Table 26-2 Diseases of the Skeleton with Identified Genetic Defects

Disorder	Gene Symbol	Affected Molecule	Clinical Phenotype
Defects in transcription factors producing abnormalities in mesenchymal condensation and related cell differentiation			
Brachydactyly types D and E	*HOXD13*	Transcription factor	Short, broad terminal phalanges of first digits
Camptomelic dysplasia	*SOX9*	Transcription factor	Sex reversal, abnormal skeletal development
Cleidocranial dysplasia	*RUNX2*	Transcription factor	Abnormal clavicles, Wormian bones, supernumerary teeth
Holt-Oram syndrome	*TBX5*	Transcription factor	Congenital abnormalities, forelimb anomalies
Nail-patella syndrome	*LMX1B*	Transcription factor	Hypoplastic nails, hypoplastic or aplastic patellas, dislocated radial head, progressive nephropathy
Waardenburg syndrome types 1 and 3	*PAX3*	Transcription factor	Hearing loss, abnormal pigmentation, craniofacial abnormalities
Defects in hormones and signal transduction proteins producing abnormal proliferation or maturation of osteoblasts, osteoclasts or chondrocytes			
Achondroplasia	*FGFR3*	Receptor	Short stature, rhizomelic shortening of limbs, frontal bossing, midface deficiency
Hypochondroplasia	*FGFR3*	Receptor	Disproportionately short stature, micromelia, relative macrocephaly
Osteopetrosis, autosomal dominant	*LRP5*	Receptor	Increased bone density, hearing loss, skeletal fragility
Osteopetrosis, infantile form	*RANKL*	Receptor ligand	Increased bone density
Osteoporosis-pseudoglioma syndrome	*LRP5*	Receptor	Congenital or infant-onset loss of vision, skeletal fragility
Thanatophoric dysplasia	*FGFR3*	Receptor	Severe limb shortening and bowing, frontal bossing, depressed nasal bridge
Defects in extracellular structural proteins			
Achondrogenesis type 2	*COL2A1*	Type II collagen	Short trunk
Metaphyseal dysplasia, Schmid type	*COL10A1*	Type X collagen	Mildly short stature
Osteogenesis imperfecta types 1-4	*COL1A1, COL1A2*	Type I collagen	Bone fragility
Defects in metabolic enzymes and transporters			
Osteopetrosis with renal tubular acidosis	*CA2*	Carbonic anhydrase	Increased bone density, fragility, renal tubular acidosis
Osteopetrosis, late onset type 2	*CLCN7*	Chloride channel	Increased bone density, fragility

Modified from Mundlos S, Olsen BR: Heritable diseases of the skeleton. Part I: Molecular insights into skeletal development—transcription factors and signaling pathways. FASEB J 11:125-132, 1997; Mundlos S, Olsen BR: Heritable diseases of the skeleton. Part II: Molecular insights into skeletal development—matrix components and their homeostasis. FASEB J 11:227-233, 1997; Superti-Furga A, et al.: Molecular-pathogenetic classification of genetic disorders of the skeleton. Am J Med Genet 106:262-293, 2001; Krakow D, Rimoin DL: The skeletal dysplasias. Genet Med 2010:12(6):327-341.

descriptions to one that also includes recently identified genetic defects. Table 26-2 lists some of the better characterized developmental abnormalities based on the nature of the genetic defect. The relationships between genes and phenotypes illustrate that various point mutations in a single gene (e.g., *COL2A1*) can result in different phenotypes while mutations in diverse genes (e.g., *LRP5, RANKL*) can give rise to similar clinical phenotypes.

Defects in Nuclear Proteins and Transcription Factors

Defects in nuclear proteins and transcription factors, especially homeobox proteins, cause disorganized mesenchymal condensation and abnormal differentiation of osteoblasts and chondrocytes. These defects manifest as abnormally developed bones.

- *Brachydactyly types D and E,* caused by mutation in the homeobox *HOXD13* gene, produces shortening of the terminal phalanges of the thumb and big toe.
- Loss-of-function mutations in the *RUNX2* gene result in *cleidocranial dysplasia*, an autosomal dominant disorder characterized by patent fontanelles, delayed closure of cranial sutures, Wormian bones (extra bones that occur within a cranial suture), delayed eruption of secondary teeth, primitive clavicles, and short height.

Defects in Hormones and Signal Transduction Proteins

Achondroplasia is the most common skeletal dysplasia and a major cause of dwarfism. It is an autosomal dominant disorder resulting in retarded cartilage growth. Affected individuals have shortened proximal extremities, a trunk of relatively normal length, and an enlarged head with bulging forehead and conspicuous depression of the root of the nose. The skeletal abnormalities are usually not associated with changes in longevity, intelligence, or reproductive status. It is caused by gain-of-function mutations in the FGF receptor 3 (FGFR3). Normally, FGF-mediated activation of FGFR3 inhibits endochondral growth. Constitutive activation of FGFR3 exaggerates this effect, suppressing growth. Approximately 90% of cases stem from new mutations, almost all of which occur in the paternal allele.

Thanatophoric dysplasia is the most common lethal form of dwarfism, affecting about 1 in every 20,000 live births. Affected individuals have micromelic shortening of the limbs, frontal bossing, relative macrocephaly, a small chest cavity, and a bell-shaped abdomen. The underdeveloped thoracic cavity leads to respiratory insufficiency, and these individuals frequently die at birth or soon after. The histologic changes in the growth plate show diminished proliferation of chondrocytes and disorganization