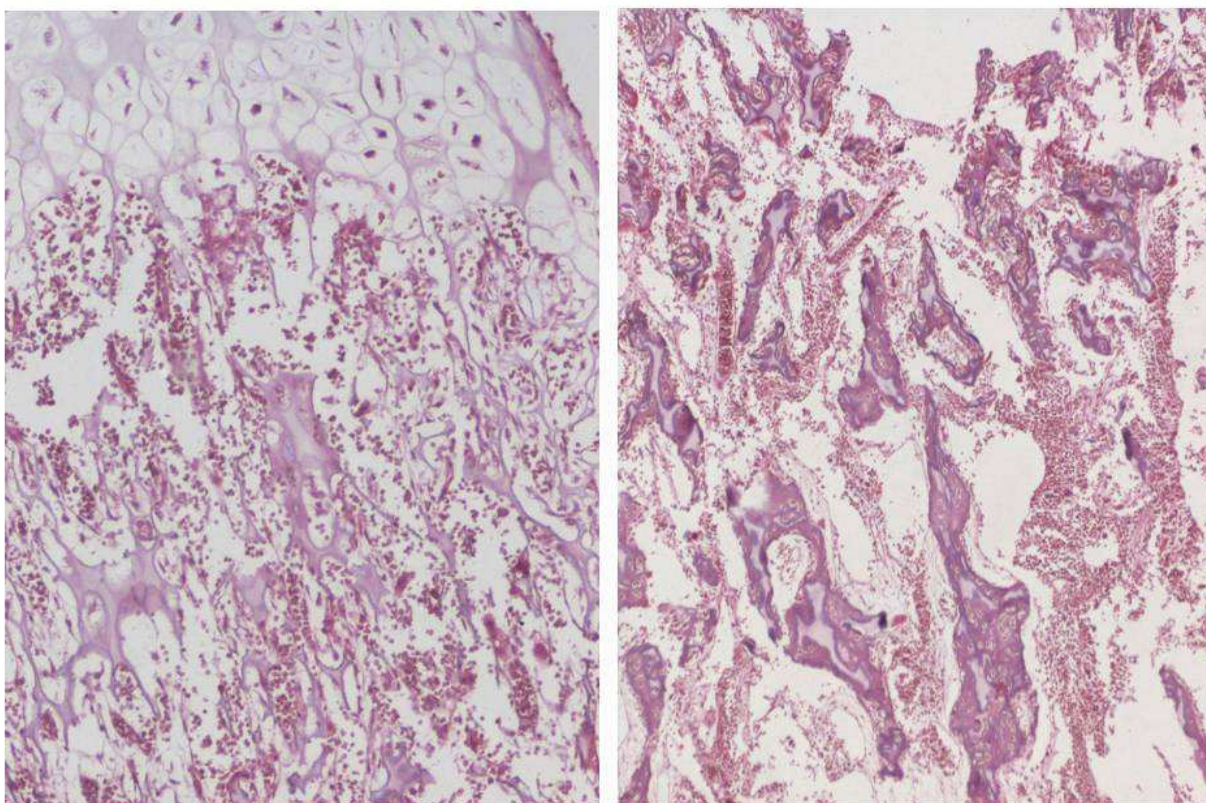


Fig. 8. Histology is comparable in Osteogenesis Imperfecta type 2a (left) and type 2b (right). The bony spicules of the primary spongiosa are narrow and covered by meager basophilic woven bone. Part of the normal growth plate is seen on top left. Towards the diaphysis, the bone marrow predominates over the bony trabeculae (right).



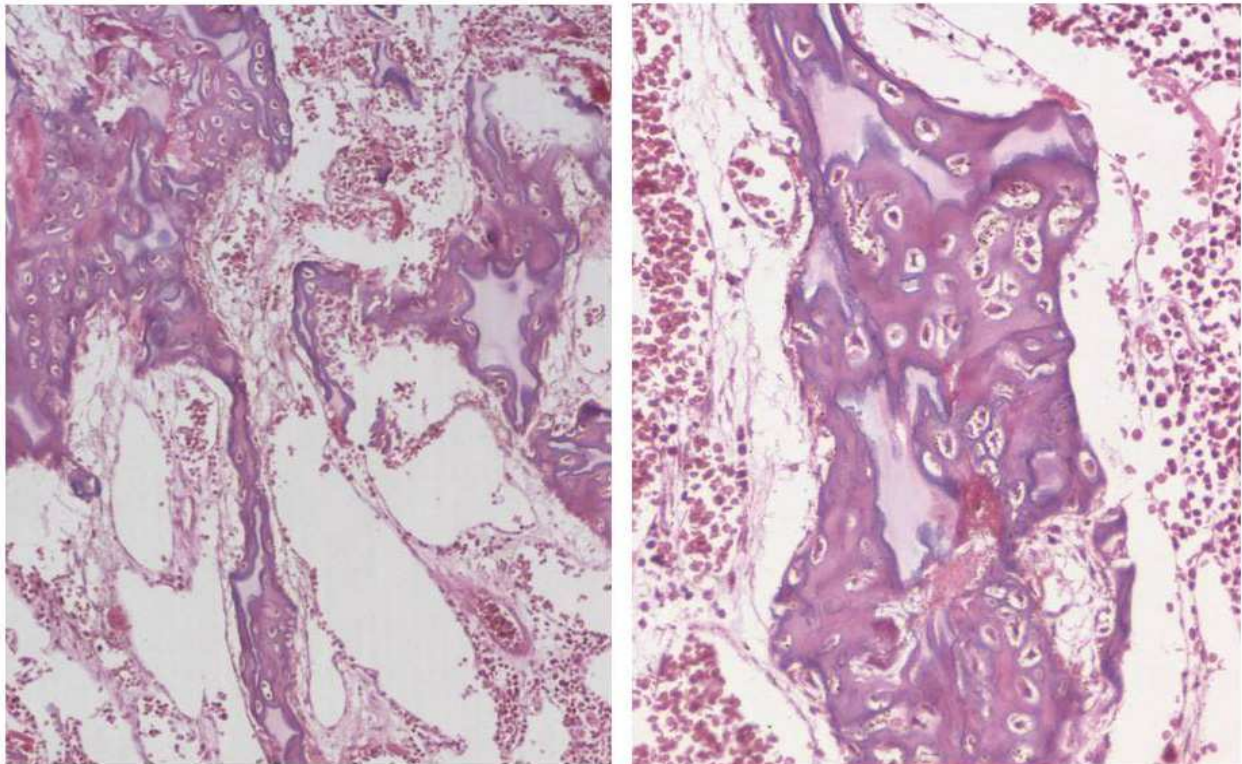


Fig. 9. Osteogenesis Imperfecta type 2b. There is increased number of osteocytes at the periphery of the bony spicules and at subperiosteal sites.

#### 6.4 Group 9: Short-rib dysplasia (with or without polydactyly) - SR(P)

**Index cases: SR(P) type II (Majewski), SR(P) type III (Verma-Naumoff), chondroectodermal dysplasia (Ellis-van Creveld)**

##### 6.4.1 Short-rib-polydactyly syndromes

There are at least 4 distinct types:

- Type I Saldino-Noonan
- Type II Majewski
- Type III Verma-Naumoff
- Type IV Beemer-Langer (polydactyly unlikely)

Types I and III may represent a phenotypic spectrum of the same entity as may types II and IV. Indeed, there are overlapping characteristics between all 4 types and several cases are described that cannot fit in a particular type (Gilbert-Barness, 2007).

All SRPs are autosomal recessive. Types I/III are caused by mutations in the *DYNC2H1* gene. The molecular background is not identified in the remaining ones. The association of SRP skeletal dysplasias with particular extraskeletal malformations, such as Dandy-Walker malformation, cardiovascular, gastrointestinal and genitourinary abnormalities, renal cysts and ductal plate malformation of the liver indicates that these syndromes probably belong to the expanding group of ciliopathies (Badano et al., 2006; Konstantinidou et al., 2009b).

In our series, 4 fetuses were diagnosed with SRP at autopsy, one with type II/Majewski (Fig. 10), two with type III/Verma-Naumoff, and one with SRP of undetermined type (aged 12 weeks of gestation).

**External inspection** in SRP dysplasias reveals a very narrow chest, very short limbs, and polydactyly (rare in type IV). The combination of these findings contributes to an early sonographic prenatal diagnosis, achieved as early as the 12<sup>th</sup> week of gestation in our series.



Fig. 10. Short-Rib-Polydactyly type II (Majewski) at 22 weeks. There is a median cleft lip, the chest is very narrow and the limbs are short. Micropenis and combined preaxial and postaxial polysyndactyly of hands and feet are also seen.

**Radiographic features** (Fig. 11): There is mild platyspondyly in types I/III, the ribs are very short and horizontal, and the long bones are short. Metaphyseal spurs are present in types I and III (Fig. 11 right), while in types II and IV the metaphyses are smooth. In our index case of type II (Majewski) the tibia is the shortest of all long bones (Fig. 11, left). Polydactyly is



postaxial (in types I, II, III), preaxial (type II) or combined preaxial and postaxial (type II) and is common in all types, except type IV. Fusion of metacarpals is seen in type II-Majewski (Fig. 11 left), (as in chondroectodermal dysplasia Ellis-van Creveld).

Jeune syndrome and Ellis-van Creveld syndrome are also classified under the group of Short-Rib (with or without Polydactyly) dysplasias. These may be indistinguishable in the fetus.



Fig. 11. Short-Rib-Polydactyly type II at 22 weeks (left) and type III at 23 weeks (right). The ribs are short. The tibia is the shorter long bone in type II. Metaphyses are spiked in type III.

**Extraskkeletal abnormalities** noted in our index case of SRP type II (Majewski) consisted in a median cleft lip, micropenis and a Dandy-Walker malformation of the cerebellum. Microscopically, the kidneys showed renal tubular and glomerular cysts and in the liver persisting ductal plate was noted.

In our index case of SRP type III (Verma-Naumoff) there was mild hydrops, moderately hypoplastic lungs, a complex cardiovascular defect with atrioventricular canal defect type I and interruption of the aortic arch, intestinal malrotation, small kidneys with tubular cysts and portal fibrosis with persisting ductal plate of the liver, and there was no polydactyly.

#### 6.4.2 Chondroectodermal dysplasia (Ellis-van Creveld)

Two fetuses in our series were diagnosed with Ellis-van Creveld (EvC) syndrome at post-mortem examination, both at 23 weeks of gestation (Fig. 12).



Fig. 12. Ellis-van Creveld syndrome (chondroectodermal dysplasia) at 23 weeks. There is postaxial polydactyly of both hands (left) and postaxial polysyndactyly (right). The chest is narrow and the limbs are moderately short.

**At autopsy**, organ dissection of the two female fetuses showed pulmonary hypoplasia, renal tubular cysts and persisting ductal plate in the liver. One fetus had postaxial hexadactyly and the other postaxial polysyndactyly of both hands (Fig. 12).

Molecular genetic analysis was not performed in either case. The presence of postaxial polydactyly favored the diagnosis of EvC versus Jeune Asphyxiating Thoracic Dysplasia (ATD), which in the fetus may be indistinguishable from EvC or SRP type II. In childhood, the typical disorders of ectodermal dysplasia, i.e. hypoplastic nails, thin hair and abnormal teeth combined with postaxial polydactyly would suggest the diagnosis of EvC versus Jeune ATD. Ellis-van Creveld and Jeune ATD are compatible with life; SRP type II is invariably lethal in the perinatal period.

**Radiographic findings** (Fig. 13) included short ribs, short long bones with rounded metaphyses, fibular hypoplasia in one case, vertically shortened ilia with notches and a V-shaped 3<sup>rd</sup> metacarpal in one case.

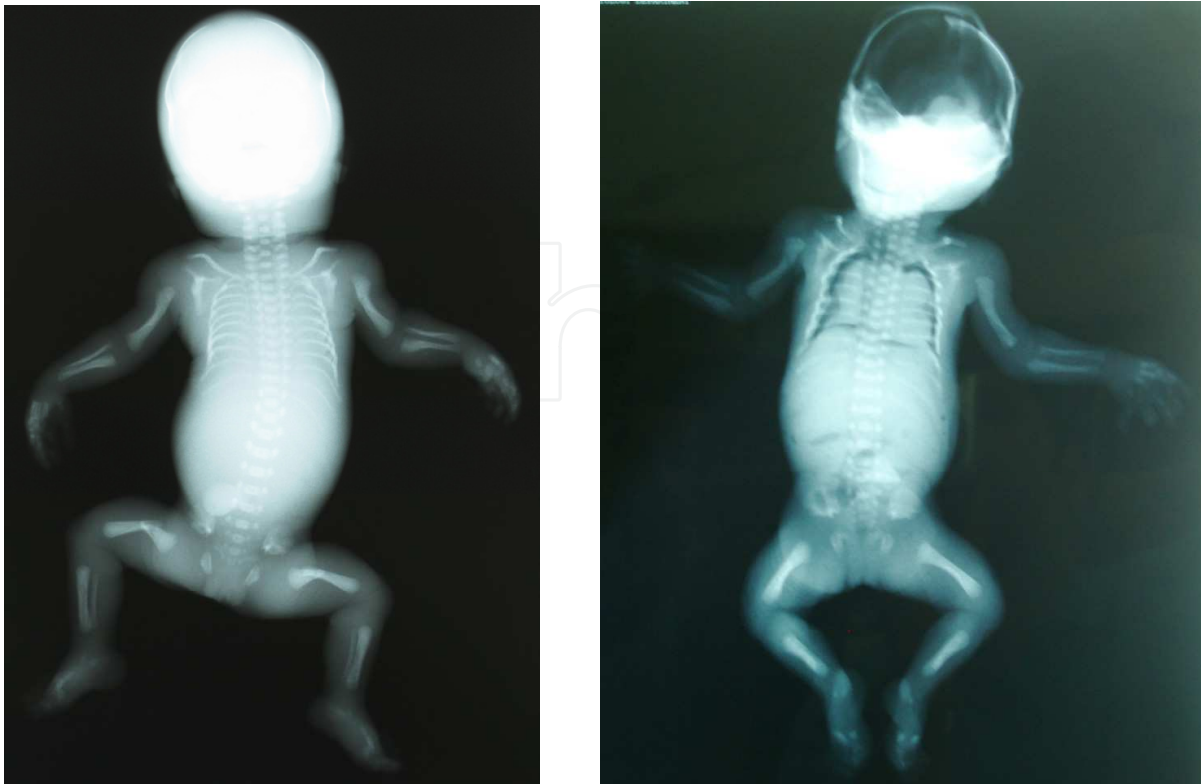


Fig. 13. EvC (same cases as in Fig. 12): The ribs are short. The long bones are short with rounded metaphyses. The radiographic findings may be indistinguishable from Jeune ATD.

**Histology** of the epiphyseal growth plate shows retardation and disorganization in the formation of columns (Fig. 14).

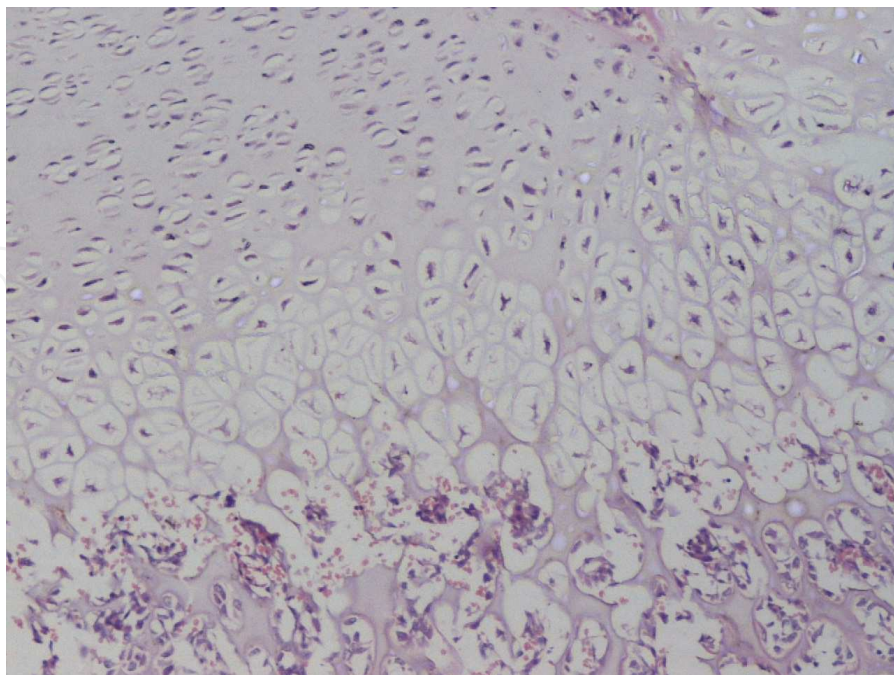


Fig. 14. Retardation and focal disorganization of the femoral epiphyseal growth plate in Ellis-van Creveld syndrome at 23 weeks.



**6.5 Group 35: Dysostoses with predominant vertebral involvement with and without costal involvement**

***Index case: Spondylocostal / Spondylothoracic dysostosis***

**6.5.1 Spondylocostal / Spondylothoracic dysostosis**

Various genetically distinct axial dysostoses with predominant vertebral and costal involvement were previously named as *Jarcho-Levin syndrome*, a label that has been eliminated by the 2010 revision of the Nosology. This heterogeneous group of disorders characterized by multiple spinal malsegmentation may be autosomal recessive, autosomal dominant or sporadic. It has been suggested that thoracic asymmetry characterizes Spondylothoracic dysostosis, whereas a short but overall symmetric thorax is a feature of Spondylocostal dysostosis (Solomon, 1978; O’ Neill, 2011a).

There were 5 cases of spondylocostal /spondylothoracic dysostosis in our series (10%). Fetal age ranged from 13 to 37 weeks of gestation. One case referred to a liveborn neonate born to a mother who had not received prenatal sonographic control.

In all cases there were characteristic external, radiographic and pathological findings. The fetus with spondylocostal/spondylothoracic dysostosis has a short neck with low frontal and occipital hairline, short trunk in contrast to extremities of normal length, and scoliosis (Fig. 15).



Fig. 15. Spondylothoracic / Spondylocostal dysostosis in two fetuses of 16.5 weeks (left - formalin-fixed) and 23.5 weeks (middle and right). Scoliosis, short neck, short deformed thorax and hirsutism in the older fetus are obvious.

**Extraskeletal findings** consisting in neural tube defects, hindbrain malformations, cardiovascular and genitourinary anomalies have been described in the former heterogeneous *Jarcho-Levin syndrome*. It is suggested that associated visceral anomalies are more common in sporadic cases of spinal malsegmentation than in the familial types of spondylocostal / spondylothoracic dysostosis (O' Neill, 2011a).

Our first index familial case is represented by a male fetus of 16.5 w, who was the second affected offspring of the family with features of spondylothoracic dysostosis (Fig. 15, left). At autopsy, we noted a Dandy-Walker variant of the cerebellum, asymmetry of thoracic and abdominal organs, hypospadias, and renal tubular microcysts.

The second index case, a female fetus of 23.5 w, offspring to consanguineous parents, had an atrial septal defect, a retroesophageal right subclavian artery and ectopic pancreatic tissue in the spleen.

**Radiography** shows the characteristic vertebral anomalies including vertebral segmentation with hemivertebrae and block vertebrae accompanied by deformity of the ribs. Fused ribs result in a typical 'crab-like' radiologic appearance of the thoracic skeleton (Fig. 16). The skeleton is otherwise normal.



Fig. 16. Vertebral segmentation and deformity of the ribs with thoracic asymmetry in spondylothoracic dysostosis. Left: 23.5 w - Right: At term, crab-like appearance of the ribs



In the early lethal form of spondylocostal/spondylothoracic dysostosis patients die perinatally with respiratory complications; other forms of the syndrome allow survival to a later age.

## 6.6 Group 38: Limb hypoplasia-reduction defects group

**Index cases: Roberts syndrome, Split Hand-Foot malformation with tibial hypoplasia**

### 6.6.1 Roberts syndrome

Roberts syndrome is a rare autosomal recessive condition caused by mutation in the *ESCO2* gene, the protein product of which is required for the establishment of sister chromatid cohesion during S phase. In the fetus it is manifest with facial clefting and symmetrical limb defects, resulting in tetraphocomelia in most cases (Kniffin, 2010). Alternatively the syndrome is called “Long bone deficiencies associated with cleft lip-palate”. Hypertelorism, facial hemangioma and clitoral or penile enlargement are also features of the syndrome. Another name of this condition often found in literature is “Roberts phocomelia” or “the (SC) pseudothalidomide syndrome”, because of the resemblance to malformations seen in the thalidomide embryopathy. “Phocomelia” is an old term for nearly total deficiency of the long bones of a limb, (Greek *phoka* = seal, *melos* = limb; *phocomelia* = seal limb).



Fig. 17. Median cleft lip and palate, micrognathia, hypertelorism, upper limb phocomelia, ectrodactyly and syndactyly, hypoplastic femora, and penile enlargement in a 12.5-week male fetus with Roberts syndrome.

Karyotypic analysis shows in 50% of cases a characteristic centromeric abnormality of the chromosomes, namely, puffing and splitting of sister chromatides. The finding was present in one 25-week male fetus of our series, confirming the diagnosis of Roberts' syndrome (Pavlopoulos et al., 1998), and was absent from a second male fetus of 12.5 weeks (Fig. 17).

### 6.6.2 Split Hand-Foot malformation with tibial aplasia

The Split Hand-Foot malformations are a group of genetically heterogeneous disorders, presenting as isolated forms (five genetically different forms) or in combination with tibial hypoplasia or aplasia. The latter condition [OMIM #119100] is autosomal dominant, with a recently determined molecular defect mapping on chromosome 1q42.2-q43 (O' Neill, 2009b).



Fig. 18. Cleft hand, tibial aplasia, and bifid femur in a 16.5-week male fetus

Our index case refers to a male fetus of 16.5 weeks sent for autopsy after termination of pregnancy because of sonographically diagnosed limb reduction defects (Fig. 18). A possible secondary aetiology should be ruled out, given that limb defects are often sporadic, attributed to vascular disruptions or amniotic band syndrome. At autopsy, we noted a cleft hand, absent tibia, bifid femur and hypoplasia of other long bones. This led to the diagnosis of the genetic disorder *Split hand/foot malformation with tibial aplasia*, alternatively named *Split-hand/foot malformation with long bone deficiency* [OMIM #119100]. The postmortem diagnosis conducted the genetic investigation and enabled genetic counseling of the family.

## 7. Conclusion

The pathologist will perform the post-mortem examination of a fetus or infant affected by a genetic skeletal disorder in cases of intrauterine death caused by lethal skeletal dysplasias, or, more often nowadays, when the detection of skeletal abnormalities on prenatal ultrasound leads to the termination of pregnancy. The presence of skeletal abnormalities mandates an

extended study of the fetus. Pediatric radiologists who have experience in radiologic assessment of skeletal disorders of infants and children can provide expertise in this area. However, in many institutions it is the task of the pathologist to deal with the skeletal disorders at autopsy. It is important that pathologists carrying out fetal and perinatal autopsies should be familiar with the phenotypic manifestations of the more common skeletal disorders, including the interpretation of radiologic findings. The association with extraskeletal abnormalities in particular settings also contributes to the diagnostic approach. The histology of the cartilage and bone and of the epiphyseal growth plate proves very useful in a restricted number of skeletal dysplasias. As specific diagnosis and classification of genetic skeletal disorders is difficult, a collaborative approach among pathological, radiological and genetic services is optimal to provide the parents with all available information regarding the diagnosis and prognosis of fetal and perinatal genetic skeletal disorders.

## 8. Acknowledgment

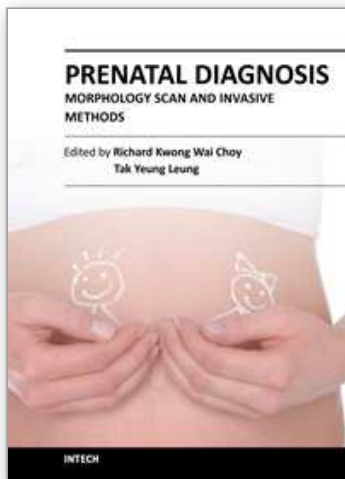
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## **Prenatal Diagnosis - Morphology Scan and Invasive Methods**

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This book provides detailed and comprehensive coverage on various aspects of prenatal diagnosis-with particular emphasis on sonographic and molecular diagnostic issues. It features sections dedicated to fundamentals of clinical, ultrasound and genetics diagnosis of human diseases, as well as current and future health strategies related to prenatal diagnosis. This book highlights the importance of utilizing fetal ultrasound/clinical/genetics knowledge to promote and achieve optimal health in fetal medicine. It will be a very useful resource to practitioners and scientists in fetal medicine.

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