GENETIC AND CONGENITAL DISEASES OF BONE

Skeletal dysplasias = heterogeneous group of genetic disorders affecting bone formation/remodeling.

Common features: **dwarfism (often disproportionate), abnormal bone shapes, fragility**.

Terminology often reflects defect distribution (generalized, localized) or lesion type.

Pathogenesis may involve:

- **Defective cartilage growth** (chondrodysplasias, achondroplasia).
- **Defective matrix synthesis** (e.g. type I collagen in osteogenesis imperfecta).
- **Defective remodeling** (e.g. osteopetrosis).

Non-genetic mimics: toxins, infectious agents, mineral deficiencies during fetal development.

Chondrodysplasias: disproportionate dwarfism due to defective interstitial cartilage growth → premature closure of growth plates; common across cattle, sheep, pigs, horses, dogs, cats.

Species-specific:

- **Cattle**: Bulldog calves (Dexter, Holstein), Telemark dwarfism, "snorter" dwarfs, long-headed dwarfs (PRKG2 mutation), EVC2-related dwarfism.
- **Sheep**: Spider lamb syndrome (FGFR3 mutation), Texel dwarfism (SLC13A1 mutation), Ancon mutants, Merino dwarfism with renal hypoplasia.
- **Pigs**: Landrace dwarfism, COL10A1-related Schmid-type metaphyseal dysplasia.
- **Horses**: Friesian dwarfism, Miniature horse ACAN mutations.
- **Dogs**: Multiple breed-specific chondrodysplasias; genes include ITGA10, SLC13A1, COL9A2/3, COL11A2; syndromes with ocular dysplasia.
- **Cats**: Scottish Fold osteochondrodysplasia (fd gene), physeal dysplasia with slipped capital femoral epiphysis, rare metaphyseal dysplasias.

Disease / Syndrome	Species / Breed	Etiology / Gene	Inheritance	Pathogenesis	Gross Features	Histologic Features	Special Stains / IHC	Other Key Points
Achondroplasia / Chondrodysplasia (general)	Multiple spp.	Defects in cartilage growth (various genes)	Variable	Defective interstitial cartilage growth → premature closure of physes	Disproportionate dwarfism, shortened long bones, craniofacial deformities	Loss of orderly columns of chondrocytes, thickened/disorganized physes	–	Used interchangeably with "chondrodystrophy" in vet med

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Bulldog dwarfism (Dexter, Miniature breeds)	Cattle	**ACAN** mutations (aggrecan)	Incomplete dominant (heterozygotes short-legged; homozygotes lethal)	Failure of endochondral ossification	Short domed head, prognathia inferior, cleft palate, very short/rotated limbs, large ventral hernia	Growth plates absent; densely packed chondrocytes, no columnar arrangement; abnormal cartilage canals	–	Aborted <7 mo; commercial carrier test available
Bulldog dwarfism (Holstein)	Cattle	Unknown; likely structural gene defect	Autosomal recessive	As above	Similar to Dexter + pulmonary hypoplasia, stenotic trachea	As above	–	Parents phenotypically normal
Telemark dwarfism	Cattle	Unknown	Autosomal recessive	Defective endochondral ossification	Bulldog-like craniofacial defects; short rotated limbs	Similar to bulldog	–	Born alive, die shortly after birth (suffocation)
Snorter dwarfism	Hereford, Angus cattle	Unknown	Autosomal recessive (partial expression in heterozygotes)	Premature closure of synchondroses, defective cartilage growth	Short, broad head, bulging forehead, noisy respiration, chronic bloat	Mild: short/irregular columns of chondrocytes	Radiographic lumbar exostoses	Now rare due to breeding programs
Long-headed (dolichocephalic) dwarfism	Angus, Holstein, Simmental cattle	**PRKG2** nonsense mutation	Autosomal recessive	Defective phosphorylation of SOX9 → impaired collagen II/X regulation	Long tapered head, crooked limbs, slow growth	Disorganized growth plates	–	PRKG2 adjacent to growth/milk QTLs
EVC2 dwarfism	Japanese Brown, Tyrolean Grey cattle	**EVC2** mutation	Autosomal recessive	Defective Sonic Hedgehog signaling via primary cilia	Short rotated long bones, enlarged metaphyses	Disorganized physes, reduced proliferative/hypertrophic zones, premature closure	Cytoplasmic vacuoles in chondrocytes	–
Spider lamb syndrome	Suffolk, Hampshire sheep	**FGFR3** mutation (T→A, position 1719)	Autosomal recessive	Defective growth plate regulation → excess cartilage,	Long legs/neck, scoliosis, kyphosis,	Disorganized hypertrophic cartilage, multiple ossification centers that fail to coalesce	Radiographs: irregular ossification in	Carrier test available

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				abnormal ossification centers	knock-kneed, Roman nose		sternum/elbow	
Texel dwarfism	Sheep (NZ)	**SLC13A1** mutation (sodium-sulfate transporter)	Autosomal recessive	Defective GAG sulfation	Dwarfism, varus forelimb deformities, flaccid trachea	Chondrocyte disorganization, chondrolysis, cystic clefts, abnormal tracheal cartilage	↓ chondroitin-4-sulfate	Severe arthropathy
Merino brachygnathia–cardiomegaly–renal hypoplasia syndrome	Sheep	Unknown	Autosomal recessive	Multisystem defect	Stillborn dwarfs with cardiomegaly, renal hypoplasia	Renal hypoplasia, liver congestion; no bone lesions	–	Unique multisystem dysplasia
Landrace dwarfism	Pigs	Unknown	Autosomal recessive	Defective growth plate	Disproportionate dwarfism, abnormal gait	Decreased proliferative zone, irregular hypertrophic zone	–	Degenerative arthropathy develops
Schmid-type metaphyseal chondrodysplasia	Pigs (Yorkshire)	**COL10A1** missense mutation (Type X collagen)	Autosomal dominant	Defective type X collagen trimerization	Shortened, widened long bones; excessive physeal cartilage	Expanded hypertrophic zone, disorganized columns, cartilage tongues into metaphysis	–	Analogous to human Schmid disease
Friesian dwarfism	Horses	Linked to Chr14 locus	–	Abnormal growth plate development	Large head, broad chest, long back, short limbs	Disorganized proliferative & hypertrophic zones	–	Hyperextension of fetlocks
Miniature horse dwarfisms (4 types)	Horses	**ACAN** mutations	Autosomal recessive	Aggrecan defect	Bulldog-like dwarfism	–	–	Multiple forms
Alaskan Malamute chondrodysplasia	Dogs	Unknown	Autosomal recessive (variable expression)	Abnormal endochondral ossification + hemolytic anemia	Short-legged dwarfs, bowing of radius/ulna, carpal enlargement	Thickened physes, tongues of cartilage, microfractures	Mimics rickets	Associated anemia (stomatocytosis)
Norwegian Elkhound / Karelian Bear dog dwarfism	Dogs	**ITGA10** nonsense mutation	Autosomal recessive	Defective integrin-α10 → impaired chondrocyte–	Short legs, bowed radius/ulna,	Chondrocyte inclusions (blue, alcian blue–PAS+),	EM: finely granular inclusions	Pathognomonic inclusions

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				matrix interaction	short vertebrae	reduced proliferative zone		
Pointer chondrodysplasia	Dogs	Unknown	Autosomal recessive	Defective growth plate/cartilage	Dwarfism, "bunny-hopping" gait, prognathism	Irregular thickened physes, cystic chondrocyte spaces	–	Severe degenerative arthropathy
Great Pyrenees chondrodysplasia	Dogs	Unknown	Autosomal recessive	Growth plate disorganization	Short dwarfs, angular limb deformities	Vacuolated chondrocytes (dilated rER)	–	Delayed ossification
Pseudoachondroplastic dysplasia	Miniature Poodles	**SLC13A1 deletion**	Autosomal recessive	Defective GAG sulfation	Small size, bowed limbs, enlarged epiphyses	Sparse cartilage matrix, irregular columns, stippled ossification centers	–	Also trachea/nasal defects
Multiple epiphyseal dysplasia	Beagles	Likely recessive	Abnormal ossification centers	Swaying gait, stippled epiphyses radiographically	Mineralized lacunae, abnormal subarticular ossification	–	Resolves into ossification centers	
Scottish Deerhound osteochondrodysplasia	Deerhounds	Unknown	Autosomal recessive	Abnormal endochondral ossification	Bunny-hopping gait, bowed limbs, kyphosis	PAS+ diastase-resistant inclusions in chondrocytes	–	Variable lesions in physes
Oculoskeletal dysplasia (Labrador, Samoyed)	Dogs	**COL9A3** (Labrador, drd1) / **COL9A2** (Samoyed, drd2)	Recessive (skeletal), incomplete dominance (ocular)	Defective collagen IX	Short forelimbs, valgus deformities, ocular lesions (cataracts, retinal detachment)	Disorganized physes, tongues of cartilage	–	Radiographic screening at birth
Skeletal dysplasia 2	Labrador Retrievers	**COL11A2** mutation	Autosomal recessive (incomplete penetrance)	Defective collagen XI	Mild dwarfism (short legs, normal trunk)	Mild disorganization of growth plates	–	Mild form
Scottish Fold osteochondrodysplasia	Cats	**fd gene** (autosomal dominant, incomplete	Dominant	Defective endochondral ossification	Short misshapen distal limbs, stiff gait, short tail, exostoses	Disorganized cartilage columns, necrotic foci in articular cartilage	–	Homozygotes severe; UK ban

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		penetrance)						
Physeal dysplasia with slipped capital femoral epiphysis	Cats (Siamese, Maine Coon, DSH)	Unknown	Familial tendency	Persistent dysplastic physes	Young overweight cats, femoral head epiphysis slip	Chondrocyte clusters in abundant matrix	–	Resembles human slipped capital femoral epiphysis

- **Osteogenesis imperfecta (OI)**
- **Osteopetrosis**
- **Congenital hyperostosis**
- **Osteochondromatosis**
- **Idiopathic multifocal osteopathy**
- **Limb dysplasias** (syndactyly, polydactyly, polymelia, hemimelia, etc.)
- **Skull anomalies**
- **Sternum/ribs anomalies**
- **Pelvis anomalies**
- **Vertebral anomalies** (including CVM, brachyspina, etc.)

Disease	Etiology (genetic/agent)	Pathogenesis	Gross Features	Histologic Features	Key Diagnostic Points
Osteogenesis imperfecta (OI)	Mutations in **COL1A1, COL1A2 (type I collagen genes)** → autosomal dominant (humans, some dogs). Recessive forms: defects in collagen-folding proteins (e.g., **SERPINH1 in Dachshunds** = defective HSP47). Other mutations: **COL1A1/COL1A2 missense in dogs**, defects in dentinogenesis-related collagen, etc.	Defective synthesis/processing of type I collagen → brittle bones, abnormal dentin, sclera, tendons.	- Brittle bones with multiple fractures (intrauterine & postnatal).- Blue sclera.- Fragile teeth (dentinogenesis imperfecta, pink-translucent).- Joint laxity, crouched stance in calves.- Calves: calluses on ribs (healed intrauterine fractures), porous cortices.- Sheep: domed head, brachygnathia inferior, extreme bone fragility, skin fragility in some outbreaks.- Dogs: brittle teeth, joint laxity.	- Bones: porous cortices, woven bone predominates, trabecular microfractures, thin basophilic osteoid rims, lack of secondary spongiosa, absence of Haversian systems (dogs).- Dentin: thin, irregular, hypomineralized, reduced tubules.- Tendons: hypercellular fibroblasts with vacuoles.- Ultrastructure: thin collagen fibrils.	- **Differentiate from osteopetrosis:** OI = collagen defect, osteopetrosis = defective osteoclast resorption.- Common in **calves, lambs, Dachshunds, other dogs, cats**.- Blue sclera + brittle teeth highly suggestive.- Genetic tests available in some breeds.

Osteopetrosis ("marble bone disease")	Defective osteoclast function:- **SLC4A2 deletion** (Red Angus).- **CLCN7 mutation** (Belgian Blue).- Mutations in **ATP6i, RANKL** (in humans/animals).- Can also be acquired (BVDV, FeLV, CDV).	Osteoclasts absent/dysfunctional → failure to resorb primary spongiosa → bones dense, marrow cavity obliterated.	- Small, premature, stillborn calves (esp. Angus, Hereford, Simmental, Belgian Blue).- Brachygnathia inferior, impacted teeth, protruding tongue.- Dense radiodense bones with absent medullary cavity.- Skull thickened, foramina hypoplastic (optic nerve hypoplasia, blindness).- Vertebrae shortened.- Belgian Blue: gingival hamartomas.	- Normal growth plates, but metaphyses filled with dense chondro-osseous tissue (persistent primary spongiosa).- Osteoclasts few/abnormal (no ruffled borders).- Osteoblasts sparse, little cytoplasm.- Cortex relatively normal.- Teeth: enamel, dentin, cementum interwoven.	- Differentiate from OI: osteopetrosis = **dense bones, marrow obliteration, brachygnathia**.- Genetic tests available for **SLC4A2, CLCN7**.- Seen in **cattle, horses, sheep, dogs, deer**.
Congenital hyperostosis (pigs)	Unknown. Suspected: vascular abnormality (intrauterine positioning, hypertension lesions in vessels). Not proven hereditary.	Abnormal periosteal bone deposition + edema.	- Piglets stillborn or die shortly after birth.- Thickened forelimbs (esp. radius/ulna).- Hard limbs, periosteal bone, edematous soft tissues.	- Radiating trabeculae of woven bone under periosteum.- Edematous connective tissue infiltrating muscle + dermis.- Active periosteal osteoblasts.	- Differs from infantile cortical hyperostosis in humans (COL1A1 mutation).- Limbs enlarged, periosteal bone + edema hallmark.
Osteochondromatosis	Autosomal dominant inheritance (dogs, horses, humans).	Dysplastic growth of cartilage from physes/subarticular cartilage → exostoses.	- Tumor-like cartilaginous exostoses, single/multiple, often bilaterally symmetrical (horses).- Present at birth (horses), arise in youth (dogs).	Hyaline cartilage cap with endochondral ossification into trabecular bone.	- Important differential from neoplastic chondrosarcoma.- Stops growing at skeletal maturity.
Idiopathic multifocal osteopathy (dogs)	Unknown. Possible genetic. Human equivalent: Winchester syndrome (**MMP2 mutations**).	Multifocal osteolysis → fibrosis replaces bone.	- Lesions in skull, cervical vertebrae, proximal radius/ulna/femur.- Dogs affected in young adulthood.	- Fibrous tissue replacing bone + mineralized acellular matrix.- Scalloped bone edges with osteoclasts.	- Rare.- Differential: Winchester syndrome in humans.
Limb dysplasias (syndactyly,	- **Syndactyly:** mutations in **LRP4/Mefg7**	Disturbed limb bud development, failure of	- Syndactyly: fused digits (may involve bone or soft tissue).- Polydactyly:	- Fusion or absence of phalanges/cartilage.-	- Breed-specific genetic tests in some cases (e.g.,

polydactyly, polymelia, hemimelia, etc.)	(cattle).- **Polydactyly:** variable, autosomal dominant in cats; SNPs in **LMBR1 gene regulatory region** in some dogs.- **Polymelia (developmental duplication):** recessive in Angus.- **Hemimelia:** recessive in Galloway, Shorthorn, Chihuahua dogs.	digit separation, duplication, or agenesis.	extra digits (often medial).- Polymelia: extra limb, often from neck/shoulder.- Hemimelia: partial limb absence (tibia, radius, etc.).	Fibrous replacement in aplastic regions.	syndactyly in Holstein, Angus).- Important in differential diagnosis for limb deformities in calves, small animals.
Skull anomalies	- Brachygnathia inferior: autosomal recessive suspected in cattle/sheep.- Brachygnathia superior: unknown, seen in Angus calves with DJD.	Failure of normal craniofacial development.	- Shortened mandible (inferior) or maxilla (superior).- Dome-shaped head (brachygnathia superior).	- DJD changes in cartilage (brachygnathia superior cases).	- Inferior more common; usually cosmetic but can impair nursing.
Sternum & ribs anomalies	Familial in Bengal cats, chondrodystrophic breeds. Congenital (pectus excavatum, clefts).	Malformation of sternum/ribs; abnormal diaphragm traction.	- Pectus excavatum: concave chest.- Sternum clefts: schistosomus reflexus (eventration, lordosis).	- Defective sternal cartilage growth.	- Differentiate congenital vs. acquired (swimmer pups).
Pelvis anomalies	Developmental notochord defects.	Agenesis or hypoplasia of sacrum/pelvis.	- Sacral agenesis, pubic separation, ectropion bladder, anorectal anomalies.	- Hypoplastic or absent vertebrae, malformed pelvic bones.	- Seen in Bulldogs; often severe malformations.
Vertebral anomalies (CVM, brachyspina, others)	- **CVM (Complex Vertebral Malformation):** mutation in **SLC35A3** (UDP-N-acetylglucosamine transporter).-	Abnormal somite segmentation or chondrification/ossification of vertebral column.	- CVM: shortened cervical/thoracic spine, arthrogryposis, scoliosis, cleft palate, cardiac anomalies.- Brachyspina: short spine, long slender limbs, growth	- CVM: malformed vertebrae, abnormal cartilage.- Brachyspina: irregular ossification, missing epiphyses, fusion of diaphyses.	- CVM and brachyspina important in Holstein breeding → genetic testing required.- Both

	Brachyspina: deletion in **FANCI gene** (DNA repair).- Others: hemivertebrae, block vertebrae, butterfly vertebrae, spina bifida (recessive or teratogenic).		retardation, cardiac/renal/ovarian malformations.- Others: fused vertebrae, abnormal curvature (kyphosis, scoliosis).		lethal in homozygotes.

Genetic diseases indirectly affecting the skeleton

- **Lysosomal storage diseases** affecting skeleton:
  - **Mucopolysaccharidoses (MPS I–VII)** → enzyme deficiencies → GAG accumulation.
    - Skeletal vs CNS lesions depend on stored product.
    - MPS I, VI, VII most severe for skeleton.
  - **Mucolipidosis II (I-cell disease)** → defective trafficking of lysosomal enzymes.
  - **GM1 gangliosidosis** → β-galactosidase deficiency → variable skeletal impact.
- **Porphyrias**:
  - Congenital or acquired enzyme defects in heme biosynthesis → porphyrin deposition in bones, teeth, urine, skin → discoloration + photosensitivity ± hemolysis.

Disease	Species / Breeds	Etiology (gene / enzyme defect)	Inheritance	Pathogenesis	Gross Features	Histologic Features	Key Diagnostic / Other Points
MPS I (Hurler's syndrome)	Cats (DSH), Dogs (Plott Hound, Rottweiler, Afghan Hound, Boston Terrier)	**α-L-iduronidase deficiency**	Autosomal recessive	Accumulation of dermatan + heparan sulfate → skeletal + CNS lesions	- Cats: facial dysmorphia, corneal opacity, coxofemoral subluxation, pectus excavatum, cervical vertebral fusion (no dwarfism).- Dogs: stunted, facial dysmorphia, corneal opacity, progressive lameness, osteopenia, severe	- Fibroblasts, chondrocytes, hepatocytes: storage vacuoles.- Growth plates: disorganized.- No metachromatic granules in neutrophils, occasional lymphocyte vacuoles.	Cats with MPS I may have ↑ meningiomas.Key: osteopenia + severe DJD in dogs.

					DJD, vertebral dysplasia, kyphoscoliosis, spinal cord compression.		
MPS II (Hunter syndrome)	Labrador Retriever	**Iduronate-2-sulfatase deficiency**	X-linked recessive (in humans; single dog case)	Accumulation of dermatan + heparan sulfate	Coarse facial features, enlarged digits, generalized osteopenia (mild skeletal lesions)	Similar to MPS I but milder	Only single canine case reported.
MPS VI (Maroteaux-Lamy)	Siamese cats (also Mini Doberman, Schnauzer, Poodle, Chessie, Corgi)	**Arylsulfatase B deficiency** (mutations L476P, D520N)	Autosomal recessive	Accumulation of dermatan sulfate	- Cats: broad face, small ears, corneal opacity, large paws, pectus excavatum (by 2 mo).- Epiphyseal dysplasia, short stature, severe DJD, spinal deformities, vertebral fusions, rib broadening, osteophytes compressing spinal cord (ataxia/paresis).	- Growth plates poorly organized, lack of columns.- Chondrocytes swollen with vacuolated cytoplasm.- Inclusions in hepatocytes, muscle, fibroblasts, cornea, heart valves, skin.	- **Early urinary dermatan sulfate** ↑.- **Metachromatic neutrophil granules**.- L476P = severe; D520N = mild (carrier frequency 11.4%).
MPS VII (Sly syndrome)	Dogs (Brazilian Terriers, GSD, mixed breeds), Cats (DSH)	**β-glucuronidase deficiency**	Autosomal recessive	Accumulation of dermatan, heparan, chondroitin sulfate	- Terriers: brachycephaly, dwarfism, delayed ossification (cartilaginous carpal/tarsal bones).- GSD/mixed dogs: epiphyseal/vertebral dysplasia, joint laxity, corneal opacity, thickened valves.- Cats: like MPS VI.	- Neutrophils: **metachromatic granules**.- Chondrocyte inclusions.	Mimics MPS VI.Diagnostic: neutrophil granules + β-glucuronidase assays.

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Mucolipidosis II (I-cell disease)	Cats (DSH)	**N-acetylglucosamine-1-phosphotransferase deficiency**	Autosomal recessive	Defective trafficking of lysosomal enzymes → accumulation of multiple substrates	Facial dysmorphia, growth retardation, angular limb deformities, epiphyseal dysplasia, vertebral fusion (no corneal opacity)	Similar to MPS (I/VI/VII)	No corneal opacity = distinguishing feature.
GM1 gangliosidosis	Cats, calves, sheep, dogs (Shiba Inu, Portuguese Water Dog, Alaskan Husky, Beagle, Springer Spaniel)	**β-galactosidase deficiency** (sheep also α-neuraminidase)	Autosomal recessive	Accumulation of gangliosides	- Alaskan Husky & Springer Spaniel: proportional dwarfism.- Springer: coarse facial features (frontal bossing, wide eyes).- Dogs: irregular intervertebral spaces; abnormal femoral heads, DJD.	Retarded vertebral endochondral ossification (Husky, possibly nutritional confound).	Skeletal lesions not universal (Beagle: neurovisceral only).Key: dwarfism + coarse face in some dogs.
Congenital erythropoietic porphyria	Cattle (Hereford, Holstein, Ayrshire, Shorthorn, Jamaica Red/Black), Cats, Duroc pigs	**Uroporphyrinogen III cosynthetase (UROS) deficiency**	Autosomal recessive	Accumulation of type I porphyrins (uroporphyrin I, coproporphyrin I)	- Red-brown teeth and bones, urine red/brown (darkens in sun).- Photodynamic dermatitis.- Hemolytic anemia.	Porphyrins in mineralized tissues (bright red-pink fluorescence under UV).	Classic: **teeth, bones, urine fluoresce pink under UV**.In cats: also acute intermittent porphyria (HMBS mutation, dominant, no photosensitivity, normal UROS).
Congenital erythropoietic protoporphyria	Cattle (Limousin)	**Ferrochelatase deficiency**	Autosomal recessive	Accumulation of protoporphyrin	Photosensitivity but **no bone/teeth discoloration**	–	Distinguish from UROS deficiency.
Acquired porphyria	Lambs (Australia), Deer (NZ)	Toxic-induced block in heme synthesis (suspect **chlorinated hydrocarbons**,	–	Porphyrins accumulate during active mineralization	- Pink bone cortices (not teeth).- Fluorescent under UV.- Affects	Porphyrins extracted from bone (coproporphyrin,	Key: **teeth not affected** (contrast with congenital).Environmental contamination possible.

		1,2,4-trichlorobenzene from lindane metabolism)			actively mineralizing areas (outer cortex).	protoporphyrin).	

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