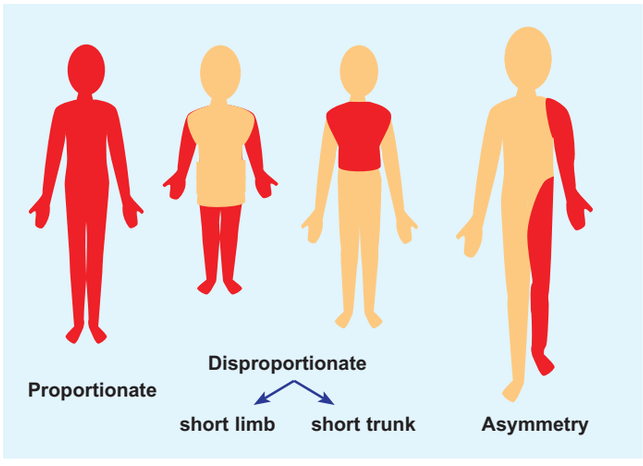
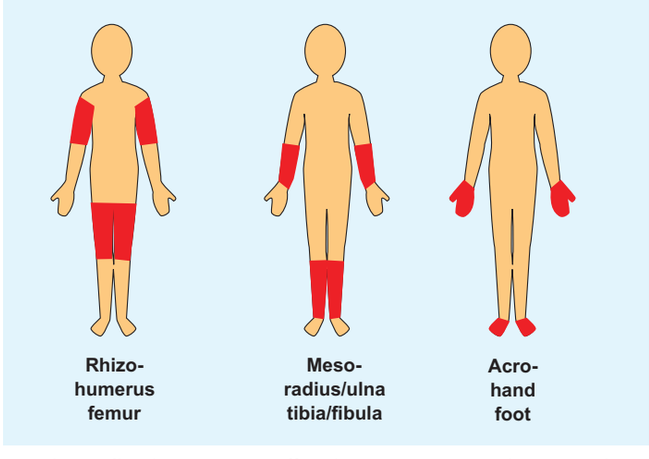
CHAPTER 12

SYNDROMES



A Short stature This may proportionate or disproportionate, or it may affect a region of the body asymmetrically.



B Micromelia Shortening may affect the "root" or proximal segment, the "middle" segment, or the "tip" of the limb.

Syndrome	Facies
Achondroplasia	Frontal bossing, depressed nasal bridge
Apert	Proptosis, downsloping palpebral fissures
Camptodactyly	Flat face
Cantu syndrome	Full lips, long philtrum
Cornelia de Lange	Synophrys, "carp" mouth
de Barsy	Progeroid
Down	Mongoloid
Emanuel	Low-hanging columella
Freeman-Sheldon	Whistling face
Hurler	Gargoyle
Larsen	Dish face
Pseudoachondroplasia	Normal face
Proteus	Elephant man
Rubinstein-Taybi	Squinting smile
Silver-Russell	Triangular face

C Facies Many syndromes may be distinguished by appearance of the face.

GENERAL CONSIDERATIONS

The title *syndromes* is used for lack of a more inclusive term. Syndromes are arranged in alphabetical order for simplicity. There is no comprehensive system of classification that is complete, because of diverse causes, heterogeneity of presentation, evolution of expression with growth, as well as rapid and continual medical discovery. These are diseases first and orthopedic problems second: most important is evaluation, because orthopedic management will not solve the primary problem and may deliver a fair outcome at best. This contrasts with disorders of the musculoskeletal system that occur in an otherwise normal child, where orthopedic management is the focus. All tissues of the skeleton may be affected, from bone to cartilage to surrounding soft tissues. The clinical presentation is broad, from premature osteoporotic fracture in the adult to perinatal lethal. While individually the disorders may be rare, collectively, their incidence may be as high as 1/5,000 births. It is important to realize that many diagnoses do not represent a single disease but rather a heterogeneous group of disorders of which only some subtypes are well characterized while others originate in single case reports.

Language

Syndrome, used by Galen as a compound of Greek συν: "with, together" and δρομοσ: "a course, race, running," signifies "a concurrence" of signs in, or the clinical presentation of, a disease.

Short stature may be defined as <2 standard deviations below mean height or below 2.5 percentile. An alternative guideline is height <5 ft. (150 cm). Short stature may be divided into proportionate, affecting the entire body equally, or disproportionate. Terms such as midget for the former and dwarf for the latter are not universally accepted. Little person is neutral and is aligned with the Little People of America.

Disproportion of short stature may arise from the limbs, referred to as micromelia (Greek μικρος: "small" and μελος: "limb"). Disproportionate shortening of the "trunk" is known as microcormia (Greek κορμος) [A]. Limb shortening may be asymmetric. Alternatively, limbs may be short at the "root," known as rhizomicromelia (Greek ριζα); at the "middle" segment, known as mesomicromelia (Greek μεσος); or at the "tip," known as acromicromelia (Greek ακρος) [B]]. This terminology comes from radiographic classification based upon the region of bone principally affected, such as epiphysis *versus* metaphysis versus diaphysis. The convenience of this system has led to its wide adoption; however, it is simplistic, bears no relationship to morbidity, and frequently suggests a connection between entities where there is none.

Of the skeleton, dysplasia (Greek δυς: "bad" and πλασσω: "I form") represents a generalized affection of the skeleton. Dysostosis (Greek οστεον: "bone") refers to involvement of a single bone or a group of physically or functionally related bones. Dysmorphism (Greek Morpheus, God of Sleep who may take any human "form" in dreams) is applied to a "bad form" of body part, often the *facies* (Latin) or "face" that can distinguish a specific disorder [C].

Classification

These disorders have been given descriptive names according to clinical presentation, pathogenesis, or radiographic appearance. Achondroplasia emphasizes cartilage as locus of disease, while osteogenesis imperfecta distinguishes bone as the abnormal tissue. Other skeletal dysplasia may be grouped according to whether they affect the metaphysis or the epiphysis of a long bone. Identification of genetic mutations has allowed molecular typing. For example, the type II collagenopathies span a spectrum from the severe Kniest dysplasia to spondyloepiphysial dysplasia and Stickler disease to the relatively mild precocious osteoarthritis. Challenges of molecular classification include:

- The molecular defects are numerous and evolving.
- Clinically unrelated disorders may have the same molecular defect. Achondroplasia is caused by mutation of one type (3) of fibroblast

growth factor receptor, while other types produce the craniosynostosis syndromes of Pfeiffer (1) and Crouzon (2).
- Clinically related disorders may have different molecular defects. Mutations in the gene encoding type IX collagen and the gene encoding cartilage oligomeric matrix protein both have been found in multiple epiphysial dysplasia.
- The molecular defects are heterogeneous, obscuring the biologic pathways to disease. The highest expression of fibroblast growth factor receptor 3 is in the brain, yet it is the expression in cartilage during endochondral ossification that is responsible for the clinical manifestations of achondroplasia.

Despite these limitations, knowledge of molecular biology may aid understanding of the tissue distribution of disease. Type I collagen is the principal structural protein of bone, dentin, and sclera, hence the association (and clinical subclassification) of osteogenesis imperfecta with dentinogenesis imperfecta and blue sclerae. Type II collagen occurs in cartilage and vitreous humor. As a result, Stickler arthroophthalmopathy may include osteoarthritis and retinal detachment.

Evaluation

Assess clinical features, support with imaging, and verify with histologic analysis and laboratory studies if available.

Stature After facial appearance, stature is most distinguishing. Stature may be short, normal, or tall. Short stature may be proportionate, such as in endocrinopathy, or disproportionate, such as skeletal dysplasias. Few syndromes feature tall stature, such as Marfan. Neuromuscular disorders do not affect stature significantly.

Family history Many syndromes are inheritable. They may be autosomal or X-linked and dominant or recessive. Others represent new spontaneous mutations. Neurofibromatosis type 1 is transmitted as an autosomal dominant to half affected children, while in the other half, the disorder arises spontaneously.

Development Some syndromes are characterized by global delay, such as Prader-Willi syndrome. Others affect cognitive or motor function separately, such as muscular dystrophy. Developmental delay may be temporal or permanent; for example, in achondroplasia, motor development may be delayed in the first 2 years, due to macrocephaly and ligamentous laxity.

System Divide conditions into those that affect the musculoskeletal system and those that affect other systems and viscera [D]. Within the musculoskeletal system, conditions may be categorized geographically according to the part affected.

Pathognomonic features From Greek παθος: "disease" and γιγνωσκω: "I know," these may form the nidus around which other findings may be assembled. This approach represents a primary focus on the disease, in contrast with the system approach, which focuses on the manifestation [E].

Imaging

RÖNTGENOGRAMMES These form the basis of evaluation. They may describe a disease geographically.

- Part of the skeleton, for example, spondylo- for spine
- Part of a long bone, for example, epiphysial, metaphysial, and diaphysial

Röntgenogrammes may describe the skeleton qualitatively.

- Increased density, for example, osteopetrosis
- Reduced density, for example, osteogenesis imperfecta
- Mixed, for example, stippling of epiphysis in chondrodysplasia punctata

Röntgenogrammes may reveal features that, while not always present in every patient, are pathognomonic [E].

Radiographic features vary according to age. Many features that may aid diagnosis in childhood disappear by adulthood, such as epiphysial stippling. These features are considered dynamic, a manifestation of abnormal bone development.

Part	Abnormality	Syndrome
Spine	Kyphosis—thoracolumbar	Achondroplasia; metatropic dysplasia; mucopolysaccharidoses
	Kyphosis—cervical	Diastrophic dysplasia; Larsen
	Atlantoaxial instability	Down; Dyggve—Melchior—Causen; Kniest; mucopolysaccharidoses; spondyloepiphysial dysplasia
	Sacrococcygeal	Carpenter; caudal regression
Hip	Coxa vara	Type II collagenopathy
Foot	Club	Arthrogryposis; Bruck; camptomelic dysplasia; caudal regression; diastrophic dysplasia; Escobar; Freeman—Sheldon; Larsen; Melnick—Needles; Möbius; nail—patella
	Polydactyly	Carpenter; chondrodysplasia punctata; chondro—ectodermal dysplasia; Grebe; Rubinstein—Taybi
	Syndactyly	Apert
Long bone	Bowing	Neurofibromatosis (tibia); multiple exostosis (forearm); mesomelic dysplasia
Knee	Patella	Meier—Gorlin; nail—patella; Rubinstein—Taybi; small patella
Elbow	Radial head dislocation	Beals; Cornelia de Lange; nail—patella; mesomelic dysplasia; otopalatodigital
Forearm	Radial anomaly	Goldenhar; Holt—Oram; TAR; VACTERL
Wrist	Supernumerary fusion	Apert; chondro—ectodermal dysplasia; multiple synostosis; otopalatodigital
Hand	Polydactyly	chondro—ectodermal dysplasia
	Syndactyly	Apert
Skin	structure	Bruck; chondrodysplasia punctata; Ehlers—Danlos; melorheostosis; multiple synostosis; pterygium; oculodentodigital dysplasia; proteus; pterygium
	pigmentation	McCune—Albright; neurofibromatosis; oculodentodigital
Joint		Arthrogryposis; epiphysial dysplasia
Muscle		Amyoplasia; Poland
Nerve		cerebral palsy; Friedreich ataxia; Lesch—Nyhan; oculodentodigital dysplasia; Sanfilippo
Blood		Ehelers—Danlos; Klippel—Trénaunay—Weber; Marfan; melorheostosis
Nail		Apert; chondro—ectodermal dysplasia; multiple synostosis; nail—patella; oculodentodigital; otopalatodigital; pycnodysostosis
Hair		Metaphysial chondrodysplasia of McKusick; oculodentodigital dysplasia; trichorhinophalangeal

D Geographical distribution Syndromes may be distinguished and grouped by anatomic part affected.

Pathognomonic feature	Syndrome
Caudal reduction in interpedicular distance	Achondroplasia
Champagne pelvis	
Elephant ilia	
Cloverleaf skull	Antley-Bixler
Mitten hand and foot	Apert
Macroglossia	Beckwith-Wiedemann
Accordion femora	Osteogenesis imperfecta
Saber tibiae	
Wormian bones	
Blue sclerae	Marshall-Smith, osteogenesis imperfecta
Cauliflower ears—calcification of pinnae	Diastrophic dysplasia
Hitch-hiker thumb—bracchydactyly of first metacarpal	
Cervical kyphosis	
Iliac horns	Nail-patella
Patella: a-/hypo-plasia	Meier-Gorlin; nail-patella
Absent or bifid clavicles	Cleidocranial dysostosis
Hot-cross bun skull	
Double hump vertebrae	Dygvve-Melchior-Clausen
Exostoses directed away from physis	hereditary multiple exostosis
Exostoses directed toward physis	metachondromatosis
Accessory calcaneal apophysis	Larsen syndrome
Lace-border iliac crests	Dyggve-Melchior-Clausen
Monophalangic hallux	Fibrodysplasia ossificans progressiva
Whistling face	Freeman-Sheldon
Ashkenazim	Familial dysautonomia; Gaucher; Tay-Sachs
Erlenmeyer flask femur	Craniometaphysial dysplasia; Gaucher
Swiss cheese epiphysial degeneration	Kniest dysplasia
Café-au-lait patches	'Coast of Maine': M^{c}Cune-Albright
	'Cost of California': neurofibromatosis
Lisch nodule	Neurofibromatosis
Coccyx prolongation like a tail	Metatropic dysplasia
Synostosis	Antley-Bixler; Apert; femoral-facial syndrome; mesomelic dysplasia; multiple synostosis
Madelung deformity	Leri-Weill dyschondrosteosis
Sandwich vertebrae, rugger jersey spine, endobones.	Osteopetrosis (of Albers-Schönberg)
Tree frog feet.	otopalatodigital
Secondary ossification center at base of second metacarpal and metatarsal	
Second metacarpal pseudo-epiphysis	Silver-Russell

E Pathognomonic features These may offer direction in a sea of complexity.

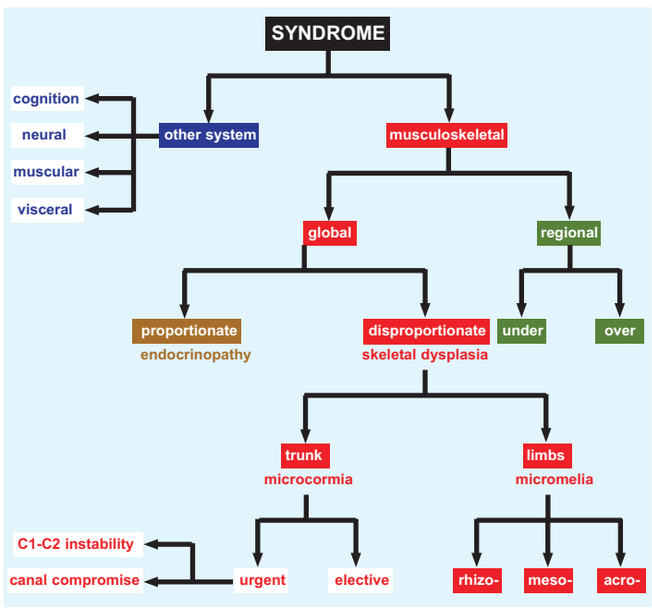
Ultrasonography This modality may establish a prenatal diagnosis. The fundamental finding is short limbs for gestational age. A small thorax (including reduced thoracic:abdominal ratio) is a feature of lethal skeletal dysplasias. There may be clinical expression of osseous disease, for example, fractures in osteogenesis imperfecta. There may be delayed or absent ossification, for example, of the clavicles in cleidocranial dysplasia. There may be regional abnormalities, for example, clubfoot in diastrophic dysplasia.

Other imaging modalities These are employed according to specific relevance to disease. In achondroplasia, foramen magnum stenosis may be measured on computed axial tomography. Published disease-specific standards are available based upon such measurements. Critical stenosis of the vertebral canal due to spine deformity may be evaluated by magnetic resonance imaging.

Laboratory analysis This most commonly is performed of blood, urine, and skin. Chromosome number, size, position, and staining pattern may be determined by karyotyping blood. Hormone serum levels, for example, growth hormone, thyroxine, and thyroid stimulating hormone, identify endocrinopathy. The mucopolysaccharidoses are characterized by enzyme deficiency leading to reduction of product and accumulation of precursor that is detected by urine assay. The clinical diagnosis of Marfan syndrome may be confirmed by immunohistochemical staining or pulse-chase analysis of fibrillin-1 protein in cultured skin cells obtained from skin biopsy. Biochemical and molecular analysis of skin and blood for type I collagen mutation aids the diagnosis and typing of osteogenesis imperfecta. Ehlers-Danlos VI may be confirmed by insufficiency of hydroxylysine on analysis of hydrolyzed dermis, reduced lysyl hydroxylase activity in cultured skin fibroblasts, and altered ratio of lysyl pyridinoline to hydroxylysyl pyridinoline in urine.

Algorithm

The following is a singular and simplified approach to turn the key and open the door to this multidisciplinary area into which may be drawn the orthopedic surgeon at times insecure and intimidated [F].



F A simple algorithm for initial navigation of a syndromic patient.

ACHONDROPLASIA

Most common skeletal dysplasia, with incidence ~ 1:25,000 live births.

Gain-of-function fibroblast growth factor receptor 3 (FGFR3) mutation on chromosome 4p16.3 codon 380 glycine. Chondrocyte activation of FGFR3 increases bone formation and accelerates fusion of ossification centers with premature synchondrosis closure, limiting endochondral bone growth.

This may be transmitted as autosomal dominant with complete penetrance; however, most are new spontaneous mutations. A family of FGFR3 mutations is recognized ranging from mild (hypochondroplasia) to moderate (achondroplasia) to severe (thanatophoric dysplasia).

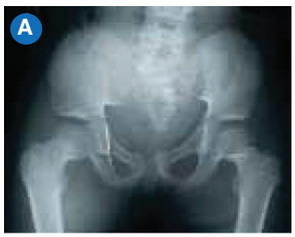
Features do not become apparent on ultrasonogram until after 16 weeks.

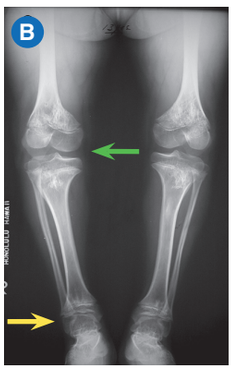
Abnormal endochondral with spared membranous ossification produces a large head with narrow foramen magnum, "champagne pelvis" with constricted triradiate cartilage [A], long clavicles with broad shoulders, long fibulae with varus ankles and knees [B], and short pedicles with lumbar spinal stenosis [C]. Hypotonia in infancy, rhizomicromelia [D], frontal bossing with midface hypoplasia, trident hand [E], thoracolumbar kyphosis, joint contractures (including at the hips exaggerating lumbar lordosis), and "chevron" metaphysis.

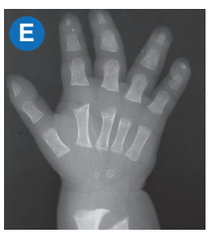
Decompression of brainstem for foramen magnum stenosis, based upon MRI compared with normative data, somatosensory evoked potentials, and polysomnography. Spine osteotomy and fusion for thoracolumbar kyphosis. Due to pedicle hypoplasia, decompression for lumbar spinal stenosis must include articular process excision, requiring fusion and instrumentation. Osteotomy for genua vara. Physiodesis of distal fibula for ankle varus.

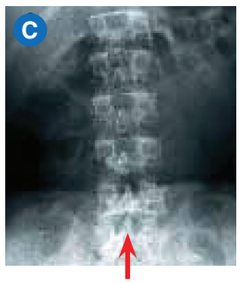
Nonsurgical treatment includes weight control, management of frequent middle ear infections and dental crowding, adenotonsillectomy and nasal mask continuous positive airway pressure for obstructive sleep apnea.

Pharmacotherapy includes growth hormone (although there is no consensus), and BMN-111, a stabilized version of C-type natriuretic peptide that inhibits the FGFR3 pathway.









Future strategies for treatment include the following:

- Chemical inhibitors of FGFR3 tyrosine kinase
- Antibodies to interfere with binding of FGF ligands to FGFR3
- C-type natriuretic peptide antagonism of FGFR3 downstream signaling by inhibition of mitogen-activated protein kinase pathway in growth plate chondrocytes, thereby recovering bone growth

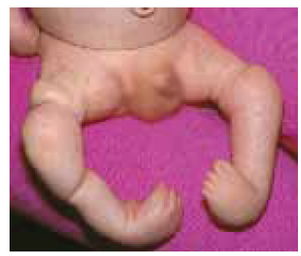
ACRODYSOSTOSIS

Type 1 caused by heterozygous mutation in PRKAR1A gene on chromosome 17q24, and type 2 by mutation in PDE4D gene on chromosome 5q12.

Peripheral dysostosis (short tubular bones) of hands and feet. Reduced interpedicular distance producing spinal stenosis. Stippling of cone-shaped epiphysis resolves spontaneously in the first few years of age.

AMNIOTIC BAND SYNDROME

Also known as Streeter anomaly.



Herniation of members through ruptured amnion results in constriction, vascular occlusion, and necrosis. ADAM (amniotic deformity, adhesions, mutilations) complex includes associated terminal transverse defects and cleft lip and palate. LBWD (limb body wall defect) includes associated body wall and visceral defects explained by pressure on the embryo during the first 4 weeks.

AMYOPLASIA

See arthrogryposis.

ANTLEY-BIXLER SYNDROME

Mutation of cytochrome P450 oxidoreductase on 7q11.23.

Trapezoidocephaly secondary to lambdoid and coronal synostosis, radiohumeral and radioulnar synostosis, and camptodactyly.

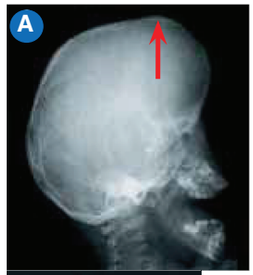
Abnormal steroidogenesis and genitourinary and cardiac anomalies.

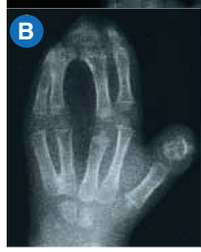
Airway obstruction may lead to demise in the neonatal period.

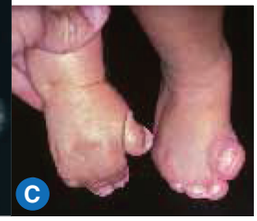
APERT SYNDROME

Mutation in fibroblast growth factor receptor 2 gene (FGFR2). By contrast with dominant mutations in the FGFR3 gene, which affect endochondral ossification resulting in achondroplasia, dominant mutations of FGFR1 and FGFR2 cause the craniosynostosis syndromes of Apert, Crouzon, and Pfeiffer, which involve bones arising by membranous ossification.

Autosomal dominant; however, most *de novo* mutations.



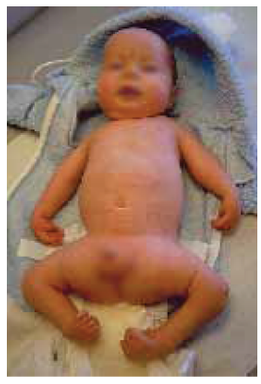




Wheaton first reported two cases of what Apert called acrocephalosyndactyly. Acrocephaly is due to coronal synostosis [A]: early decompressive craniectomy may limit mental deficiency. Syndactyly and synonychia produce "mitten" hand [B] and "sock" foot [C]: the former is an indication for release, and the latter for osteotomy or ostectomy to relieve pressure. Failure of cervical segmentation, broad thumbs and halluces, and carpal and tarsal coalition. Cardiac, respiratory, nervous, abdominal, and genitourinary anomalies.

ARTHROGRYPOSIS

Originally termed arthrogryposis multiplex congenita. Arthrogryposis refers to a heterogeneous group of disorders of which the common feature is multiple congenital joint contractures.



Fetal akinesia due to maternal disease, intrauterine constraint, or vascular compromise retards development of nerves, muscles, or connective tissues. The earlier and longer the loss of movement, the more severe the deformities. Muscle is replaced by fibrofatty tissue. Arthrogryposis without other system disease is subclassified as amyoplasia. Distal arthrogryposis, affecting hands and feet, is autosomal dominant. Intelligence is normal. Limited joint motion, medial rotation of shoulders, extension of elbows, flexion and ulnar deviation of wrists, camptodactyly, thumb in palm, hip dislocation, knee contracture, clubfoot, and scoliosis. Loss of cutaneous creases with joint dimpling. Operative reduction of dislocated hips is controversial. Femoral shortening facilitates treatment of flexion contracture. Center the arc of motion at 15 degrees: walking is easier on straight knees. Talectomy may be necessary for clubfoot. Stiffness limits correction of scoliosis.

BEALS SYNDROME

Type	Features
I	Known as auriculo–osteodysplasia. Autosomal dominant. Short stature, auricular anomalies including elongation of lobe with secondary posterior lobule, radiocapitular dysplasia with head of radius dislocation, hip dysplasia.
II	Known as congenital contractural arachnodactyly. Mutation in fibrillin-2 gene at 5q23-q31. Marfan syndrome without visceral involvement and with crumpled ear helices as the hallmark, due to expression of fibrillin-2 in auricular cartilage.

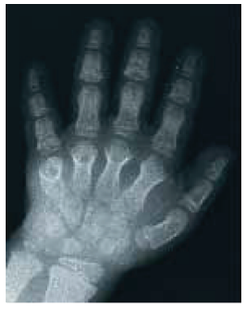
BECKWITH-WIEDEMANN SYNDROME

Mutations in several imprinted genes within 11p15.5 region, as well as mutation of 5q35. The former also is affected in Silver-Russell syndrome, while the latter in Sotos syndrome.

Autosomal dominant with variable expressivity, as well as *de novo* mutation.

Overgrowth, including macroglossia, exophthalmos, limb hypertrophy, and visceromegaly. Tumor diathesis, including Wilms tumor, hepatoblastoma, neuroblastoma, and adrenal carcinoma. Posterior helical ear pits, abdominal wall defects including umbilical hernia, and renal anomalies. Neonatal hypoglycemia and history of hydramnios and prematurity.

BRACHYDACTYLY



Multiple mutations identified for different types and subtypes. Classified into groups A to E, each of which are subclassified. First syndrome in humans in which Mendelian inheritance was described.

Premature physial closure; variable short stature; short metacarpals, metatarsals, and phalanges; and variable shortening of humerus, radius, and ulna. Hypersegmentation with an extra ossicle producing phalangeal deviation distinguishes type C.

BRACHYOLMIA (BRACHYRHACHIA)

Named from Greek βραχυς: "short" and ολμος: "trunk," whence the synonym brachyrhachia, from Greek ραχις: "spine".

Type	Features
1	Hobaek, Toledo. Autosomal recessive. Scoliosis, endplate irregularity, intervertebral narrowing, corneal opacities (Toledo), precocious calcification of costal cartilage.
2	Maroteaux. Autosomal recessive. Affects the spine less, and is associated with precocious calcification of the falx cerebri.
3	Autosomal dominant, caused by a gain of function mutation in the gene for transient receptor potential cation channel subfamily V member 4, a Ca^{2+} channel. Allelic with Charcot-Marie-Tooth and spinal muscular atrophy, distal subtype. Kyphoscoliosis and flattened, irregular cervical vertebrae.
4	Autosomal recessive, caused by mutation in gene encoding enzyme bifunctional 3′-phosphoadenosine 5′-phosphosulfate synthetase 2. The enzyme synthesizes 3′-phosphoadenosine 5′-phosphosulfate from ATP and inorganic sulfate, providing the source for cellular sulfation.

BRUCK SYNDROME

Type	Mutation
1	Mutation of FKBP10 gene on 17q21.
2	Mutation of PLOD2 gene on 3q23-q24.

Deficiency of bone-specific telopeptide lysyl hydroxylase, resulting in aberrant cross-linking of type I collagen. Lysine residues in the triple helix are normally hydroxylated. Enzyme normal in cartilage and ligament.

Fractures and Wormian bones resemble osteogenesis imperfecta. Normal sclerae and teeth. Contractures resemble arthrogryposis, hence the appellation "osteogenesis imperfecta with joint contractures." Pterygia, scoliosis, and clubfoot.

CAFFEY DISEASE (INFANTILE CORTICAL HYPEROSTOSIS)

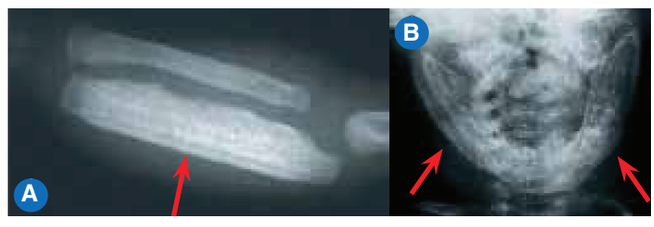
Mutation of 17q21.31-q22, which encodes the α-1 chain of type 1 collagen; however, no features of osteogenesis imperfecta.

Autosomal dominant as well as *de novo* mutation.

Onset in the first few months of life with spontaneous resolution by 2 years with minimal sequelae. Despite its name, it has been detected by ultrasonogram *in utero* (prenatal form) and in adulthood.

Inflammatory presentation, including fever and hot, tender long bones [A] and mandibles [B], which show diaphysial periosteal deposition.

This is distinct among hereditary disorders in being transient and leaving no residue.



CAMP(T)OMELIC DYSPLASIA

Greek καμπη: "bending, flexion, and twisting" and μελοσ: "limb," to describe the characteristic feature of long bone bowing, especially of the tibiae, clubfoot, and hip dislocation.

17q24 mutation with haploinsufficiency of SOX 9.

Cutaneous dimpling at apex of bowing. Cleft palate, micrognathia, flat face, and pterygium colli. Thoracic dysplasia, including tracheobronchial hypoplasia, bladeless scapulae, slender or absent ribs, reduced cage volume, and sternal mineralization. Congenital heart and kidney disease. Death is frequent in infancy due to respiratory insufficiency.

Gonadal dysgenesis may culminate in sex reversal of affected XY cases.

CARPENTER SYNDROME

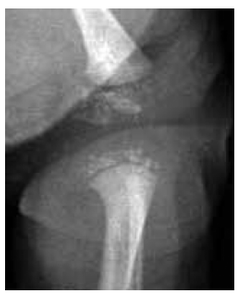
Autosomal recessive mutation in Ras-associated protein RAB23 gene on 6p11.

Also called acrocephalopolysyndactyly. Craniosynostosis produces a "pointed head." Brachysyndactyly of the hands and preaxial polysyndactyly of the feet. Correction of genu valgum to stabilize patellae. Pilonidal dimple with absent coccyx.

Variable mental retardation, short stature, obesity, and eye, ear, cardiovascular, and genitourinary anomalies.

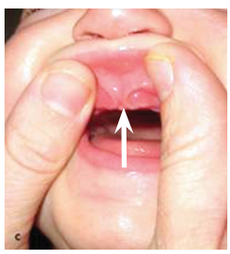
CHONDRODYSPLASIA PUNCTATA (CONRADI-HÜNERMANN)

Dominant mutation in the gene encoding delta(8)-delta(7) sterol isomerase emopamil-binding protein on Xp11.23-p11.22, an enzyme essential to cholesterol biosynthesis. Rhizomicromelic dwarfism characterized by asymmetry of involvement and by calcific stippling of trachea, thorax, spine, pelvis, coracoid process, and glenoidal cavity. The latter typically resolves after first year of life. Kyphoscoliosis and clubfoot. Cutaneous disease, including striated ichthyosiform hyperkeratosis, whorled pigmentation, cicatricial alopecia, and "orange-peel" skin. Ocular anomalies, including cataracts, nystagmus, and glaucoma. Warfarin teratogenicity, by inhibition of synthesis of gamma-carboxyglutamic acid, which is involved in both clotting and calcification, may lead to chondrodysplasia punctata.



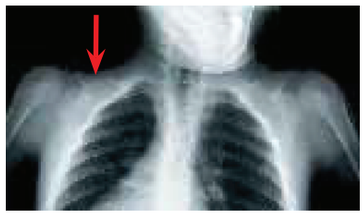
CHONDROECTODERMAL DYSPLASIA (ELLIS-VAN CREVELD)

Mutation in Ellis-van Creveld gene on 4p16. Micromelic dwarfism characterized by postaxial polydactyly, capitate–hamate fusion, genua valga, clubfoot, nail dystrophy, and rib hypoplasia with narrow chest. Upper lip anomaly described as "lip-tie" [A] and tooth eruption at birth described as "natal teeth." Cardiac and male genitourinary anomalies and variable mental retardation. Largest pedigree in the Old Order Amish of Lancaster County, Pennsylvania, whose members were described as having "six-fingered dwarfism." On the way to a pædiatric conference in England (1938), the Scott Ellis met the Dutchman van Creveld while sitting in the same compartment of a train, where they discussed a case they each had seen independently.



CLEIDOCRANIAL DYSPLASIA

Autosomal dominant loss-of-function mutation in runt-related transcription factor 2 gene (RUNX2) on 6p21.1.



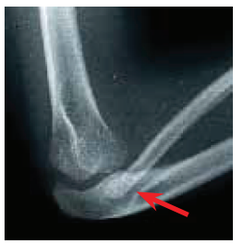
Head has been likened to a "hot cross bun" due to persistent open sutures. The head also is known as "Arnold" head, after a Muslim Chinese progenitor from South Africa with >1,000 descendants.

Midline defects, including hypoplastic or aplastic clavicles with hypermobile shoulders, short middle phalanges, coxa vara, symphysis pubis diastasis, scoliosis, and spondylolisthesis. Dental anomalies.

Formerly called "dysostosis" to emphasize the regional nature of anomalies of the head and shoulder.

CORNELIA DE LANGE SYNDROME

Autosomal dominant as well as *de novo* mutation in Nipped B-like (NIPBL) gene on 5p13.1, which encodes a component of cohesin, a protein complex that coheres sister chromatids during cell division. Characteristic facies, including synophrys, crescentic, or "carp" mouth, long philtrum, anteverted nares, and ptosis.



Mental and growth retardation, "growling" cry, hirsutism, and ocular, cardiac, genitourinary, gastrointestinal, and pulmonary anomalies. Self-injurious and autistic behavior. Micromelia disproportionately affecting the upper limb, including ulnar dysgenesis, radial head dislocation, oligodactyly, proximally placed thumb, clinodactyly of smallest finger, and single palmar flexion crease.

de Lange was Professor of Pædiatrics at the University of Amsterdam, where she was followed by van Creveld. The disorder was described 17 years earlier (1916) by Brachmann, whose studies were interrupted by a call to the German Army.

CRANIODIAPHYSIAL DYSPLASIA

Mutation in the SOST gene on 17q12-q21.

Hyperostosis of skull encroaches on foramina and osseous canals leading to cranial nerve palsy and hearing loss, of face results in "leonine facies," and of the skeleton bones produces diaphysial sclerosis and medullary stenosis, in particular of ribs, clavicles, and sternum.

CRANIOMETAPHYSIAL DYSPLASIA

Autosomal dominant form caused by mutation in the human homolog of mouse progressive ankylosis gene on 5p15.2-p14.1. Additional autosomal recessive form mapped to chromosome 6q21-22.

Skull and facial manifestations similar though less severe than above. Metaphysial rather than diaphysial involvement is distinguished by "Erlenmeyer flask" deformity in long bones.

de BARSY SYNDROME

This is one of the progeroid syndromes, which are distinguished by cutis laxa with subcutaneous paucity of fat and prominence of veins, together with "pseudohydrocephalic" head, producing an "old appearance," from Greek γερων: "old man."

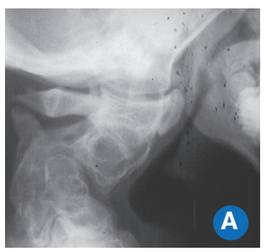
This type most affects the skeleton: multiple joint dislocations and subluxations, in particular of the hip, scoliosis, and vertical talus.

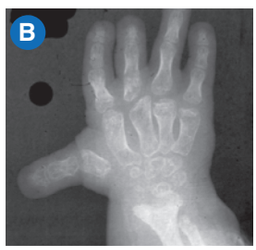
Other features include corneal clouding, short stature, and mental retardation.

DIASTROPHIC DYSPLASIA

Mutation in the solute carrier family 26 (sulfate transporter), member 2, gene (SLC26A2) on 5q32-q33.1. Allelic to epiphysial dysplasia, multiple. Greek δια-, an emphatic prefix, and στρεφω, "I twist," describe the "severely twisted" clubfeet and spine. The latter includes thoracolumbar kyphoscoliosis and cervical kyphosis [A]. Short first metacarpal producing "hitchhiker thumb" [B] and calcification of pinnae producing "cauliflower ear." The former permits diagnosis on ultrasonogram at 16 months *in utero*. Multiple joint contractures and malformations, in particular of the hips, which show flattening and a "double-hump" deformation.

Other features include cleft palate, collapse of the tracheobronchial tree, and restrictive pulmonary disease.



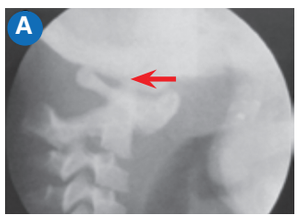


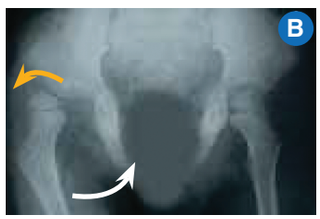
DOWN SYNDROME (TRISOMY 21)

Genomic dosage imbalance at 21q22.3 producing phenotypic variability. Diagnosis by Quad test (serum α-fetoprotein, estriol, β-HCG, and inhibin A) in second trimester of pregnancy: a positive test is followed by amniocentesis.

Risk increases with maternal age: 9-fold from 30 years to 40 years. Incidence is 1:1,000.

"Mongoloid" facies; simian (Latin *simia*: "ape") crease (single transverse palmar); hypotonia; ligamentous laxity; instability of C1-C2 [A], hips [B], and patella; flat feet; and scoliosis.





Screen for C1-C2 instability in symptomatic patient, including local signs, such as torticollis and neck stiffness, and global signs, such as myelopathy. Asymptomatic or general screening is contraindicated:

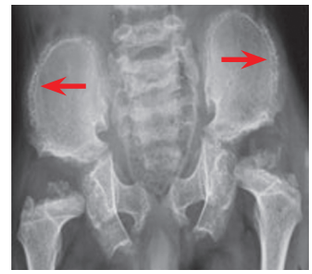
- Symptoms and signs precede neural injury.
- Radiographic instability may alternate with stability without clinical correlation.
- Atlantoaxial fusion has a high complication rate.

Cognitive impairment; hearing loss, usually conductive; hypothyroidism; and congenital malformation of heart, in particular atrioventricular septal defect; gut, such as duodenal atresia; blood, in particular leukemia; and brain, including senile plaques and neurofibrillary tangles leading to premature Alzheimer disease.

The disorder was first described by John Langdon Haydon Down of London, whose *Observations on an Ethnic Classification of Idiots* (1866) included a description of the "Mongoloid" type. While this study has been condemned as racist, the final sentence suggests no such intention, as Down regarded the "degeneracy" across racial barriers "to furnish some arguments in favour of the unity of the human species."

Down also first described a mentally delayed obese girl whose hands and feet remained small as a hypogonadal adult, seven decades before the report of Prader, Labhart, and Willi.

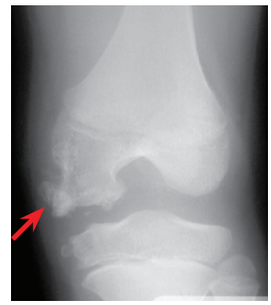
DYGGVE-MELCHIOR-CLAUSEN SYNDROME



Mutation in dymeclin gene at 18q21.1.

Dymeclin is necessary for correct organization of Golgi apparatus. Allelic with Smith-McCort dysplasia. Psychomotor retardation, hip instability with waddling gait, odontoid hypoplasia with C1-C2 instability, platyspondyly, vertebral anterior beaking and kyphoscoliosis, hypoplasia of scapula and glenoid cavity, epiphysial/apophysial irregularity manifesting as "lace-border" iliac crests, widening of sacroiliac joints and symphysis pubis, and camptodactyly.

DYSPLASIA EPIPHYSIALIS HEMIMELICA



Also known as Trevor disease. Non-Mendelian and nonfamilial. Boys more than thrice girls. Osteocartilaginous tumors arising from epiphysis, often lower limb, multilevel, and ipsilateral. Lesions cause pain, swelling, and deformity, starting during infancy or early childhood. Radiolucency of lesions delays diagnosis. Manage by excision and osteotomy for deformity correction. Recurrence is common, necessitating repeat operation(s).

EHLERS-DANLOS SYNDROMES

A group of hereditable disorders characterized by:

- Skin hyperextensibility. Acrogeria. Collagen fibers seen on electron microscopy of skin have been likened to hieroglyphics.
- Articular hypermobility. Instability of hip, patella, elbow, and shoulder.
- Tissue fragility. Prematurity in 50% due to premature rupture of fetal membranes. Vascular and visceral rupture. Bruisable skin that heals with "cigarette paper" scars. Hernia and pneumothorax.
- Skeletal deformity. Kyphoscoliosis, spondylolisthesis, atlantoaxial rotatory displacement, flatfoot, and pectus deformity. Tendency to recurrent deformity after correction.

The disorder may be classified into 10 subtypes, but V, VIII, and X may not be distinct entities. The subtypes have distinguishing features, with variable overlap. Most have autosomal dominant transmission.

Type	Mutation
I	Type V collagen α-1 chain on 9q34.3. Type V collagen α-2 chain on 2q32.2. Type I collagen α-1 chain on 17q21.33.
II	Type V collagen α-1 chain on 9q34.3.
III	Tenascin-XB on 6p21.3. Type III collagen α-1 chain on 2q32.2.
IV	Type III collagen α-1 chain on 2q32.2.
V	Abnormal collagen cross-linking due to deficiency of lysyl hydroxylase.
VI	Lysyl hydroxylase on 1p36.22.
VII	Type I procollagen N-proteinase on 5q35.3.
VIII	12p13.
IX	Cu(2+)-transporting ATPase, alpha polypeptide on Xq21.1. Allelic to Menkes syndrome.
X	Fibronectin.

Type	Features
I	Classic gravis: "severe".
II	Classic mitis: "mild". Mildness may delay or preclude diagnosis.
III	Hypermobility without skeletal deformity.
IV	Vascular. Autosomal dominant or recessive. Spontaneous rupture of major vessels and viscera. Aneurysm, fistula.
V	X-linked.
VI	Ocular-scoliotic. Kyphoscoliosis from infancy. Retinal detachment, scleral fragility, rupture of ocular globe.
VII	Dermatosparaxis ("skin tearing") due to abnormal type I collagen in skin. Autosomal recessive.
VIII	Peri-odontitis: gingival recession, premature loss of teeth, resorption of alveolar bone.
IX	Skull. Occipital horns adjacent foramen magnum directed caudad. Wormian bones. Coarse hair.
X	Striae distensae. Petechiae due to defect in platelet aggregation.

EMANUEL SYNDROME

Malsegregation of the t(11;22)(q23;q11.2) translocation, a rare example in humans of reciprocal (non-Robertsonian) exchange of genetic material between chromosomes.

Kyphosis and scoliosis and hip dislocation.

Ear: preauricular tag and sinus, low set, hearing loss, and otitis media.

Eyes: hooded eyelids, strabismus, and myopia.

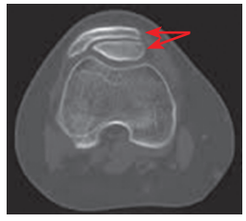
Psychomotor delay; seizures; cardiovascular anomalies, including aortic and pulmonary stenosis and septal defects; and genitourinary anomalies, including absent kidney and cryptorchidism.

EPIPHYSIAL DYSPLASIA, MULTIPLE

Genetic heterogeneity manifested by six types, designated EDM1-6.

Type	Features
1	Mutation in the gene for cartilage oligomeric matrix protein on 19p13.11. Includes milder form (Ribbing) and more severe form (Fairbank). Allelic to pseudoachondroplasia. Diagnosis aided by reduced serum levels of cartilage oligomeric matrix protein
2	Mutation in gene encoding type 9 collagen α-2 chain on 1p33-p32.2, which also has been implicated in susceptibility to intervertebral disc disease with sciatica.
3	Mutation in gene encoding type 9 collagen α-3 chain on 20q13.33. Myopathy may distinguish this type.
4	Mutation in the solute carrier family 26 (sulfate transporter), member 2 gene (SLC26A2) on 5q32-q33.1. Allelic to diastrophic dysplasia, atelosteogenesis II, achondrogenesis IB. Distinguished by clubfoot and double-layered patella (red arrows).
5	Mutation in matrilin-3 gene on 2p24.1. Allelic to one form of spondylo-epimetaphysial dysplasia.
6	Mutation in gene encoding type 9 collagen α-1 chain on 6q13.

Normal to moderate short stature. Delayed and irregular epiphysial formation leads to long bone deformity, in particular coxa vara, genua vara or valga, and brachydactyly as well as premature osteoarthritis.



Multiple epiphysial involvement distinguishes this disorder from Legg-Calvé-Perthes disease. Sparing of the spine distinguishes it from spondyloepiphysial dysplasia.

ESCOBAR SYNDROME

See pterygium syndrome.

FAMILIAL DYSAUTONOMIA

Also known as Riley-Day syndrome, congenital insensitivity to pain, and hereditary sensory and autonomic neuropathy type III.

Mutations in the inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein (IKBKAP) gene on 9q31.3.

Diminished pain and temperature perception leads to self-inflicted injuries. Vasomotor instability often triggered by stress, hyperhidrosis, alacrima, cutaneous blotching, and absence of fungiform papillae on tongue. Lack of axon flare after intradermal injection of histamine. Gastrointestinal and renal dysfunction. Increased prevalence in Ashkenazi Jewish descent.

Orthopedic problems include fracture, autoamputation, osteomyelitis, septic arthritis, neuropathic arthropathy, vibratory loss, areflexia, and scoliosis.

Emotional lability and absence of pain dictate conservative management.

FANCONI ANÆMIA

Genetically heterogeneous with 15 complementation groups. Common feature is abnormal DNA breakage, cross-linking, and repair.

Myelophthisis with pancytopenia requires bone marrow transplant.

Short stature. Radial defects, including hypoplastic/absent/bifid thumb as well as absent radius, require reconstruction.

Genitourinary anomalies, including hypoplastic/absent/horseshoe/ectopic kidney, hypogonadism, cardiac septal defects, hyperpigmentation with *café au lait* spots, and malignant diathesis.

FEMORAL–FACIAL SYNDROME

Facies characterized by long philtrum, thin upper lip, hypoplastic alae nasi, and microretrognathia.

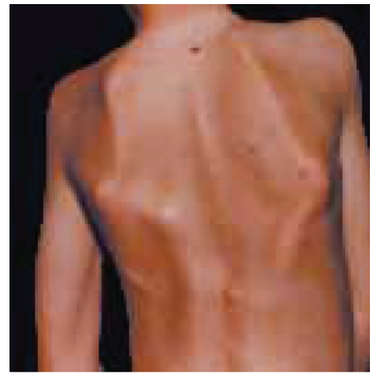
Femoral hypoplasia/aplasia with acetabular dysplasia. Radioulnar and radiohumeral synostosis. Congenital scoliosis. Sacral dysplasia may resemble caudal regression syndrome. Feet with preaxial polysyndactyly and clubfoot. Sprengel anomaly.

Cardiac and genitourinary anomalies.

One-third of patients have a prenatal history of maternal diabetes.

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Distinguish *myositis ossificans*, a general term for heterotopic ossification that may be subclassified as *traumatica* when it follows injury and is not hereditable.



Mutation in activin A receptor type I gene on 2q24.1 results in abnormal signal transduction in response to bone morphogenetic protein type I.

Episodic and unpredictable heterotopic ossification of striated muscle, in craniocaudad, axial to appendicular, and proximal to distal directions.

Only signs at birth are halluceal deformation and monophalangism. Clinodactyly, digital reduction defects, vertebral fusion, hearing loss, and alopecia.

Pain and ankylosis, which may be exacerbated by trauma (both accidental and iatrogenic).

Mean age of onset 5 years; confinement to wheelchair by third decade.

Restrictive pulmonary disease may lead to respiratory failure.

Eighty percent of patients receive an incorrect initial diagnosis. Diagnosis is clinical: while lesions may be confused with malignancy, avoid biopsy as it exacerbates condition.

FREEMAN-SHELDON SYNDROME

Also known as whistling face–windmill vane hand syndrome and craniocarpotarsal dystrophy.

Mutation in embryonic skeletal muscle myosin heavy chain 3 gene on 17p13.1.

A type of distal arthrogryposis.

Small mouth with pursed lips resembles whistling. Camptodactyly with ulnar deviation has been likened to a windmill vanes. Kyphoscoliosis. Contractures of hips (without or with dislocation), knees, and shoulders. Clubfoot and vertical talus.

Myopathy and seizure. Malignant hyperthermia may impact operation.

FRIEDREICH ATAXIA

Mutation in frataxin gene on 9q21.11. Second locus on 9p reflects genetic heterogeneity. Frataxin is involved in mitochondrial iron homeostasis.

Autosomal recessive. Most common inherited ataxia.

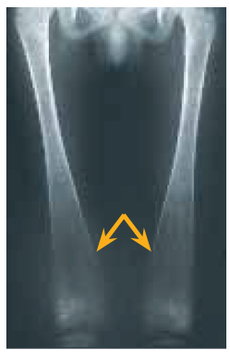
Ataxia, absent deep tendon reflexes, impaired proprioception and vibratory sense, dysarthria, extensor plantar response (Babinski), and nystagmus.

Pes cavus and scoliosis.

Preadolescent onset; confinement to wheelchair by fourth decade.

Hypertrophic cardiomyopathy: death most frequently from heart failure.

GAUCHER DISEASE



Mutation in gene encoding acid β-glucosidase on 1q22.

Autosomal recessive lysosomal storage disease cerebroside lipidosis.

Cells of mononuclear phagocyte origin (such as macrophages) laden with glucosylceramide (glucosylcerebroside), known as Gaucher cells, accumulate in bone marrow, spleen, liver, lung, ocular limbus, and skin, leading to pancytopenia, hepatosplenomegaly, interstitial restrictive lung disease, pingueculae, and cutaneous pigmentation.

Continuum and wide spectrum of severity: perinatal lethal to asymptomatic adult.

Osteolysis, bone crises, and pathologic fractures. Widening of distal metaphysis of femur likened to "Erlenmeyer flask" (orange). Osteonecrosis of head of femur managed by hip arthroplasty.

Type	Features
1	Non-neuropathic.
2	Neuropathic—acute. Perinatal or infantile lethal.
3	Neuropathic—chronic. Later onset, slower progression.

Partial splenectomy for thrombocytopenia, to balance risk of sepsis.

Multifaceted treatment includes enzyme replacement, chemical chaperone, substrate reduction, and bone marrow transplantation.

Increased prevalence in Ashkenazi Jewish descent.

GOLDENHAR SYNDROME

Linked to 14q32.

Also known as oculoauriculovertebral dysplasia and hemifacial microsomia.

Anomalies of first and second branchial arch derivatives.

Facial reconstruction for asymmetric eye and ear anomalies.

Spine fusion for congenital scoliosis. Reconstruction for radial ray anomalies, which are ipsilateral to facial anomalies.

Congenital heart disease, including tetralogy of Fallot and coarctation of aorta. Central nervous system lesions, including hydrocephalus and cerebellar hypoplasia. Genitourinary anomalies, including multicystic or ectopic kidney.

GUILLAIN-BARRÉ SYNDROME

Familial type caused by mutation in the peripheral myelin protein 22 gene on 17p12. Allelic with Charcot-Marie-Tooth disease type 1.

Acute demyelinating polyneuropathy resulting from aberrant immune mechanism suggested by preceding upper respiratory infection or *Campylobacter jejuni* enteritis.

Ascending symmetric flaccid paralysis, proximal muscles more affected, ophthalmoplegia, and dysphagia. Variable sensory involvement, including loss of proprioception, and autonomic dysfunction, such as arrhythmia.

Involvement of respiratory muscles may necessitate ventilator support.

Cerebrospinal fluid analysis shows albuminocytologic dissociation: elevated protein without elevated cell count, in contrast with infection.

Treat with plasmapheresis or immunoglobulin *per venam*.

HAND–FOOT–GENITAL SYNDROME

Mutation in the homeobox A13 gene on 7p15.2.

Genitourinary anomalies, including double uterus and bifid scrotum.

Short first metacarpal and metatarsal result in proximal location of hypoplastic thumbs and halluces. Smallest finger clinodactyly–brachydactyly. Carpal and tarsal fusions.

HÆMOPHILIA

Type	Features
A	Mutation in gene encoding coagulation factor VIII on Xq28. Recessive affects boys. Mild (40% of cases): 6–30% factor level, hæmorrhage after trauma. Moderate (10%): 1–5%. Severe (50%): <1%, at least monthly spontaneous hæmorrhage. 1:10000
B Christmas disease	Mutation in gene encoding coagulation factor XI on Xq27.1. Recessive. 1:30,000 Named after patient Stephen Christmas (1947–1993). B(M): inhibition of factor VII by abnormal factor IX prolongs PT. B Leyden: factor IX increases after puberty to eliminate hæmorrhagic diathesis.

Laboratory tests show normal platelet count and prothrombin time (PT), but a prolonged activated partial thromboplastin time (aPTT).

Hemorrhage into joints and muscles, in contrast with bleeding disorders due to platelet defects or von Willebrand disease, in which mucosal bleeding predominates.

Hemarthrosis begins after walking and is characterized by swelling, pain, stiffness, and inflammatory arthritis. Muscle hemorrhage causes necrosis, contractures, and neuropathy by entrapment.

Chronic synovitis unresponsive to factor replacement is associated with HLA-B27 allele, which prevents downregulation of inflammatory mediators after hemarthrosis.

Orthopedic management includes synovectomy, arthroplasty, and radial head resection.

Medical treatment consists of factor VIII infusion. Add gamma globulin and cyclophosphamide to induce tolerance in 10% of patients who develop antibodies to factor VIII.

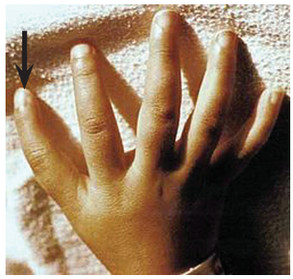
Heterozygous female carriers have 50% factor levels, reducing coagulability without clinical signs. Mortality is reduced 20% due to reduction in ischemic heart disease.

Hæmophilia affected the Romanov imperial dynasty of Russia and Queen Victoria of England, who was a carrier.

HOLT-ORAM SYNDROME

Autosomal dominant mutation in T-box 5 gene on chromosome 12q24.21. T-box 5 is a transcription factor involved in heart development and limb identity.

Also known by the descriptive appellations heart–hand syndrome and atriodigital dysplasia.



Congenital cardiac defects, including atrial septal defect and hypoplastic left heart.

Preaxial upper limb anomalies, including absent, bifid, or triphalangeal fingerlike thumb (arrow), proximal and distal thumb metacarpal epiphysis, radial club hand and hypoplasia, radioulnar synostosis, and carpal abnormality.

Anomalies of shoulder girdle and thorax. Asymmetric involvement of upper limbs, left greater than right, consistent with cardiac link.

HOMOCYSTINURIA

Autosomal recessive mutation in gene encoding cystathionine β-synthase on chromosome 21q22.3. Cystathionine β-synthase converts homocystine to cystathionine. Elevated homocystine and by-product methionine, diagnosed in urine.

Developmental delay, seizures, and ocular anomalies in particular ectopia lentis within the first decade, which requires operative treatment.

Thromboembolism is the major cause of morbidity and early death. Prophylactic anticoagulation for high-risk periods such as pregnancy.

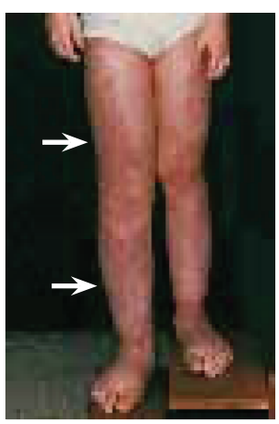
Osteoporosis by second decade manifested by "codfish" vertebrae on lumbar röntgenogramme. Kyphoscoliosis and dolichostenomelia, but limited joint mobility, which distinguishes this disorder from Marfan syndrome.

Treat with dietary restriction of protein, betaine therapy, and pyridoxine (B6). Responsiveness to pyridoxine distinguishes a milder phenotype from the more severe nonresponsive phenotype.

KLIPPEL-FEIL SYNDROME

See Spine chapter.

KLIPPEL-TRÉNAUNAY-WEBER SYNDROME



Mutation of 8q22.3, or gain-of-function translocation of 8q22;14q13, possibly involving gain of function of the gene encoding the angiogenic factor VG5Q.

Also known as angioosteohypertrophy syndrome.

Klippel-Trénaunay syndrome refers to cutaneous hæmangiomata, slow-flow venous and lymphatic malformations, and limb hypertrophy (white). When arteriovenous fistulae are present, the cutaneous manifestations are more diffuse and more pink, and the name of Weber is appended.

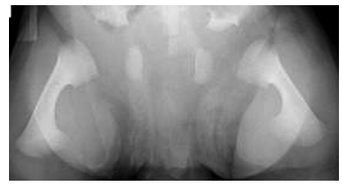
Visceral dysfunction due to vascular malformations, such as thrombocytopenia, pulmonary embolus, high-output cardiac insufficiency, and seizure.

Length equalization by physiodesis of affected limb may be necessary. Synovial vascular hypertrophy may elicit pain and benefit from arthroscopic débridement. Surgical debulking is controversial.

Compression stockings reduce blood and lymph pooling and thereby pain, swelling, and ulceration. Sclerotherapy thickens and ultimately blocks abnormal vascular channels.

KNIEST DYSPLASIA

Mutation of a-1 chain of type II collagen on 12q13.11.



Severe type II collagenopathy.

Phenotype reflects distribution of type II collagen in cartilage and vitreous humor.

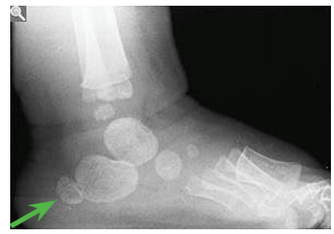
Disproportionate short stature, kyphoscoliosis, hypoplasia/aplasia of dens axis producing atlantoaxial instability, "dumbbell" long bones with splayed metaphysis/epiphysis, "Swiss cheese" epiphysial degeneration, coxa vara, joint narrowing, and contractures.

Myopia, retinal detachment, cataracts, and lens dislocation.

LARSEN SYNDROME

Autosomal dominant mutation of filamin B gene on 3p14.3. Filamin B cross-links protein actin to regulate communication between cell membrane and cytoskeletal network. This is allelic with atelosteogenesis type I.

Autosomal recessive mutation in β-1,3-glucuronyltransferase 3 gene on 11q12.3. The enzyme catalyzes glycosaminoglycan–protein linkage in proteoglycans.



Cluster island of La Reunion (Indian Ocean off east coast of Africa).

1:1,500 compared with 1:100,000 in Western countries.

Dislocations of large joints, in particular hip, knee, and elbow.

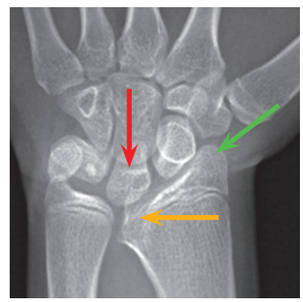
Accessory calcaneal (green) and carpal ossification centers, equinovarus and equinovalgus, "spatula" fingers, brachydactyly, congenital scoliosis, and cervical kyphosis.

"Dish" facies due to prominent forehead with flat midportion.

Stabilize spine, reconstruct dislocations, and correct foot deformity.

LÉRI-WEILL DYSCHONDROSTEOSIS

Pseudo–autosomal dominant mutation in the short stature homeobox gene on Xp22.33 and Yp11.32, or deletion of the SHOX downstream regulator. Allelic with Langer mesomelic dysplasia, of which the phenotype is more severe.



Mesomicromelia with bowing and Madelung deformity. Madelung deformity represents a growth disturbance of the volar ulnar part of the distal physis of radius, which results in volar translation of wrist and hand and dorsal displacement of the normally growing distal ulna. It is characterized by lucency (orange) at the locus of growth disturbance, triangular distortion of the distal epiphysis (green), and pyramidalization (red) of the wrist as it falls into the defect.

Girls more severely affected than boys.

LESCH-NYHAN SYNDROME

X-linked recessive mutation in hypoxanthine guanine phosphoribosyltransferase gene on Xq26.2-q26.3. The enzyme salvages purines from degraded DNA to reintroduce into purine synthetic pathways. While complete or severe (<1% activity) deficiency is the feature of Lesch-Nyhan syndrome, mild deficiency causes hyperuricemia and gout.

Hyperuricemia and hyperuricosuria causing nephrolithiasis.

Neural signs predominate: psychomotor delay, choreiform movements, athetosis and spasticity, dysarthria, and dysphagia.

Short stature, hip dysplasia, scoliosis, fractures, self-mutilation and digital autoamputations, and infections.

MAFUCCI SYNDROME

See Ollier disease.

MARFAN SYNDROME

Mutation of fibrillin-1 gene on 15q21.1.

Fibrillin-1 is the major constitutive element of extracellular microfibrils, distributed in elastic and nonelastic connective tissue. The microfibrils store in an inactivated form transforming growth factor-β (TGF-β); abnormal microfibrillar architecture results in increased release and thereby activation of TGF-β for cellular proliferation, differentiation, motility, and apoptosis. Thus, the effect of fibrillin-1 mutation is both primarily structural and secondary to hyperactivity of TGF-β.

Fibrillin-1 provides force-bearing structural support, its synthesis correlating with late morphogenesis and appearance of well-defined organ structures. Synthesis of fibrillin-2, of which mutation causes congenital contractural arachnodactyly (of Beals *q.v.*), coincides with early morphogenesis and the beginning of elastogenesis, during which it regulates elastic fiber assembly. Fibrillin is distributed in the periosteum, aortic media, and suspensory ligament of the lens, hence the three principal systems affected.

Tissue	Features
Skeletal	disproportionate tall stature • upper:lower segment < 0.85 • arm span:height > 1.05 • mean adult male height 190 cm • mean adult female height 175 cm dolichocephaly micro-/retro-gnathia pectus: carinatum, excavatum, asymmetry dural ectasia scoliosis + kyphosis spondylolisthesis protrusio acetabuli dolichostenomelia arachnodactyly articular hypermobility or contracture pes planus
Cardiac	aortic root dilatation: regurgitation + dissection aortic aneurysm pulmonary artery dilatation
Ocular	ectopia lentis myopia retinal detachment cataract
Other	high arched palate dental crowding pneumothorax striae distensae abdominal hernia

Puberty onset 2 years premature.

Trisomy 8, of which most cases are mosaic hence mildness of presentation, resembles skeletal features of Marfan syndrome.

Cardiovascular disease accounts for mortality. Treatment is pharmacologic, including β-adrenergic blockade and angiotensin II receptor antagonists, and surgical, such as aortic valve and root graft.

Orthopedic care is focused upon deformity of the spine (*q.v.*). Triradiate physiodesis has been advocated for protrusio acetabuli.

The condition first was described by Giovanni Morgagni (1682–1771), at autopsy of a prostitute distinguished by her tall stature and long, gracile limbs (in particular the fingers), who died *in coitu* of aortic dissection.

Antoine Marfan (1858–1942) described the condition in a 5-year-girl as dolichostenomelia, from Greek δολιχος: "long," στενοσ: "thin," and μελοσ: "limb." Niccolò Paganini (1782–1840), whose death was attributed to internal hemorrhage, is believed to have been affected by Marfan syndrome, including the arachnodactyly and articular hypermobility that aided his virtuosity at violin. Abraham Lincoln (1809–1865) probably had multiple endocrine neoplasia type 2B, which mimics the skeletal features of Marfan syndrome.

Diagnosis is based upon family history and a systemic score.

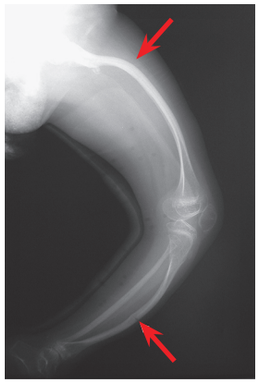
Family history	No family history
Aortic root dilatation Ectopia lentis systemic score ≥ 7	Aortic root dilatation AND • fibrillin-1 mutation • ectopia lentis • systemic score ≥ 7
Systemic score	
Wrist and thumb sign	3
Dural ectasia	2
Protrusio acetabuli	2
Pes planus	2
Pectus carinatum	2
Pectus excavatum, asymmetry	1
Scoliosis or kyphosis	1
Elbow contracture	1
Craniofacial dysmorphia	1
Myopia	1
Mitral valve prolapse	1
Striae distensae	1

Disproportionate tall stature.

Arachnodactyly Thumb sign is defined as thumb interphalangeal joint reaching ulnar border of hand (*green*). Wrist sign is defined as ringing of the wrist by thumb reaching distal interphalangeal joint of smallest finger.

MARSHALL-SMITH SYNDROME

Mutation in nuclear factor 1 X–type gene on 19p13.3.



Accelerated or disharmonic skeletal maturation. Osseous fragility may result in "nontraumatic" fractures and secondary deformity. Absence of osteopenia suggests a qualitative rather than a quantitative defect in bone. Orthopedic management includes bisphosphonates and fracture stabilization.

Characteristic facies includes prominent forehead, micrognathia, exophthalmos, and blue sclerae.

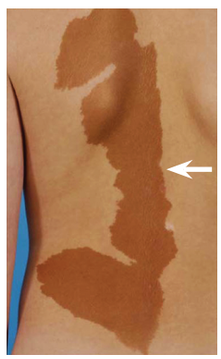
Osseous fragility and blue sclerae resemble osteogenesis imperfecta.

Psychomotor delay and failure to thrive.

Respiratory compromise accounts for the majority of mortality.

M^{C}CUNE-ALBRIGHT SYNDROME

Gain-of-function or constitutively activating postzygotic somatic cell mutation of guanine nucleotide–binding protein α-stimulating activity polypeptide 1 gene (GNAS1) on 20q13.32.



Clinical triad:

- Polyostotic fibrous dysplasia of long and craniofacial bones
- *Café au lait* cutaneous patches with irregular or "coast of Maine" borders
- Precocious puberty

Deformity, such as Shepherd crook femur, and morbid fracture produced by fibrous dysplasia require orthopedic intervention, including bisphosphonate and operation.

Craniofacial hyperostosis may produce deafness and blindness due to neural foraminal compression.

Cutaneous patches are asymmetric and often end abruptly at the body midline. They may be distinguished from those of neurofibromatosis, which have smooth or "coast of California" borders, are smaller, and include axillary freckling.

Signs of puberty, such as vaginal bleeding and spermatogenesis, may be seen in the first half of the first decade.

Endocrinopathy is variable in type and extent, including in addition to hyperthyroidism, pituitary gigantism, and Cushing syndrome due to hyperadrenocorticism.

MEIER-GORLIN SYNDROME

Five types caused by mutations in ORC1 gene on 1p32.3 (1), ORC4 gene on 2q22.3 (2), ORC6 gene on 16q11.2 (3), CDT1 gene on 16q24.3 (4), and CDC6 gene on 17q21.2 (5).

Also known as ear–patella–short stature syndrome.

Microtia, auditory canal atresia, hearing loss, micrognathia, and cleft palate.

Thoracic dysplasia with pulmonary compromise and genital anomalies.

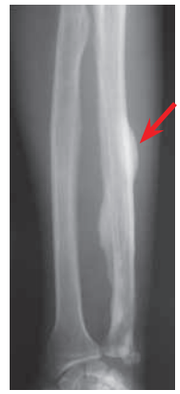
Aplastic/hypoplastic patellae, congenital spine deformity, articular laxity, clubfoot, and camptodactyly–clinodactyly.

MELNICK-NEEDLES SYNDROME

See otopalatodigital syndromes.

MELORHEOSTOSIS

Mutation in the LEMD3 gene on 12q14.3. LEMD3 is a protein integral to the inner nuclear membrane that is involved in gene expression.



The term is derived from Greek μελος: "limb," ρεω: "I flow," and οστεον: "bone" to describe longitudinal flowing hyperostosis along the cortex of long bones resembling wax dripping along a candlestick. Bones are affected asymmetrically and may correspond with a sclerotome.

Involvement of surrounding soft tissues leads to painful and deforming contractures, muscle atrophy, and scleroderma. Associated vascular anomalies such as hæmangiomata, lymphangiectasis, vascular nevi, glomus tumors, stenosis, and aneurysms.

MESOMELIC DYSPLASIA

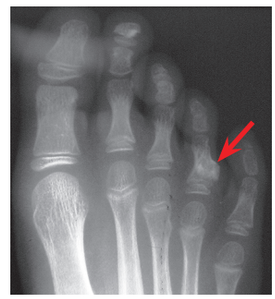
Mesomicromelia and synostosis are the cardinal features. Radioulnar, carpal, tarsal, and metatarsal synostosis, radial capital subluxation, and bowing of long bones, including "rhomboid" tibiae and fibulae.

Four types may be distinguished.

Type	Features
Kantapura	Mutation on 2q24-q32.
Langer	Mutation in short stature homeo box gene. Allelic with Léri-Weill dyschondrosteosis. Distinguished by mandibular hypoplasia.
Nievergelt	Autosomal dominant mutation of α–1 chain of type 10 collagen on 6q22.1. Mild short stature.
Savarirayan	Mutation of LAF4 gene on 2q11.2.

METACHONDROMATOSIS

Autosomal dominant mutation in protein tyrosine phosphatase nonreceptor type 11 gene on 12q24. The protein tyrosine phosphatase family are signaling proteins.



The disorder is allelic with Noonan syndrome (*q.v.*).

Combines features of enchondromatosis (of Ollier *q.v.*) and hereditary multiple exostoses (*q.v.*). Distinguished by:

- Direction of exostoses toward adjacent joints
- Predominance in hands and feet
- Potential for spontaneous regression
- Lack of malignant potential

Involvement of the hip may resemble.

Legg-Calvé-Perthes disease.

METAPHYSIAL CHONDRODYSPLASIA

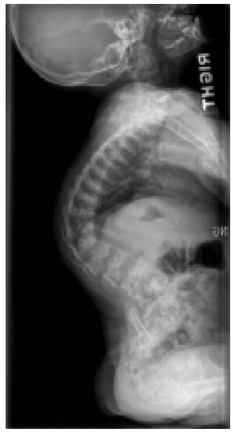
Metaphysial involvement contrasts with epiphysial sparing and results in contractures rather than primary osteoarthritis.

Bowing of long bones produces varus deformity in lower limbs.

Stature varies from mild (Schmid) to moderate (M^{c}Kusick) to severe (Jensen).

Type	Features
Jansen	Mutation in parathyroid hormone receptor 1 gene on 3p21.31. Ligand-independent activation disrupts endochondral ossification. Cranial sclerosis leading to deafness, choanal stenosis or atresia. Skeletal manifestations resemble hyperparathyroidism, including osteopenic fractures. Hypercalcæmia and hypercalcuria with nephrocalcinosis. Hypophosphatæmia, hyperphosphaturia, elevated 1,25 dihydroxy vitamin D and alkaline phosphatase.
McKusick	Autosomal recessive mutation of RNA component of mitochondrial RNA processing endoribonuclease on 9p13.3. Appellation 'cartilage-hair hypoplasia' reflects distinguishing feature of sparse, small caliber hair. Immune deficiency manifested as susceptibility to infection and increased risk of malignancy. Hæmocytopenia. Clustered in Old Order Amish and in Finland.
Schmid	Autosomal dominant mutation of a-1 chain of type 10 collagen on 6q22.1.

METATROPIC DYSPLASIA



Mutation in the transient receptor potential cation channel subfamily V member 4 gene on 12q24.11. TRPV4 is a Ca^{2+} channel.

Allelic with brachyolmia type 3, spondyloepiphysial dysplasia (Maroteaux), spondylometaphysial dysplasia (Kozlowski), and Charcot-Marie-Tooth type 2C.

The term describes a "change" (Greek τροπη) in clinical presentation of severity of deformity from limbs (resembling achondroplasia) to trunk (resembling Morquio syndrome) with growth. At birth, the limbs are markedly affected with relative sparing of the trunk; with advancing age, progressive and severe kyphoscoliosis becomes the predominant feature.

Prolongation of the coccyx or the presence of a cutaneous fold over the posterior aspect of the pelvis gives the appearance of a tail.

Deformity of the iliac alae results in a "halberd" pelvis. The ends of femora and humeri are said to be "trumpeted," rather than "dumbbell" in Kniest dysplasia. Microcalcification of epiphysis, hyoid, and cricoid cartilages.

MÖBIUS SYNDROME

Gene locus on 13q12.2-q13.

Congenital cranial neuropathy, most frequently facial and abducens, leading to facial paralysis and impaired ocular abduction.

Arthrogryposis, digital anomalies, clubfoot, scoliosis with increased sagittal plane spine deformity.

Absence of pectoralis muscles reflects association with Poland syndrome.

MUCOPOLYSACCHARIDOSES

Characterized by intracellular accumulation and urinary excretion of mucopolysaccharides [A] due to deficiency in degradative lysosomal enzymes. Mucopolysaccharide is the historical term for glycosaminoglycan (GAG). Proteoglycans, formerly known as protein polysaccharides or mucoproteins, refers to a molecule of "protein and sugar." It has three components:

- Glycosaminoglycan (GAG). This represents an unbranched chain of repeating disaccharide units of which one is an amino sugar. With the exception of hyaluronic acid, the GAGs carry a high negative charge on the account of sulfate and carboxyl groups added to their sugar residues.
- Core protein, to which GAGs are covalently bonded at a serine residue by a tetrasaccharide bridge.
- Link protein, which noncovalently attaches proteoglycan to hyaluronic acid, the principal carbohydrate polymer of the extracellular matrix.

Proteoglycan monomers interact specifically though noncovalently with hyaluronic acid to form very high molecular weight "aggregates." The major proteoglycan of cartilage is aggrecan, of which the core protein may have covalently attached as many as 100 chondroitin sulfate and 50 keratan sulfate GAGs. Cartilage also contains small, nonaggregating proteoglycans, including decorin, which "decorates" the surface of type II collagen fibrils, and biglycan, of which the core protein bears "two" chondroitin sulfate GAGs. The molecular structure and negative charge of proteoglycans enable them to occupy a large volume for mass and to attract water according to the Gibbs-Donnan equilibrium. They form a porous hydrated gel, which resists compression and regulates the passage of molecules and cells through the extracellular matrix. By contrast, collagen fibrils form a scaffold, which maintains the structural integrity of the extracellular matrix and primarily resists tensile forces.

There are several types of mucopolysaccharidoses. Type II is X-linked. Type III is predominantly a neural disease. Type IV is most common. Types VI and IX may have normal intelligence.

Type	Features
Ih (Hurler) **Is (Scheie)**	Autosomal recessive mutation in α–L-iduronidase gene on 4p16.3. Scheie was formerly type V. Appear normal at birth, manifesting after 6 months. Developmental and growth retardation after 2 years. Gargoyle facies, with exophthalmos, corneal clouding, thick eye-brows and large tongue. Odontoid hypoplasia with atlanto-axial instability, 'cod-fish' vertebrae, lumbar gibbus, kyphoscoliosis. 'Oar-shaped' ribs, epiphysial deformation including hip dysplasia and genua valga. Cardiopulmonary anomalies, including myopathy and arrhythmia, hernias, hepatosplenomegaly. Dermal melanocytosis, hypertrichosis.
II (Hunter)	X-linked recessive mutation in iduronidate 2-sulfatase on Xq28. Urinary excretion of chondroitin sulfate B (dermatan sulfate) and heparitin (heparan) sulfate.
III (Sanfilippo)	Autosomal recessive mutation in N-sulfoglucosamine sulfohydrolase gene on 17q25.3 resulting in impaired degradation of heparan sulfate, excreted in urine. Severe nervous system disease with relative sparing of skeleton.
IV (Morquio)	Autosomal recessive mutation in β–galactosidase gene on 3p22.3. Urinary excretion of keratan sulfate.
VI (Maroteaux-Lamy)	Autosomal recessive mutation in arylsulfatase B gene on 5q14.1.
VII (Sly)	Autosomal recessive mutation in β–glucuronidase gene on 7q11.21. Hydrops fœtalis.
IX	Mutation in hyaluronidase gene on 3p21.31. Multiple peri-arthric masses representing hyaluronan-induced aggregation of histiocytes resulting form failure of catabolism of hyaluronan by hyaluronidase.

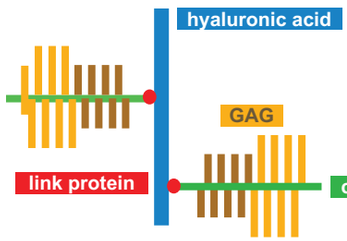
Hurler and Scheie represent a spectrum of severe to mild disease. Scheie may be so mild that diagnosis is in adulthood. The other disorders are subtyped by letter according to disease severity.

Carpal tunnel syndrome is a common feature of the mucopolysaccharidoses, due in part to excessive lysosomal storage in the flexor retinaculum. Spine [B] and hip [C] are the other foci of orthopædic care.

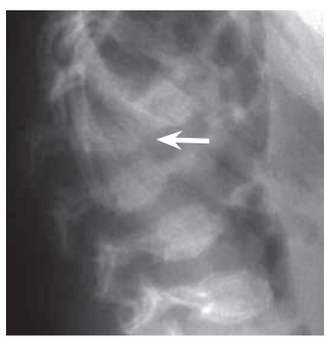
Anteoperative assessment must include cardiac evaluation and cervical spine imaging.

Medical treatment includes enzyme replacement and bone marrow transplantation. The latter, performed before age 2 years, prolongs survival and, while they may delay or halt extraskeletal disease progression, they may not affect skeletal manifestations.

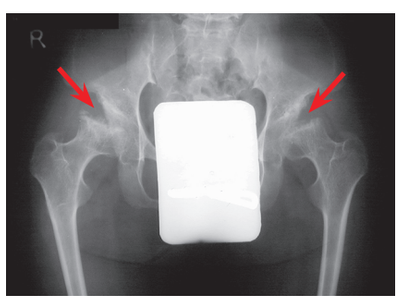
A form of mucopolysaccharidosis, claimed to be due to glucosamine-6-sulfate sulfatase deficiency, named Di Ferrante syndrome, and given the designation VIII, was found to be erroneous and retired after the discovery of type IX.



A Extracellular matrix Proteoglycans are glycosylated proteins consisting of a core protein to which one or more types of glycosaminoglycan are covalently linked.



B Lumbar gibbus in Hurler syndrome Failure of formation of upper lumbar vertebra allows the superjacent vertebra to fall forward into the deficiency space.



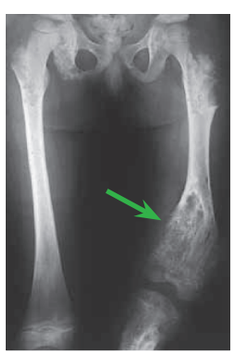
C Hip dysplasia in Morquio syndrome Untreated hip dysplasia may lead to severe coxarthritis.

MULTIPLE ENCHONDROMATOSIS

Benign tumors of cartilage located in metaphysis of long bones, where lesions are asymmetric and deforming.

Hands and feet most involved.

Orthopedic management focuses on limb equalization and realignment osteotomy.



Type	Features
Ollier	Malignant transformation to chondrosarcoma 10-30%.
Mafucci	Associated with hæmangiomata. Higher rate of malignant transformation, including of extraskeletal tissue.

MULTIPLE EXOSTOSES

Also known as multiple osteochondromata and diaphysial aclasis, describing a lesion of "bone" capped by "cartilage" showing "lack of an interruption" of the "diaphysis" from the primary bone.

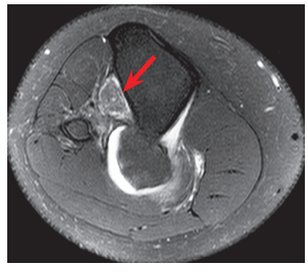
There are three types, distinguished genetically.

Type	Features
I	Autosomal dominant mutation in exostosin-1 (EXT1) gene on 8q24, resulting in activation of the hedgehog signaling pathway. 70% of all cases, most morbid form.
II	Autosomal dominant mutation in exostosin-2 gene on 11p11.2.
III	Mapped to locus on 19.

Lesions arise from physis, grow away from adjacent joint, and affect long bones, flat bones (except skull), and vertebrae.

This contrasts from the solitary form of the disease:

- The exostoses are deforming, including bowing, shortening, and joint dysplasia.
- Mild short stature.
- Malignant transformation is approximately 1%. Symptoms and signs include pain and rapid growth.



Restraint is fundamental to orthopedic management.

Indications for operation include:

- Pain, such as at prominent lesions that may be struck.
- Dysfunction, such as compression of tibial nerve producing denervation of tibialis posterior muscle (red).
- Deformity, such as tethering by a shortened ulna , which may lead to radial bowing, ulnad displacement of the wrist, and head of radius dislocation.
- Unacceptable appearance.
- Concern for malignant transformation.

MULTIPLE SYNOSTOSIS SYNDROME

Three subtypes are distinguished by mutation.

Type	Features
1	Mutation in homolog of mouse Noggin gene on 17q22.
2	Mutation in growth/differentiation factor-5 on 20q11.22. GDF5 belongs to the transforming growth factor –β superfamily. Allelic with several disorders, including brachydactyly types A and C.
3	Mutation in fibroblast growth factor 9 gene on 13q12.11. FGF9 is a member of fibroblast growth factor family.

The alternate appellation facioaudiosymphalangism syndrome describes the principal clinical manifestations.

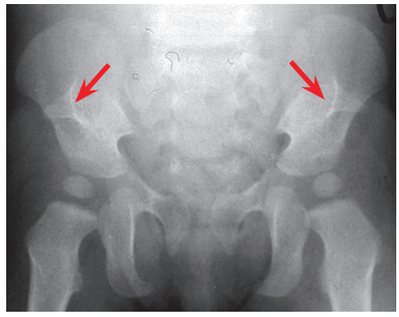
Narrow face, nasal hypoplasia, and conductive deafness due to middle ear ankylosis.

Multiple synostoses, including carpal and tarsal coalitions, brachydactyly, radial head (sub)luxation, vertebral fusion and hypoplasia producing stenosis, and pectus deformity.

Absent cutaneous creases over interphalangeal joints, aplastic/hypoplastic nails.

NAIL–PATELLA SYNDROME

Autosomal dominant mutation in LIM homeobox transcription factor 1-b on q34.1. LMX1B plays a role in dorsoventral patterning of the vertebrate limb and renal development. Absence or hypoplasia/dysplasia of nails and patellae, as well as of pectoralis, biceps, and quadriceps muscles, represents ventral patterning of the dorsal aspects of the limbs.



Short stature, iliac horns, limited elbow motion with radial head hypoplasia and dislocation, scapular anomaly, scoliosis, and clubfoot.

Renal disease, including glomerulonephritis with proteinuria and hematuria, ends in renal failure in 10% of patients.

Sensorineural deafness, glaucoma, cataract, and cleft lip and palate.

NEUROFIBROMATOSIS

Type	Features	
1 - Peripheral	Autosomal dominant mutation in neurofibromin gene on 17q11.2. Neurofibromin is a tumor suppressor inhibiting p21 ras oncoprotein. Also known as von Recklinghausen disease. 90% of cases with a 1:4000 incidence. Diagnosis requires 2 of the following:	
	Diagnosis - 2 features	
	Café-au-lait patches	≥ 6 > 5 mm before puberty > 15 mm after puberty
	Neurofibromata	> 2 subcutaneous 1 plexiform
	Freckling	axillary or inguinal
	Osseous lesion	sphenoid dysplasia scoliosis congenital pseudarthrosis
	Family history	First-degree relative with NF1
	Lisch nodule	hamartoma of iris
	Optic glioma	
2 - Central	Autosomal dominant mutation in merlin (neurofibromin 2) gene on 22q12.2. Sensorineural hearing loss, ocular anomalies but no Lisch nodules, central and peripheral neuropathy, neural tumors including vestibular schwannoma (of vestibulocochlear cranial nerve VIII), meningioma, ependymoma, astrocytoma. Central affection delays diagnosis. Stereotactic radiosurgery or microsurgical resection of vestibular schwannoma.	

Simple neurofibromata, made up of Schwann cells and fibrous tissue, rarely produce deficit. Plexiform neurofibromata, which are highly vascular, lead to disfigurement and gigantism, which may require limb equalization.

Café au lait patches have smooth or "coast of California" borders, in distinction from the rough or "coast of Maine borders" in McCune-Albright syndrome.

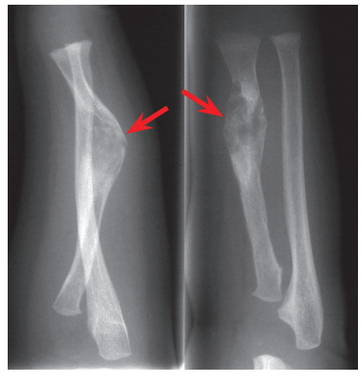
Scoliosis may be idiopathic or "dystrophic." The former behaves and is treated as such. The latter is characterized by short and sharp angulation, osseous erosion by intraspinal lesions and dural ectasia, and spinal instability. Bracing plays no role, and early anterior together with posterior fusion is indicated because of the risk of pseudarthrosis. Neural risk is significant, untreated or treated.

Pseudarthrosis may involve any bone, though most often the tibia, presenting as an anterolateral bow. This is treated by prophylactic bracing to avoid fracture, and operative treatment after fracture, including compressive external fixation or medullary nailing with autogenous osseous graft or vascularized fibula transference. Bone morphogenetic protein as adjuvant is controversial.

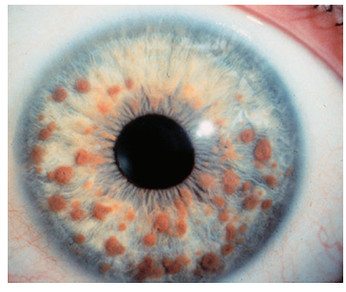
Other features include cognitive impairment, macrocephaly without hydrocephalus, seizures, and vascular anomalies. Neurofibromatosis 1 carries an increased tumor risk, including leukemia and pheochromocytoma.

While the Irish surgeon Robert W. Smith (1849) was first to report two men with "a vast number of neuromatous tumors in the subcutaneous cellular tissues," von Recklinghausen's description in tribute to his professor Rudolph Virchow gave the enduring eponym for neurofibromatosis 1.

Feature	%
Café-au-lait patches	95
Lisch nodules	90
Axillary freckling	80
Cutaneous neurofibromata	60
Cognitive impairment	60
Family history	50
Scoliosis	40
Pseudarthrosis	15
Malignancy	10
Spinal neurofibromata	2



Pseudarthrosis of radius
Deformity begets dysfunction.



Lisch nodules These represent a yellow to brown pigmented hamartoma of the iris, consisting of dendritic melanocytes. They do not affect vision, but aid diagnosis.

OCULODENTODIGITAL DYSPLASIA

Autosomal dominant and recessive mutations in the gap junction α-1 protein gene on 6q22.31. The protein is a member of the connexin family and is a component of gap junctions, which form intercellular channels for diffusion.

Ocular: microphthalmos, glaucoma, and cataract.

Dental: hypoplastic enamel, microdontia, and premature tooth loss.

Digital: camptodactyly, syndactyly of ring and smallest fingers as well as of toes, and aphalangia.

Hip dysplasia and hyperostosis, in particular of vertebrae and skull, which can result in neural compression. Osseous involvement other than digits has given rise to the alternate appellation oculodentoosseous dysplasia.

Neural features include spasticity, dysarthria, and hearing loss.

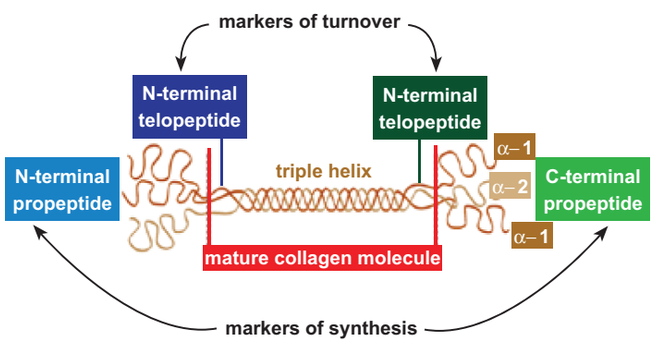
Fine, sparse hair and orange–yellow palmoplantar keratoderma.

OSTEOGENESIS IMPERFECTA

The Dutch anatomist W. Vrolik named the condition osteogenesis imperfecta. It also is known as fragilitas ossium: "brittleness of bones."

Mutation of gene encoding type I collagen α-1 chain on 17q21.33 or α-2 chain on 7q21.3.

Collagen, derived from Greek κολλα: "glue", and the suffix -γεν: "giving rise to," is the name given to a family of proteins that comprise the principal constituents of the extracellular matrix of tissues of the musculoskeletal system. The collagen molecule is composed of three polypeptide chains, two α-1 and one α-2, and is therefore a trimer. Although the primary structure of each polypeptide chain differs among collagen types, repeating three amino acid motifs are strictly preserved, represented by the formula -(GLY-X-Y)n-. Every third residue is a glycine (Gly). X and Y can vary; however, a high proportion of amino acids at the X position tends to be proline (Pro), and a high proportion at the Y position tends to be hydroxyproline (Hyp). Those portions of a collagen chain, which follow this typical motif, are helical and are known as collagenous domains; those that do not are termed noncollagenous domains. The individual chains may be identical, encoded by the same gene, in which case they form a homotrimer, or they may be different gene products, forming a heterotrimer. Cleavage of amino terminal and carboxyl terminal propeptides during or after secretion converts procollagen to collagen. The tertiary structure of each collagen chain is a left-handed helix, and the three chains wrap around one another to form a right-handed super helical molecule.



Mutations may result in exclusion or inclusion of an allelic product. In heterozygous-excluded mutations (haploinsufficiency), failure of secretion and incorporation into a protein trimer, or of synthesis (null alleles), of a polypeptide chain, produce mild disease due to a quantitative reduction of normal molecules. In the homozygote, the severity of disease is proportional to the amount of allelic product excluded. Included mutations (dominant negative), such as deletions, insertions, duplications, point mutations, rearrangements, and exon-skipping mutations, result in a more morbid phenotype because the abnormal allelic product is expressed in the extracellular matrix where it "poisons" all molecules into which it is incorporated. Severe phenotypes result from glycine mutations, because this is the smallest and only amino acid (lacking a side chain) that can fit in the center of the triple helix. Assembly of the collagen molecule commences at the carboxyl terminus. This produces a "phenotypic gradient": mutations in the carboxyl terminal region produce more severe phenotypes based upon a greater potential for disruption of the triple helix. Exceptions to these principles exist: for example, certain mutations are lethal, which do not involve glycine and regardless of location.

Osteogenesis imperfecta is the most common lethal skeletal dysplasia. Phenotype reflects distribution of type I collagen.

Tissue distribution	Feature
Bone	• Osteopenia, with trabecular loss, cortical thinning and gracility of long bones. • Fracture (e.g., of long bones, avulsion of olecranon). • Deformity, including accordion femora, saber tibiae, scoliosis, cod-fish vertebrae, protrusio acetabuli, basilar invagination (type III). • Conductive deafness due to otosclerosis. Wormian bones
Dentin	Blue-grey discoloration, brittleness and excessive wear, malocclusion, late tooth eruption, constricted coronal radicular junctions, obliterated pulp cavities and caries.
Skin	Easy bruisability, bleeding. Decreased elasticity, distensibility, hysteresis.
Connective tissue	• Translucency with visualization of underlying choroidea produces "Wedgewood blue" sclerae. • Ligamentous laxity. • Muscle rupture (e.g., of patellar tendon).

Increased turnover, woven to lamellar bone ratio, and hypercellularity conspire to weaken bone. Fracture healing and postoperative union are unretarded, often with "luxuriant" callus, although the quality of the new bone remains poor. Fracture rate is bimodal: childhood, decreases after puberty, and rises after menopause.

Hearing loss, which affects 50% of patients, begins in second decade as conductive, from osseous fragility in the middle ear, and evolves with age to sensorineural. Otosclerosis also produces vertigo.

Ole Worm, Professor of Anatomy at Copenhagen (1558 to 1654), described intrasutural bones, which may be more numerous in disease states characterized by delayed or deficient ossification.

Mechanism of operative malignant hyperthermia remains unclear.

Four clinical types are distinguished. They are subtyped as A or B based upon absence or presence, respectively, of dentinogenesis imperfecta.

Type	I	II (Vrolik)	III	IV
Mutation	α–1 or α–2 chain of type I collagen			
Inheritance	dominant	new mutation	recessive	dominant
Frequency	50%	5%	25%	20%
Severity	mild	lethal	progressive deforming	variable
Sclerae	blue	blue	blue or white	white
Hearing loss	50%	—	yes	no
Ambulation	yes	—	wheel-chair	yes
Stature	normal	—	very short	short

Ambulatory potential proportional directly to age of onset and inversely to deformity.

Several additional types have been distinguished that are characterized by brittle bones but that are caused by mutations other than of type I collagen.

Type	Features
V	Mutation of interferon -induced transmembrane protein-5 on 11p15.5. Moderate. Normal sclerae, normal teeth. Calcification of interosseous membrane of forearm, dislocation of head of radius, radiodense metaphysial bands. Osseous histology shows 'mesh-like' pattern.
VI	Mutation of pigment epithelium-derived factor (serine protease inhibitor F1) on 17p13.3. 'Fish scale' lamellæ and hyperosteoidosis suggest defect of mineralization.
VII	Mutation of cartilage associated protein on 3p22.3. First Nations community of northern Quebec.
VIII	Mutation of leprecan on 1p34.2. Concentration in cases of West African origins.
IX	Mutation of peptidylprolyl isomerase B (cyclophilin B) on 15q22.31. Overhydroxylation suggests overmodification of type I collagen.
X	Mutation of serine protease inhibitor H on 11q13.5.
XI	Mutation of FKBP10 member of peptidyl-prolyl cis/ trans isomerase family on 17q21.2.
XII	Mutation of C_2H_2-type zinc finger transcription factor SP7 on 12q13.13.
XIII	Mutation of bone morphogenetic protein 1 on 8p21.3. Resembles type III.
XIV	Mutation of transmembrane protein 38B on 9q31.2.
XV	Mutation of wingless-type MMTV integration site family, member 1, on 12q13.12. Intermediate between type III and type IV.

Types V, VI, and XI may phenotypically be likened to type IV. Type XV may have features of both type III and type IV. The other types resemble type III. Discovery of additional mutations and typing represents an area of flux.

Diagnosis is aided by analysis of type I collagen production by cultured dermal fibroblasts.

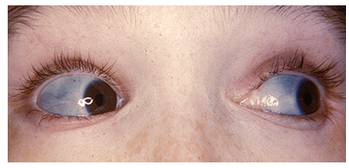
Osteogenesis imperfecta leads the differential diagnosis of nonaccidental trauma.

Minimize type and duration of immobilization for fracture in order to reduce sequelae of exacerbated osteopenia, stiffness, and weakness. Recurrent fractures and progressive deformity may be addressed by corrective osteotomy and fixation with either solid or telescoping medullary nails. Scoliosis is treated with early fusion because natural history is progression despite bracing and bone fragility undermines fixation. Symptomatic basilar invagination is treated by posterior with or without anterior decompression followed by posterior fusion.

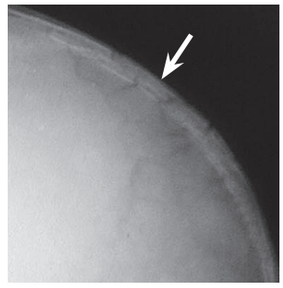
Audiologic examination and electronystagmography are indicated for hearing loss.

Bisphosphonates are synthetic analogs of pyrophosphate, a natural inhibitor of osteoclastic bone resorption. Cyclic intravenous administration decreases bone turnover; increases bone mineral density, cortical width, and trabecular number; delays onset and reduces number of fractures; improves ambulation; and increases height. Physis are unaffected.

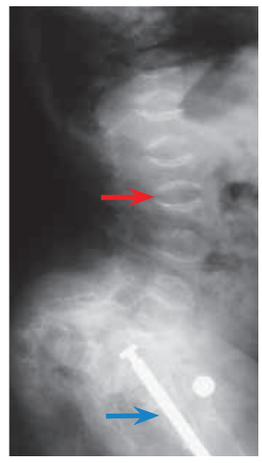
Osteogenesis imperfecta has been described in an Egyptian mummy of the twenty-first dynasty (1,000 BC). The nineteenth-century Viking king and invader of England Ivar Benløs (Ivar the Boneless), who had blue eyes and was carried into battle seated on a shield of bronze, is said to have had "gristle in the limbs where other men had bones."



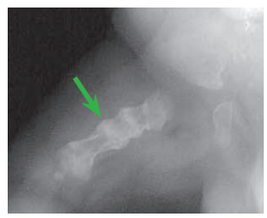
Blue sclerae Subjacent vascular plexus tinges thinned connective tissue.

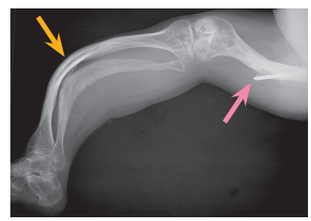


Wormian bones Multiple intrasutural bones of the skull.



Spine and operative treatment Biconcave vertebral end plates resemble "codfish" (*red*). Telescoping Bailey-Dubow rod (*blue*) strengthens femur against fracture and corrects deformity while allowing for longitudinal growth.





Deformity of long bones Multiple fractures of the femur with hypertrophic callus give the appearance of an accordion (*green*). Bowing of the tibia due to microfragility has been likened to a saber (*orange*). Note migration of Rush rod out of femur (*pink*).

OSTEOPETROSIS

Autosomal recessive also may be referred to as infantile malignant, to describe presentation in childhood and severity of clinical presentation, including death from myelophthisis. Autosomal dominant forms are more benign and typically present in adulthood. Several subtypes have been distinguished, principally based upon mutation. Autosomal dominant 2 was described by Albers-Schönberg and is known as "marble bone disease" after the radiographic appearance.

Osteoclast dysfunction leads to defective resorption of immature bone.

Encroachment upon bone marrow results in pancytopenia and infection, which of the jaw results in dental caries.

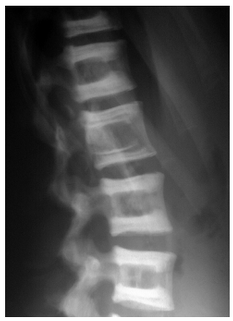
Cranial nerve compression results in blindness, deafness, and facial palsy.

Extramedullary hematopoiesis leads to hepatosplenomegaly.

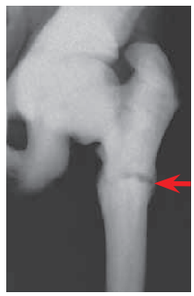
Abnormal bone turnover results in morbid fractures and deformity, which are the foci of orthopedic management. Complication rate is high. Osteosynthesis may be hindered by sclerosis. Arthroplasty is complicated by loosening and infection. Osseous union may be delayed.

Mainstay of medical treatment is bone marrow transplantation. Recombinant human interferon gamma-1b to increase superoxide generation by leukocytes and bone-resorbing agent calcitriol are indicated while awaiting, or for patients who are not candidates for, bone marrow transplantation.

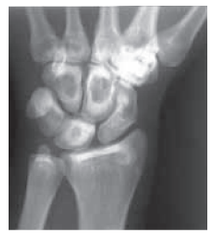
Type	Features
AD 1	Mutation of low density lipoprotein receptor-related protein 5 on 11q13.2, with full penetrance. Osteosclerosis predominates in craniofacial skeleton. Only type not associated with fractures.
AD 2	Mutation of chloride channel-7 protein on 16p13.3, with incomplete penetrance. Same mutation as AR 4. Osteosclerosis predominates in axial and appendicular skeleton. Sclerosis of upper and lower end-plates described as 'sandwich vertebrae' and 'rugger jersey spine'. Differential osteosclerosis produces 'bone within bone' or 'endobones' in the limbs. Confirm diagnosis by elevated serum levels of tartrate-resistant acid phosphatase and BB isoenzyme of creatine kinase. 50% patients require orthopædic surgery.
AR 1	Mutation of V-type proton ATPase subunit of the vacuolar proton pump on 11q13.2. Impairment in calcium homeostasis results in tetanic seizure and secondary hyperparathyroidism.
AR 2	Mutation of receptor activator of nuclear factor kappa-B ligand (RANKL) on 13q14.11. RANKL is an osteoclast cell surface receptor that binds RANK. Clinical mildness resembles dominant forms.
AR 3	Mutation of carbonic anhydrase II, which is expressed in kidney and brain, on 8q21.1. Renal tubular acidosis. The appellation 'marble brain disease' describes mental retardation associated with intracranial calcifications. Originated in Arabian peninsula.
AR 4	Mutation of chloride channel-7 protein on 16p13.3. Same mutation as AD 2.
AR 5	Mutation of osteopetrosis-associated transmembrane protein-1, which prevents acidification of osteoclast resorption lacuna, on 6q21.
AR 6	Mutation of pleckstrin homology domain-containing family M member 1 on 17q21.31. Intermediate form.
AR 7	Mutation of receptor activator of nuclear factor kappa-B (RANK) on 18q21.33. Hypogammaglobulinæmia.
AR 8	Mutation of sorting nexin 10 on 7p15.2.



Spine Endplate sclerosis leads to sandwich vertebrae that give the appearance of a rugger jersey.



Marble bone Despite the epithet, osseous fragility manifests as morbid fracture.



Wrist Bone within bone, or endobones.

OTOPALATODIGITAL SYNDROME

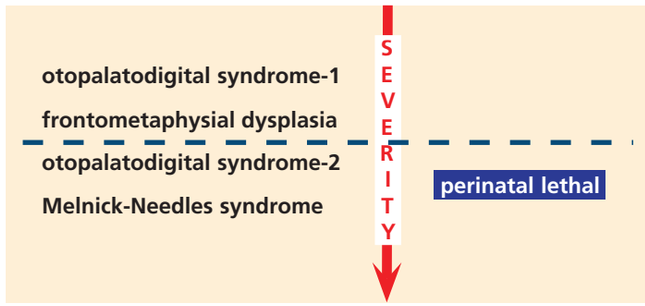
Gain-of-function mutation in filamin A gene on Xq28.

Skeletal Short stature; pectus excavatum; "coat hanger" wavy, short ribs; scoliosis; hip dysplasia; joint contractures; radial head dislocation; long bone bowing; carpal and tarsal fusion; brachydactyly; secondary ossification center at base of second metacarpal and metatarsal; wide spacing between broad toes with persistent fetal pads creates "tree frog" feet; and nail dystrophy.

Craniofacial Cleft palate, conductive deafness caused by ossicular anomalies, and dental dysplasia.

Four disorders are distinguished, representing a phenotypic spectrum of a single entity. Frontometaphysial dysplasia adds urogenital anomalies, including hydronephrosis/hydroureter, hypospadias, and cryptorchidism.

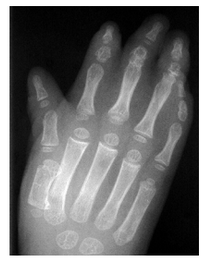
Perinatal lethal due to cardiopulmonary insufficiency.



POLAND SYNDROME

Most sporadic, though autosomal dominant pedigrees have been reported.

Ipsilateral aplasia/hypoplasia of pectoralis major and/or minor muscle, which may be associated with Sprengel anomaly; hypoplastic or fused ribs; aplasia/hypoplasia of nipple; symbrachydactyly or oligodactyly, including of thumb; and aplasia/hypoplasia of other shoulder muscles. Anteoperative MRI aids assessment of reconstructive options.



Association with Klippel-Feil syndrome (*q.v.*) and Möbius syndrome (*q.v.*) has led to the hypothesis that a vascular insult during embryogenesis is causative, termed subclavian artery supply disruption sequence.

Boys thrice as common as girls. 75% of cases are right-sided. Left-sided anomalies may be associated with dextrocardia. One bilateral case has been reported, which may be better classified as a type of thoracic dysplasia.

Unilateral gluteal hypoplasia and symbrachydactyly of the foot, due to *in utero* external iliac artery supply disruption sequence, may represent the lower limb equivalent of the Poland syndrome.

PRADER-WILLI SYNDROME

Microdeletion of paternal copies of imprinted small nuclear ribonucleoprotein polypeptide N and necdin within region 15q11-q13.

Most cases are sporadic. Paternal hydrocarbon exposure has been implicated.

Prenatal delayed onset of fetal activity.

Neonatal poor suck and swallow reflexes lead to failure to thrive, which is followed by hyperphagia and obesity and ultimately alimentary diabetes. Psychomotor delay with behavioral problems such as anger, picking, and related to food.

Hypersalivation, hypotonia, hypopigmentation, hypogonadism, reduced bifrontal diameter, ocular anomalies, cardiac insufficiency, hypoventilation, intracranial morphologic abnormalities on MRI, and dysthermia.

Kyphoscoliosis, which is the focus of orthopedic surgery, and small hands and feet with clinodactyly–syndactyly, in particular thumb adduction over index.

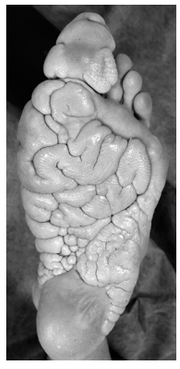
Medical treatment includes psychotherapy, dietary control, and growth hormone to improve growth, tone, and respiration and to reduce fat.

PROTEUS SYNDROME

Mosaicism for a somatic-activating mutation in the protein kinase AKT1 gene on 14q32.3.

Sporadic occurrence and progressive course.

Variable asymmetric, disproportionate, localized tissue hypertrophy leading to gigantism of trunk and/or limbs.



Lymphatic and vascular tumors in skin and subcutaneous tissue, including characteristic "cerebriform" connective tissue nevi having grooves and gyrations.

Hyperostosis of craniofacial skeleton, in particular of external auditory meatus.

Limb equalization for hemihypertrophy.

Fusion for spine deformity and decompression for spine stenosis, which may be due to kyphoscoliosis or tumor infiltration.

The disorder is named after the ancient Greek Sea God Proteus, "the polymorphous," who could change his shape like the ever-changing nature of the sea.

Joseph Carey Merrick (1862–1890), advertized as "Half a Man and Half an Elephant" by his showmen, may have been affected by this condition.

PYLE DISEASE

This also is known as metaphysial dysplasia.

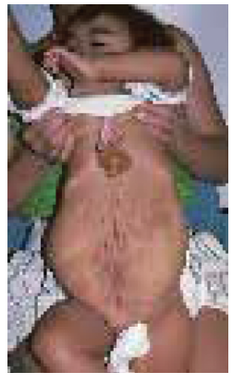
Autosomal recessive.

The distinguishing feature is bizarre röntgenographic changes, including "unremodeled" appearance of long bones, with minimal clinical consequences. Erlenmeyer flask deformity of proximal tibia and distal femur and genu valgum.

PRUNE BELLY SYNDROME

Autosomal recessive mutation in cholinergic receptor, muscarinic 3 gene on 1q43.

The disorder is named for absence of abdominal muscles with overlying skin, which is thin and lax with multiple creases due to redundancy.



Urogenital anomalies, including megacystis with disorganized detrusor muscle, hydronephrosis, and cryptorchidism.

Urinary obstruction in the fetus may produce distension and maldevelopment of abdominal wall.

Musculoskeletal manifestations include hip dysplasia with dislocation due to laxity, segmentation defects of the spine producing congenital scoliosis and of the chest such as costal fusion, clubfoot, and vertical talus.

Other management includes self-catheterization or vesicostomy, orchiopexy, and potentially dialysis and renal transplantation.

PSEUDOACHONDROPLASIA

Autosomal dominant mutation of cartilage oligomeric matrix protein gene on 19p31.11.

Allelic with epiphysial dysplasia, multiple, of Fairbanks, which is milder.

The appellation derives from a resemblance to achondroplasia, including rhizomicromelia, trident hand, and lumbar hyperlordosis.

Distinguishing features are:

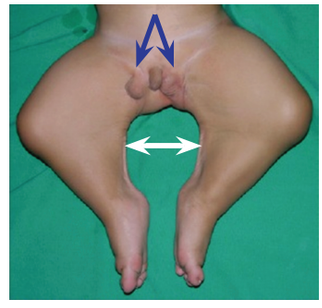
- Normal presentation at birth, with diagnosis rarely before 2 years.
- Normocephaly, including calvaria and face.
- Epiphysial involvement leading to premature osteoarthritis, with arthroplasty common by the fourth decade.
- Odontoid hypoplasia producing cervical spine instability and myelopathy, requiring stabilization.
- Absence of lumbar spine stenosis.

PTERYGIUM SYNDROME

The term derives from Greek πτερυξ: "wing," after the appearance of the skin as it stretches across a joint.

Pterygia result in primary growth disturbance and secondary physical distortion:

Musculoskeletal Kyphoscoliosis due to vertebral anomaly; articular contracture with (sub)luxation in particular of hip, knee (white), and elbow; hypoplasia of patellae and innominate bones; clubfoot; vertical talus; syndactyly and synostosis of feet more than hands; cutaneous dimples over extension side of elbows and knees; and pyramidal cutaneous overgrowth of halluceal nails.



Craniofacial Cleft lip and palate, paramedian mucous cyst of lower lip, syngnathia, ankyloblepharon filiforme adnatum, and hearing loss.

Genitourinary Bifid scrotum (blue), cryptorchidism, and hypoplasia.

Visceral Cardiopulmonary anomaly and diaphragmatic, abdominal, and inguinal hernias.

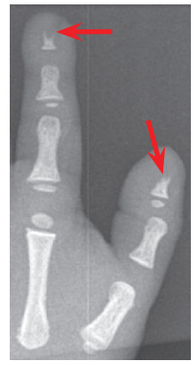
Three principal types are distinguished, with broader involvement and increasing severity.

Early pterygium release because neurovascular structures limit extent and rate of recurrence is high. Add external fixator for gradual correction after index release.

Phenotypic overlap with arthrogryposis and Freeman-Sheldon syndrome.

Type	Features
Popliteal - faciogenitopopliteal syndrome	Autosomal dominant mutation in interferon regulatory factor-6 gene on 1q32-q41. Pterygium may extend from ischium to calcaneus as it crosses the popliteal fossa.
Multiple - Escobar syndrome	Autosomal recessive mutation in the gene encoding the gamma subunit of acetylcholine receptor on 2q37.1. Dysmorphology caused by transient inactivation of neuromuscular end-plate. Pterygium colli distinctive.
Lethal - Bartsocas-Papas syndrome	Autosomal recessive mutation in receptor-interacting serine-threonine kinase-4 gene on 21q.22.3. Clustering in Mediterranean ancestry. Death from pulmonary hypoplasia and insufficiency.

PYCNODYSOSTOSIS



From Greek πυκνος: "close-packed, dense, thick," after the radiodensity of bone.

Autosomal recessive mutation of cathepsin K on 1q21.3. Cathepsin K belongs to the papain cysteine protease superfamily, among which it is unique in having an expression restricted to a specific cell type, the osteoclast.

Abnormal proteolysis in the organic matrix leads to bone sclerosis and fragility, resulting in phenotypic overlap with osteopetrosis.

Delayed suture closure, hypodontia, and caries.

Aplasia or hypoplasia of clavicle, scoliosis, spondylolysis and spondylolisthesis, brachydactyly and acroosteolysis of distal phalanges, and onychodysplasia.

RICKETS

Named after involvement of the spine, from Greek ραχις: "spine."

Defective bone mineralization due to hypocalcemia and hypophosphatemia.

In the liver, vitamin D 25-hydroxylase adds -OH to vitamin D at carbon 25. In the kidney, 1-alpha-hydroxylase adds a second -OH to produce the active metabolite $1,25(OH)_2D3$, which binds and activates the nuclear vitamin D receptor.

Four types are distinguished.

Type	Features
Hypophosphatæmic - autosomal	• Dominant mutation in fibroblast growth factor 23 on 12p13. • Recessive mutations in dentin matrix acidic phosphoprotein 1 on 4q21 and in ectonucleotide pyrophosphatase phosphodiesterase 1 on 6q22-q23.
Hypophosphatæmic - X-linked	• Dominant mutation in phosphate regulating endopeptidase homolog on Xp22.11. • More severe recessive mutation in chloride channel exchange transporter 5 on Xp11.22.
Vitamin D-deficient	Mutation in: • type 1A: 25-hydroxyvitamin D3-1-alpha-hydroxylase on 12q14. • type 1B: vitamin D 25-hydroxylase on 11p15.2.
Vitamin D-resistant	Mutation in: • type 2A: vitamin D receptor on 12q13.11, resulting in end organ insensitivity. • type 2B: nuclear ribonucleoprotein C, which interferes with the function of vitamin D receptor.

Rickets also may result from malnutrition, including inadequate consumption of vitamin D2 (ergocalciferol) in plants and lack of sunlight, of which ultraviolet radiation is necessary for synthesis of vitamin D3 (cholecalciferol), the inactive precursor.

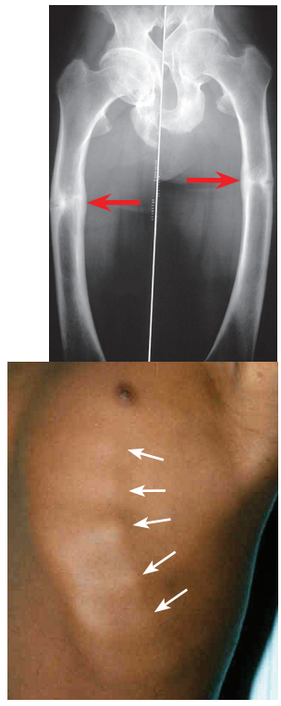
Short stature; osteomalacia; "soft" fracture, for example, greenstick (red); long bone bowing, physial widening with metaphysial irregularity; bone and joint pain; calcification of entheses; spinal stenosis; and craniotabes (soft skull).

"Bulging" epiphysis lead to articular enlargement, and hypertrophic costochondral junctions produce the "rachitic" rosary (white).

Indentation of soft ribs at the insertion of the diaphragm is known as "Harrison groove."

Muscle weakness, alopecia, and caries.

Hypocalcemia may result in seizure, hypercalciuria in nephrocalcinosis, and secondary hyperparathyroidism in subperiosteal erosions.



RILEY-DAY SYNDROME

See familial dysautonomia.

RUBINSTEIN-TAYBI SYNDROME

Autosomal dominant mutation of the transcriptional coactivator cAmp response element-binding (CREB) protein on 16p13.3.

Also known as broad thumb–hallux syndrome, after these features and the characteristic facies (heavy high-arched eyebrows, long eyelashes, low ears, grimacing smile) emphasized in the original report.

Congenital scoliosis, slipped capital femoral epiphysis, patellar and other joint instability, single palmar and plantar creases, and polydactyly.

Psychomotor delay; ocular (glaucoma, cataract), cardiac (valvular regurgitation, septal defect, pulmonic stenosis, aortic coarctation), and genitourinary (cryptorchidism) anomalies; and hirsutism. Five percent of patients develop a tumor, including neural, rhabdomyosarcoma, leukemia, and pheochromocytoma. The rate is similar to neurofibromatosis I.

Floating-Harbor syndrome (named for Boston Floating Hospital and Harbor General Hospital in Torrance where the first two cases were observed) is caused by mutation in SNF2-related CBP-activator protein, which is a coactivator of CREB protein. Its features resemble the craniofacial features of Rubinstein-Taybi syndrome.

SECKEL SYNDROME

Autosomal recessive mutation in ataxia–telangiectasia and Rad3-related protein gene on 3q22.1 (type 1). Six other subtypes distinguished by mutation.

The German pathologist and polymath Rudolph Carl Virchow (1821 to 1902) called this "bird-headed" dwarfism, after the characteristic microcephaly, large eyes, prominent sharp nose, and small chin and ears.

Scoliosis, hip dysplasia, hypoplasia of proximal radius and proximal fibula, and flexion contractures.

Central nervous system anomalies result in psychomotor delay and seizures.

SILVER-RUSSELL SYNDROME

DNA hypomethylation at the telomeric imprinting control region on 11p15.5, involving adult skeletal muscle and insulin-like growth factor 2 genes. Ten percent represent maternal uniparental disomy, in which child receives two copies of chromosome 7 from mother.

Characteristic triangular facies with broad forehead ("pseudohydrocephalic"), wide mouth, and small chin.

Body asymmetry, including hemihypertrophy; hand and foot anomalies, including second metacarpal pseudoepiphysis; congenital scoliosis; and hip dysplasia.

Genital malformations and gastrointestinal symptoms.

Tumor risk, including Wilms (nephroblastoma), hepatocellular, and craniopharyngioma.

Opposite epimutations, in which the same chromosomal region is hypermethylated, are associated with Beckwith-Wiedemann syndrome and Wilms tumor type 2.

Associated with assistive reproductive technologies.

SMALL PATELLA SYNDROME

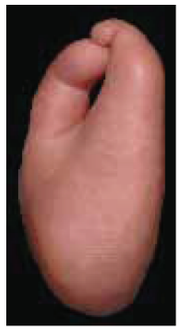
Also called ischiopatellar dysplasia and coxopodopatellar syndrome, which are more inclusive descriptors.

Autosomal dominant mutation in T-box 4 on 17q23.2. T-box 4 encodes a transcription factor with a DNA-binding T-box domain that plays a role in lower limb development.

Patellar aplasia/hypoplasia and instability, ischial hypoplasia with delayed ossification of ischiopubic junction, wide and flat proximal femoral epiphysis, infra-acetabular notching, and widened first to second web spaces in the feet.

Nails are normal, and while the pelvis is significantly involved, iliac horns are absent, which distinguish this from nail–patella syndrome.

SPLIT HAND/SPLIT FOOT MALFORMATION



This also is known as ectrodactyly, from Greek εκτρωσις: "wound resulting in loss, abortion."

Designated a malformation to emphasize a primary structural lesion, in comparison with deformity, which is secondary.

Aplasia/hypoplasia of central rays produce clefts in hands and feet resembling a "lobster claw" or "ostrich foot." Preaxial loss may produce monodactyly.

Preaxial upper limb involvement is a locus discriminator, affecting approximately 50% of types 3 and 5 and <5% of others.

Variable orofacial clefting and mental retardation.

Six types are distinguished.

Type	Features
1	Mutation in distal-less homeobox 5 on 7q21.3. Sensorineural hearing loss.
2	Linkage to Xq26.
3	Contiguous gene duplication linked to 10q24 trisomy. Renal hypoplasia.
4	Mutation in tumor protein p63 on 3q28.
5	Mutation in 2q31
6	Mutation in wingless-type MMTV integration site family member 10B on 12q13.

SPONDYLOEPIMETAPHYSIAL DYSPLASIA

Dysplasia of long bones, both epiphysis and metaphysis, and spine, after Greek σπονδυλοι = Latin *vertebra*.

Skeletal Metaphysial flaring and cupping, epiphysial irregularity, kyphoscoliosis, and anterior vertebral "tongues."

Hip, knee, and head of radius dislocation and clubfoot.

Ocular Blue sclerae, dislocation of lens, and cleft palate.

Cardiac anomalies account for demise.

Other "Doughy" skin and variable mental retardation.

Type	Features
Joint laxity type 1 (Beighton)	Autosomal recessive mutation in β–1,3 galactosyltransferase 6 on 1p36.33. Allelic to progeroid form of Ehlers-Danlos.
Joint laxity type 2 (Hall)	Autosomal dominant mutation in kinesin family member 22 on 16p11.2. Distinguished by leptodactyly.
Strudwick	Autosomal dominant mutation in type II collagen on 12q13.11. Allelic to spondyloepiphysial dysplasia, form which it may be distinguished by 'dappled' metaphysis due to alternating regions of osteosclerosis and osteopenia. Dens axis hypoplasia with C1-C2 instability.
Missouri	Mutation in matrix metalloproteinase 13 on 11q22.2. Spontaneous improvement by 2nd decade.
Shohat	Hepatosplenomegaly distend abdomen.
Aggrecan	Mutation in aggrecan on 15q.26.1.
Abnormal dentition	Oligodontia with discoloration.
Genevieve	Autosomal recessive. Hirsutism, ataxia.
Irapa	Described in Yukpa tribe of Irapa, Venezuela.
X-linked	Without or with central nervous system anomalies, psychomotor dysfunction.
Matrilin-3	Linkage to 2p24.1. Allelic to epiphysial dysplasia, multiple, type 5.
Hypotrichosis (Whyte)	Congenital absence of hair follicles, tarda skeletal involvement.
Sponastrime	Term derived from '**spon**dylar and **nas**al alterations with **stri**ated **me**taphysis', to emphasize distinguishing features.
Micromelia	Sub-type with most severe skeletal involvement.

SPONDYLOEPIPHYSIAL DYSPLASIA

Heterogeneous group affecting spine and epiphysis.

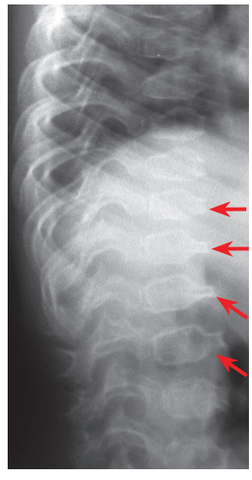
Congenita results from mutation of COL2A1 gene, which produces both α-1 chain of type II collagen and the α-3 chain of type XI collagen. Type II collagen is a homotrimer of polypeptide chains encoded by the COL2A1. The principal tissues of distribution are cartilage and vitreous humor, hence the phenotypic expression in bone (by morbid endochondral ossification), joint, and eye. This subtype is allelic with Kniest dysplasia and Stickler syndrome, which bound a spectrum from severe to mild, respectively.

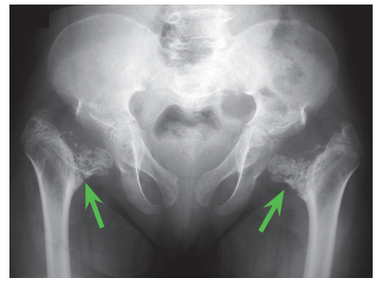
Skeletal Microcormia. Abnormal epiphysial ossification leads to premature osteoarthritis. Dens hypoplasia risks atlantoaxial instability. Thoracic kyphoscoliosis, lumbar hyperlordosis, and platyspondyly with anterior body "tongue" (red). Coxa vara produces a waddling gait (green). Articular contractures, genua valga and vara, clubfoot, and brachydactyly.

Ocular Myopia, retinal detachment, vitreoretinal degeneration, and corneal dystrophy.

Craniofacial Cleft palate and sensorineural hearing loss.

Type	Features
Congenita	Mutation in α–1 chain of collagen type II on 12q13.11.
Tarda (onset > 5 years)	Mutation in tracking protein particle complex, subunit 2 on Xp22.2. Autosomal dominant and recessive forms identified.
Maroteaux	Mutation in transient receptor potential cation channel subfamily V member 4 on 12q24.11. Allelic to brachyolmia type 3, metatropic dysplasia and spondylometaphysial dysplasia of Kozlowski.
Kimberley	Mutation in aggrecan-1 on 15q26.1.
Omani type	Mutation in carbohydrate sulfotransferase-3 on 10q22. Multiple joint dislocations. Congenital heart disease.





Coxa vara Capital femoral epiphysis are severely deformed. Proximal femoral physial–shaft angles >60 degrees.

Spinal deformity Vertebral bodies give rise to projections, which have been likened to a "tongue."

SPONDYLOMETAPHYSIAL DYSPLASIA

Heterogeneous group characterized by spinal and metaphysial changes of variable pattern and severity.

Kyphoscoliosis, dens hypoplasia with atlantoaxial instability, and vertebral bodies extend beyond pedicles like an "open staircase." Flaring of long bone metaphysis results in articular deformity such as coxa vara and may resemble rickets.

Type	Features
Kozlowski	Autosomal dominant mutation in transient receptor potential cation channel subfamily V member 4 on 12q24.11. Allelic to brachyolmia type 3, Charcot-Marie-Tooth type IIc, metatropic dysplasia, spondylo-epiphysial dysplasia (Maroteaux), spinal muscular atrophy. Carpal and tarsal ossification delay.
Sedaghatian	Autosomal recessive. Cardiorespiratory insufficiency. Central nervous system anomalies. Perinatal demise.
Richmond	X-linked. Sclerosis of skull base.
Sutcliffe	Autosomal dominant. Corner and bucket handle fractures. Mild spine involvement.
Goldblatt	Dentinogenesis imperfecta. Joint laxity.
Axial	Autosomal recessive. Retinitis pigmentosa.
Cone-rod dystrophy	Without or with central nervous system anomalies, psychomotor dysfunction.
A4	Severe changes in neck of femur.
East African	Similar to A4 without anterior vertebral tongues.
Algerian	Severe genu valgum.
Bowed forearms and facial dysmorphism	

STICKLER SYNDROME

The descriptive alternate appellation "arthroophthalmopathy" reflects tissue distribution of types II, IX, and XI collagens in cartilage and vitreous humor.

Mildest spondyloepiphysial dysplasia, including normal stature, with ocular disease most prominent.

Marfanoid habitus.

Type	Features
I	Autosomal dominant mutation in α-1 chain of type II collagen on 12q13.11.
II	Autosomal dominant mutation in α-1 chain of type XI collagen on 1p21.1. Allelic to Marshall syndrome.
III	Autosomal dominant mutation in α-2 chain of type XI collagen on 6p21.3. Allelic to otospondylomegaepiphysial dysplasia and Weissenbacher-Zweymuller syndrome.
IV	Autosomal recessive mutation in α-1 chain of type IX collagen on 6q13.
V	Autosomal recessive mutation in α-2 chain of type IX collagen on 1p34.2.

STREETER DYSPLASIA

See amniotic band syndrome.

THANATOPHORIC DYSPLASIA

The term, derived from Greek θανατος: "death" and φορεω: "I bring," describes a neonatal lethal skeletal dysplasia in the family of FGFR3 receptor mutations. See achondroplasia.

THROMBOCYTOPENIA–ABSENT RADIUS (TAR) SYNDROME

Autosomal recessive mutation of RNA-binding motif protein 8A on 1q21.1.

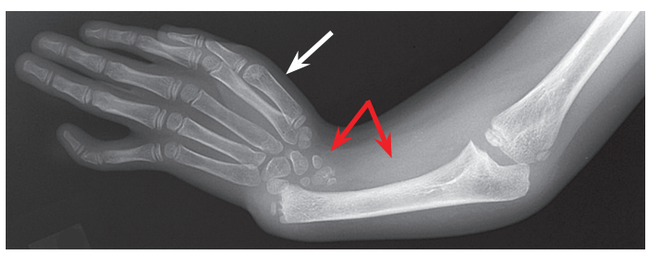
Thrombocytopenia is critical in first 2 years, when it can be lethal, is managed with platelet transfusion, and improves with age.

Radial aplasia and clubhand (red) with preservation of thumb (white).

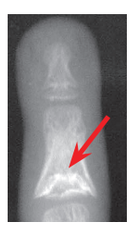
Variable involvement of lower limbs, including hip dysplasia, patellar instability, absent fibula, carpal hypoplasia, and synostosis.

Cardiovascular, renal, and central nervous system anomalies.

Distinguished from Fanconi syndrome by absence of panmyelopathy, leukemia, thumb anomalies, and pigmentary changes.



TRICHORHINOPHALANGEAL DYSPLASIA



Craniofacial Thin "hair" (Greek θριξ, τριχο-), piriform "nose" (Greek ρις, ρινο-) with bulbous tip, and dental dysgenesis.

Skeletal Conoid phalangeal epiphysis with brachydactyly, scoliosis, hip dysplasia, pes planus, and koilonychia/leukonychia.

Three types are distinguished.

TURNER SYNDROME

One type of gonadal dysgenesis, characterized by amenorrhea, sterility, and delayed sexual development.

Partial (p deletion or mosaicism) or complete absence of X chromosome (45X, XO).

Mild psychomotor delay, lymphedema, low hairline and ears, webbed neck, and "shield chest" with broadly spaced nipples.

Short stature, cubitus valgus, patellofemoral instability, scoliosis, Madelung deformity, and fourth and fifth brachydactyly.

Cardiac and renal anomalies, hypothyroidism, otitis media, and celiac disease.

Type	Features
I	Autosomal dominant haplo-insufficiency in zinc finger transcription factor on 8q23.3.
II (Langer-Giedion)	Autosomal dominant loss of functional copies of zinc finger transcription factor gene and exostosin 1 gene on 8q24.11. Phenotype combines trichorhinophalangeal syndrome and multiple exostosis.
III (Sugio-Kajii)	Autosomal dominant haplo-insufficiency in zinc finger transcription factor on 8q23.3. Distinguished from type I by severity of phalangeal and metacarpal involvement. Distinguished from Ruvalcaba syndrome by absence of mental retardation and microcephaly.

VACTERL ASSOCIATION

Expanded acronym from VATER, representing a nonrandom association of independent disorders rather than a single etiologic entity. Diagnosis requires three anomalies.

Vertebral Hemivertebrae produce congenital scoliosis and spinal dysrrhaphism.

Anal atresia

Cardiac Septal defects, patent ductus arteriosus, tetralogy of Fallot, and transposition of the great arteries.

Tracheoesophageal fistula

Renal Renal aplasia/dysplasia, vesicoureteral reflux, and ureteropelvic obstruction.

Limb Radial aplasia/hypoplasia, radioulnar synostosis, thumb hypoplasia, polysyndactyly, and tibial field defects.

Three types are distinguished.

Type	Features
VACTERL	Mutation in the Homeobox D13 gene on 2q31.1 identified in 1 patient.
VACTERL-X	X-linked. Mutation in zinc finger protein of cerebellum 3 on Xq26.3.
VACTERL-H	Associated with hydrocephalus. Mutation in the phosphatase and tensin homolog on 10q23.31 identified in 1 patient

VACTERL may be a feature of Fanconi anæmia.

VELOCARDIOFACIAL SYNDROME

Also known as Shprintzen syndrome.

Autosomal dominant mutation in T-box 1 on 22q11.21. Allelic to DiGeorge syndrome.

Craniofacial Pierre Robin sequence including cleft palate, micrognathia, and velopharyngeal insufficiency. Most common palatal anomaly syndrome. Ocular anomalies include tortuous retinal vessels and posterior embryotoxon. "Hooded" eyelids and asymmetric crying are characteristic.

Cardiac Septal defects and conotruncal anomalies.

Skeletal Arachnodactyly, scoliosis, Sprengel anomaly, and articular laxity.

Other Psychiatric disorders and hypocalcemia.

von WILLEBRAND DISEASE

Mutation in von Willebrand factor on 12p13.31.

Type	Features
1	Quantitative ***partial*** (5-30% normal levels) deficiency. 75% of cases.
2	Qualitative abnormality of von Willebrand factor. 20% of cases. Further subdivided according to whether platelet function is affected or whether there is a defect in factor VIII binding.
3	Quantitative ***severe*** (< 1% normal levels) deficiency. < 5% of cases

vWF binds platelets, which it promotes to adhere, and factor VIII, which degrades when not bound.

Treat with the vasopressin analog desmopressin acetate (1-deamino-8-D-arginine vasopressin; dDAVP).

Orthopedic management focuses on hemarthropathy—compare hæmophilia.

WHISTLING FACE SYNDROME

See Freeman-Sheldon syndrome.

WAARDENBURG SYNDROME

Autosomal dominant mutation of paired box gene 3 on 2q36.1.
The gene product is a transcription factor essential to ear, eye, and pigmentary development.

Craniofacial Sensorineural hearing loss. Dystopia canthorum giving appearance of wide-set eyes due to lateral displacement of inner canthi (W index > 2), heterochromia iridis, and synophrys.

Pigmentary Albinism, including poliosis.

Skeletal Spina bifida, winged or elevated scapulae.

Subtypes reflect heterogeneity.

Type	Features
1	Craniofacial malformations.
2	Absence of dystopia canthorum.
3	Upper limb anomalies.
4	Visceral involvement such as Hirschsprung disease.

ARTHRITIS, JUVENILE IDIOPATHIC

Disease of a joint is termed *arthritis*, from Greek αρθρον: "joint." *Arthralgia*, from Greek αλγος: "pain," is used when pain is the predominant feature, in contrast with swelling. *Arthrosis*, from Greek suffix -ωσις: "condition of," originated in anatomy in the work of Galen, who distinguished different types of articulations as diarthrosis ("in all directions"), amphiarthrosis ("in two directions or planes"), and synarthrosis (when bones are "joined together" such as at a suture). The term has been adopted into pathology to distinguish noninflammatory disease of joints, reserving arthritis for joint inflammation, which is indicated by Greek suffix -ιτις. Inflammation at a site of "insertion" of a ligament or a tendon is referred to as *enthesitis*, from Green εν-: "in" and τιθεναι: "to place."

The term juvenile idiopathic arthritis is an inclusive term. "Rheumatoid" has been abandoned because most subtypes lack this factor.

JUVENILE IDIOPATHIC ARTHRITIS		
Current		**Former**
		"Rheumatoid"
Oligo-articular		**Pauciarticular**
Poly-articular	Rheumatoid factor positive	**Polyarticular**
	Rheumatoid factor negative	
Systemic		**Still disease**
Enthesitis associated		**Spondyloarthropathy,** including ankylosing spondylitis Reiter syndrome
Psoriatic		**Psoriasis**
Undifferentiated		

Oligo-, from Greek ολιγος: "few," is defined as <5 joints. It has replaced pauci-, from Latin *paucus*: "few," to be consistent with poly-, from Greek πολυς: "much, many," and after the convention that Greek is the language of disease.

Chronic iridocyclitis (inflammation of the anterior uvea) often is asymptomatic, necessitating referral to an ophthalmologist for slit-lamp examination. Early-onset disease and positive ANA are at greatest risk.

Psoriasis is characterized by a dry, silvery, scaly rash, from Greek ψαω: "I rub (away), crumble."

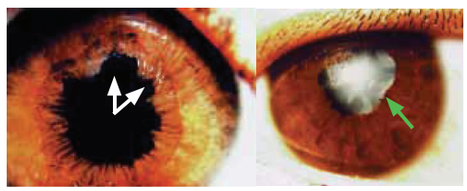
Chronic juxta-articular inflammation may produce hyperemic osseous overgrowth in early-onset disease and premature physial closure in late-onset disease. Discrepancy does not exceed 5 cm.

Orthopedic management includes:

- Arthrocentesis. This is the best step to diagnosis.
- Physiotherapy and bracing for contracture and weakness.
- Limb equalization by physiodesis, in up to half of patients.
- Arthroplasty. Overall, disease burden limits activity and prolongs implant survival.

Medical treatment includes:

- Nonsteroidal anti-inflammatory agents
- Articular injection of corticosteroid
- Disease-modifying antirheumatic drugs, such as methotrexate
- Biologics, such as tumor necrosis factor-α blockers and anti-interleukin-6 inhibitors



Iridocyclitis
Irregular pupil (*white*) and cataract (*green*)

	OLIGOARTICULAR	POLYARTICULAR	SYSTEMIC	ENTHESITIS associated
Frequency	60%	30%	10%	
Gender			=	
Age (years)	< 5	Early < 5 Late > 10	All	> 10
Joints	Large (e.g., knee) > small	Small (e.g., fingers) > large	all (including hip)	"Spondylo-arthropathy": spine + sacro-iliac + other
Presentation	Joint, iridocyclitis	Unhappy: morning stiffness, fatigue, poor appetite, weight loss, anæmia.	Systemic: "saw-tooth" fever (daily rapid return to normal temperature); "salmon-colored" migratory rash, lymphadenopathy, visceral involvement including serositis, hepatosplenomegaly, disseminated intravascular coagulation.	Syndesmophytes create a "bamboo" appearance of the spine, and reduce excursion during maximal respiration and flexion (Schober sign). Inflammatory bowel disease. Bath Ankylosing Spondylitis Disease Activity Index assesses fatigue, pain, enthesitis and morning stiffness.
ESR	→	↗	↑	↗
CRP	→	↗	↑	↗
ANA	60%	30%	15%	
RF		50% (late onset)	5%	-
HLA-B27				+

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