Practical Approach to Radiologic Diagnosis of Bone Dysplasias: Bone Dysplasia Family

Gen Nishimura

Department of Radiology, Dokkyo University School of Medicine, Tochigi, Japan

Abstract "Bone dysplasia family" refers to a group of disorders which share qualitatively similar skeletal alterations and a conceivably common pathogenesis. This concept was first described by Spranger, and has provided a practical guide for the differential diagnosis of bone dysplasias. This idea has since become a pilotage for molecular investigation on this field; for instance, the discovery of heterozygous mutations of the FGFR3 gene in achondroplasia led to the elucidation of other heterozygous mutations of the FGFR3 gene in thanatophoric dysplasia and hypochondroplasia, which had been classed as allelic disorders in the "achondroplasia family" solely based on clinical and radiologic grounds. Understanding the bone dysplasia family concept can facilitate further nosologic and molecular investigations in this molecular era, which will ultimately provide information beneficial to the management of affected individuals. Common "bone dysplasia families" are outlined here, particularly from the radiological standpoint. The importance of phenotype-genotype correlation is discussed by exemplifying the radiologic findings in achondroplastic individuals with uncommon mutations of the FGFR3 gene and radiologic variabilities in a severe form of type II collagenopathy.

Key words: bone dysplasia, achondroplasia, type II collagenopathy

Introduction

Bone dysplasia encompasses a heterogeneous group of genetic diseases with generalized impairment of osteocartilaginous growth, which manifests as commonly disproportionate, but occasionally proportionate, short stature associated with a multiplicity of meso-ecto-endodermal aberrations, such as macrocephaly in achondroplasia and vitreoretinal degeneration in type II collagenopathies. The number of individuals affected with bone dysplasias is sizeable, but the rarity of each disorder renders most physicians unfamiliar with this category, which tends toward inadequate diagnosis and management.

The concept of "bone dysplasia families" recently described by Spranger (1) assists in overcoming the difficulty in diagnosing bone dysplasias. Spranger found key radiologic findings in the phenotypic chaos of bone dysplasias and grouped together the disorders that qualitatively shared similar radiologic patterns into a "family", and it was thought that the disorders in a family may be pathogenetically related. The family concept was therefore presumed to provide not only a simple aid for the differential diagnosis but also pilotage for basic investigation of bone dysplasias. Recent discoveries of molecular defects in several
bone dysplasias have since proven the validity of the family concept for both purposes (2). For example, a variety of heterozyous mutations in the fibroblast growth factor receptor 3 (FGFR3) gene have been discovered in the “achondroplasia family”, including achondroplasia, thanatophoric dysplasia, and hypochondroplasia, which were once thought to be allelic disorders solely on morphological grounds.

The radiologic patterns of common “bone dysplasia families” are described here to provide a practical guide for the diagnosis of bone dysplasias, particularly emphasizing the radiologic pattern of the “achondroplasia family” which represents most common micromelic dwarfism. The radiologic findings in achondroplastic individuals with uncommon mutations of the FGFR3 gene are also described to emphasize the importance of the phenotype-genotype correlation in this field. The radiologic variabilities in a severe form of type II collagenopathy are also addressed to exemplify the need for molecular investigation.

**Family of Achondroplasia**

As cited, the achondroplasia family comprises three allelic disorders: achondroplasia, thanatophoric dysplasia, and hypochondroplasia. Thanatophoric dysplasia is further subdivided into type I, bent bone type, and type II, straight bone type. Recently, heterozygous mutations in the FGFR3 gene have been elucidated in the achondroplasia family (3). Of interest is the fact that this group of disorders possess common mutations of the FGFR3 gene, resulting in a single amino acid substitution from glycine to arginine at codon 380 (Gly380Arg) in the transmembrane domain of the FGFR3 gene in achondroplasia, a substitution from lysine to glutamine at codon 650 (Lys650Glu) in the intracellular tyrosine kinase 2 domain in thanatophoric dysplasia type II, and a substitution from asparate to lysine at codon 540 (Asp540Lys) in the intracellular tyrosine kinase 1 domain in approximately two thirds of hypochondroplastic individuals. Although thanatophoric dysplasia type I exhibits a variety of mutations of the FGFR3 gene, there is evidence of hot spots in the extracellular domain or transmembrane domain. These molecular features are consistent with less phenotypic variations in achondroplasia, thanatophoric dysplasia and a subgroup of hypochondroplasia.

Despite the proposal of “gain of function” in mutant FGFR3 genes, a “reduced rate” of enchondral ossification can account for most skeletal alterations in the achondroplasia family, and the greater the rate of growth, the more severe the affliction of a bone. Intramembranous ossification is currently considered normal in the achondroplasia family; nevertheless there are findings showing that intramembranous ossification or development of other mesenchymal tissues may be exaggerated in this group of disorders, as exemplified by perichondrial fibrous proliferation in thanatophoric dysplasia and the presence of primary macrocephaly in achondroplasia. Whichever is proven, relative preservation of intramembranous ossification is attributed to modification of the skeleton in the achondroplasia family.

Enchondral ossification and intramembranous ossification play different roles in osteocartilaginous development: enchondral ossification is involved in the longitudinal growth of the growth plate and its equivalents, and development of the skull base, whereas intramembranous ossification is related to circumferential metaphyseal growth at the perichondrium, circumferential diaphyseal growth at the cortices, and development of the calvaria and mandible. Awareness of these characteristics of enchondral and membranous ossification facilitates understanding the radiologic findings in the achondroplasia family. For example, the combination of impaired longitudinal growth at the growth plate with relative exaggeration of circumferential intramembranous ossification at the perichondrium causes meta-
physeal cupping that is one of the cardinal radiologic findings in the achondroplasia family.

Since achondroplasia is representative of the achondroplasia family, the radiologic features are detailed (Fig. 1A). The tubular bones are stubby, particularly in the proximal segments of the long bones, along with metaphyseal cupping. Concavity of the proximal femora and tibial tuberosities is reminiscent of metaphyseal cupping and gives rise to characteristic radiolucent bands at these regions, which serve as diagnostic hallmarks particularly in achondroplastic infants. Relative elongation of the fibulae due to unknown etiology causes varus deformity of the ankle, which occasionally requires surgical intervention. Short ribs lead to a narrow thorax, but respiratory problems and/or propensity for upper respiratory infections are not common features in achondroplasia. Normal or exaggerated development of the calvaria along with macrocephaly leads to a large head with frontal bossing. Prognathism is related to normal growth of the mandible. Hypoplasia of the skull base produces a narrow foramen magnum which impinges on the medulla oblongata or upper cervical spinal cord, and consequently may cause apnea and quadriplegia. The facial bones primarily develop as a result of intramembranous ossification but are considerably influenced by the growth of the skull base; thus mid-face hypoplasia is an obligatory feature in achondroplasia. Impairment of enchondral growth of the spine at the endplates of the vertebral bodies and neurocentral synchondroses results in decreased height of the vertebral bodies (platyspondyly) and a narrow spinal canal, respectively. Platyspondyly is apparent, though mild, in infancy, but it becomes less conspicuous with age, because posterior scalloping of the vertebral bodies develops as a result of the narrow spinal canal, finally evolving into "tall vertebrae" in childhood. The interpediculate distance of the lumbar spine is caudally increased in normal individuals, but this is reversed in achondroplastic individuals. Caudal narrowing of the interpediculate distance is understandable because the growth rate of the lower lumbar spine is much greater than that of the upper lumbar spine. Spinal canal stenosis creates cauda equina syndrome in achondroplastic older children and adults. Enchondral ossification at the iliac crests and triradiate cartilages provides cranial and caudal growth of the

A

B

Fig. 1 A: Radiograph of the pelvis in achondroplasia; B: Radiograph of the pelvis in thanatophoric dysplasia type I. Notice qualitative similarities in skeletal alterations in both entities, including short and square ilia, short greater sciatic notch, horizontal acetabulum and radiolucency of the proximal femora, but these findings are much more severe in thanatophoric dysplasia.
iliac bones, respectively. Underdevelopment of the iliac crests gives rise to short and square iliac wings, which manifests as the characteristic "elephant ear appearance of the ilia". Impaired caudal growth of the ilia leads to shortening of the greater sciatic notch and horizontal acetabular roofs. Relatively exaggerated intramembranous ossification around the triradiate cartilages causes triradiate spurs of the acetabulae (trident pelvis).

The radiologic findings in thanatophoric dysplasia are qualitatively the same as, but quantitatively more severe than, those in achondroplasia (Fig. 1B). Shortening of the tubular bones in thanatophoric dysplasia is much greater than that in achondroplasia. On the other hand, metaphyseal cupping of the long bones and radiolucencies of the proximal femora and tibial tuberosities in thanatophoric dysplasia are identical to those in achondroplasia. Hypoplasia of the ilia in thanatophoric dysplasia is similar to, but more severe than, in achondroplasia. Unlike achondroplasia, platyspondyly is extremely severe in thanatophoric dysplasia, which presents an H or inverted U appearance of the spine on frontal radiography. Thanatophoric dysplasia is subdivided into type I and II, which exhibit different mutations of the FGFR3 gene as cited above. Thanatophoric dysplasia type I is characterized by the bowing of the long bones. Bent femora manifests as the "French telephone receiver" in appearance. Thanatophoric dysplasia type II shows straight long bones and much milder platyspondyly than in type I. Cloverleaf deformity of the skull associated with dysgenesis of the temporal lobe is an essential syndromic constituent in thanatophoric dysplasia, and is generally more conspicuous in thanatophoric dysplasia type II.

Although hypochondroplastic individuals are occasionally as short as achondroplastic individuals, they show very subtle radiologic findings, including caudal narrowing of the interpediculate distance of the lumbar spine, mild hypoplasia of the ilia, and mild shortening of the proximal femora. The distal ulnae are hypoplastic with elongation of the ulnar styloid process. In some affected individuals, diagnosis does not benefit from anything but interpediculate distance narrowing of the lumbar spine, and the measurement of interpediculate distance contributes to the final diagnostic decision in questionable cases. Since mutation of the FGFR3 gene is uncovered in only 2/3 of hypochondroplastic individuals, there must be genetic heterogeneity in hypochondroplasia. Further investigation of the genotype-phenotype correlation in hypochondroplasia is therefore necessary to elucidate an accurate prognosis for hypochondroplastic individuals.

We recently encountered two achondroplastic individuals without the common Gly380Arg mutation of the FGFR3 gene: one patient had a Gly375Cys mutation instead of the common mutation (4), and the other had neither a Gly380Arg nor a Gly375Cys mutation (5). Of interest is the fact that these patients had atypical radiologic findings: metaphyseal dysplasia unusual for achondroplasia was found in the former patient, and the radiologic findings in the latter patient were overall milder than those in typical achondroplasia but significantly more severe than those in hypochondroplasia. Moreover, facial abnormalities were very subtle in both patients, and joint pain was conspicuous in the former patient. Further experience is necessary to determine whether uncommon mutations of the FGFR3 gene causes clinically significant phenotypic differences from common mutations.

Type II Collagenopathies

Type II collagenopathies represent a continuous clinical spectrum of disorders caused by heterogeneous mutations of type II collagen gene (COL2A1), which are phenotypically subdivided into two groups: the SEDC family (spondyloepiphyseal dysplasia congenita family), and
Kniest-Stickler dysplasia family. The spectrum of the SEDC family ranges through obligatorily stillborn achondrogenesis type II, perinatally lethal hypochondrogenesis, semilethal severe type of SEDC, nonlethal typical SEDC and mild precocious familial osteoarthropathy. The spectrum of the Kniest-Stickler dysplasia family encompasses lethal dyssegmental dysplasia, severe Kniest dysplasia and mild Stickler dysplasia (6). Molecular investigation of type II collagenopathies has not been completed, but the tentative results are as follows: the SEDC family tends to occur as a result of point mutations giving rise to a single amino acid substitution for glycine of triple helical domain of type II procollagen; Kniest dysplasia has a tendency toward exon-skipping mutations clustered around the amino terminal end; thus point mutation and exon skipping cause different kinds of dominant negative effects and consequently different phenotypes; by contrast, Stickler dysplasia is the result of a stop codon near the amino terminal end, leading to null allele (reduced synthesis of structurally normal type II collagen); Stickler dysplasia is genetically heterogeneous, because half of the affected families are not linked to COL2A1, and mutations in COL11A2 has been discovered in atypical Stickler dysplasia (7). Since type II collagen is a major constituent not only in the cartilaginous matrix but also in the vitreous body, type II collagenopathies have severe myopia and vitreoretinal degeneration in addition to impaired enchondral ossification. Severe midface hypoplasia occurs as a sequel of an unknown mechanism, particularly in the Kniest-Stickler dysplasia family.

The skeletal changes in the SEDC family are summarized as delayed enchondral ossification of the primary and secondary ossification centers. Delayed ossification of the primary ossification centers, which predominates in the vertebrae and pelvic bones, varies among disorders ranging from ovoid-shaped or pear-shaped vertebral bodies, delayed ossification of the pubic bones, and mild hypoplasia of the ilia in SEDC to total absence of the vertebral body, absence of the pubic and ischial bones, and concavity of the inferior and medial margins of the ilia in achondrogenesis type II (Fig. 2A, B, C). Severe undermineralization of the cervical spine, along with an ossification defect behind the foramen magnum, serves as a diagnostic sign predictive of a poor prognosis. Retarded ossification of the tubular bones presents as a concave metaphysis in achondrogenesis type II, whereas it manifests only as shortness of the tubular bones in SEDC. Hypochondrogenesis exhibits phenotypes intermediate between SEDC and achondrogenesis type II and radiologically falls somewhere between SEDC and achondrogenesis type II. Delayed ossification of the secondary ossification center (retarded epiphyseal ossification) is most conspicuous at the juxatruncal epiphyses. The femoral heads are not ossified until late childhood in SEDC. In contrast, the short tubular bones are relatively normal, the reason for which remains unknown. Atlanto-axial subluxation with odontoid hypoplasia is a major complication in older children and adults with SEDC. SEDC associated with striking metaphyseal dysplasia is rarely encountered. In such cases, the disease is currently coined spondyloepimetaphyseal dysplasia type Strudwick.

The skeletal alteration in the Kniest-Stickler dysplasia family is attributable to “ballooning” of the cartilaginous matrices, which increases the transverse diameter of the skeleton, particularly of the epimetaphyses and their equivalents. Enchondral ossification of the primary and secondary ossification centers is retarded but this finding is less striking than that in the SEDC family. The major radiologic findings in Kniest dysplasia include dumbbell deformity of the tubular bones with megaepiphyses, broad pelvis, and moderate platyspondyly. Large and rectangular vertebral bodies in Kniest dysplasia contrasts with small and ovoid vertebral bodies in SEDC. Malsegmentation (multiple coronal
Fig. 2  A: Babygram in achondrogenesis type II; B: Babygram in spondyloepiphyseal dysplasia congenita or mild phenotype of hypochondrogenesis; C: Babygram in severe phenotype of hypochondrogenesis. Notice a continuous spectrum of skeletal abnormalities in these cases, presenting as delayed ossification of the primary and secondary ossification centers in variable degrees.

clefts) of the vertebral bodies at the thoracolumbar junction has been regarded as a hallmark in Kniest dysplasia, but a coronal cleft merely signifies retarded enchondral ossification of the vertebral bodies and is occasionally found in the SEDC family.

Severe malsegmentation of the spine (anisospondyly) along with bowing of the long bones indicates dyssegmental dysplasia, although other features resemble those in Kniest dysplasia. Otospondylomegaepiphyseal dysplasia denotes cases of skeletal alterations identical to those in severe Stickler dysplasia without ophthalmological abnormalities, some of which are responsible for homozygous mutations in type XI collagen gene (COL11A2) (7).

Unlike Kniest dysplasia and dyssegmental dysplasia, Stickler dysplasia generally exhibits very subtle skeletal changes, including mild clubbing of the metaphysis, slightly enlarged epiphysis, and mild epiphyseal dysplasia, but there are cases of intermediate phenotypes between Stickler dysplasia and Kniest dysplasia, which cause diagnostic difficulty. In such cases, the appearance of the femoral head contributes to the discrimination: the ossification of the femoral head is significantly retarded in Kniest dysplasia, but this is not the case even in a severe phenotype of Stickler dysplasia. It is important to be able to predict whether an infant with a severe phenotype of SEDC family (hypochondrogenesis and semilethal type of SEDC) will survive despite respiratory distress in early age. We reviewed 12 infants who were radiologically diagnosed as having hypochondrogenesis or severe type SEDC: conspicuousness of metaphyseal splaying, the presence of metaphyseal dysplasia, and relatively large vertebral bodies suggested longer survival, although the phenotypic overlap of our patients was so strik-
ing that it precluded the clear distinction between the lethal and nonlethal cases. Further investigation of the phenotype-genotype correlation in type II collagenopathies may provide data which will assist in predicting a prognosis.

Family of Pseudoachondroplasia
—Multiple Epiphyseal Dysplasia

This family consists of pseudoachondroplasia and multiple epiphyseal dysplasia type Fairbanks. This group of disorders is genetically heterogeneous: heterozygous mutations in the cartilage oligomeric matrix protein (COMP) gene cause either the pseudoachondroplasia phenotype or multiple epiphyseal dysplasia phenotype, and multiple epiphyseal dysplasia also results from mutations in type IX collagen gene (COL9A2) (8, 9).

This family radiologically refers to a form of "spondylo-epi-metaphysial dysplasia". The major radiologic features in pseudoachondroplasia include mild platyspondyly with biconvex vertebral bodies, severe epimetaphyseal dysplasia and marked brachydactyly. The modification of the vertebral bodies normalizes with age. Epiphyseal dysplasia and brachydactyly in multiple epiphyseal dysplasia are equivalent to those in pseudoachondroplasia, but metaphyseal dysplasia and shortness of the long bones are less conspicuous in multiple epiphyseal dysplasia. In contrast to current opinion, modification of the vertebral bodies and even overt platyspondyly are essential features in some cases of multiple epiphyseal dysplasia, which results in diagnostic confusion. We had a case of multiple epiphyseal dysplasia in which platyspondyly was conspicuous in early childhood and normalized in adolescence.

Family of Diastrophic Dysplasia

The diastrophic dysplasia family consists of achondrogenesis type IB (type Fraccaro), achondrogenesis type II (de la Chapelle dysplasia, McAllister dysplasia), and diastrophic dysplasia. The former two are perinatally lethal conditions, but the latter is a non-lethal disorder. Homozygous or compound heterozygous mutations in DTDST (diastrophic dysplasia sulfate transporter gene), which encodes a novel sulfate transporter, are responsible for this group of disorders (10). Mutant DTDST genes lead to deficiency of sulfated proteoglycans in the cartilaginous matrix, which causes the common pathological findings of the cartilage in the diastrophic dysplasia family: perichondrocytic collagenous rings and sparse cartilagenous matrices.

Achondrogenesis type IB and atelosteogenesis type II apparently share common radiologic abnormalities, including a markedly disorganized axial and appendicular skeleton as well as ossification defects in the vertebral bodies. These two lethal disorders are superficially dissimilar to diastrophic dysplasia, despite the histological similarities; nevertheless meticulous observation detects overlapping features, including malalignment of the cervical spine, tapering of the distal humeri, Madelung-like deformity of the forearm and severe disorganization of the short tubular bones. Hitchhiker thumb and cervical kyphosis, both of which are hallmarks of diastrophic dysplasia, are found in atelosteogenesis type II. Advanced carpal ossification is another hallmark in diastrophic dysplasia, as is in Desbuquois dysplasia and Larsen syndrome. The advanced carpal ossification may be due to the same mechanism as precocious ossification of the cartilaginous matrix pathologically proven in diastrophic dysplasia.

Family of Metaphyseal Dysplasia
(Chondrodysplasia)

Metaphyseal dysplasia refers to a genetically and phenotypically heterogeneous group of disorders in which skeletal alterations are basi-
cally confined to the metaphyses. The most common metaphyseal dysplasia, type Schmid, is related to heterozygous mutations in type X collagen gene (COL10A2) (11). Type X collagen is exclusively expressed at the chondroosseous junction and its synthesis ceases with the closure of the growth plate, which accounts for metaphyseal modification and its subsidence with age in this entity. The presence of coxa magna facilitates distinguishing Schmid type from other metaphyseal dysplasias.

Metaphyseal dysplasia type Jansen is the most severe form of metaphyseal dysplasia. A heterozygous mutation has been elucidated in the PTH-PTHrP receptor gene, which causes gain of function, but not haploinsufficiency or dominant negative effect (12). The skeletal changes in infancy resemble those in neonatal hyperparathyroidism, and later evolve into severe "rachitic" changes. The successful molecular investigation based on candidate gene approach in metaphyseal dysplasia type Jansen was provoked by the presence of hypercalcemia in this entity, along with the hyperparathyroidism-like skeletal alteration cited above.

Other common metaphyseal dysplasias include metaphyseal dysplasia type McKusick (cartilage-hair hypoplasia) and Schwachman syndrome. Cartilage-hair hypoplasia is a mild form of metaphyseal dysplasia inherited as an autosomal recessive trait. This entity represents a multi-system disorder which possesses not only skeletal alteration but also ectodermal dysplasia with immunodeficiency. The causative gene has been mapped to 9p13 but has not yet been cloned (13). Schwachman syndrome is another multi-system disorder with pancreatic exocrine insufficiency and cyclic neutropenia inherited as an autosomal recessive trait. Skeletal changes vary among the patients, ranging from mild metaphyseal dysplasia to severe skeletal alteration resembling that in asphyxiating thoracic dysplasia.

Other Bone Dysplasia Families

Other common bone dysplasia families are the family of metatropic dysplasia, family of short rib dysplasia, family of OPD-Larsen dysplasia, family of chondrodysplasia punctata and type I collagenopathy (osteogenesis imperfecta). These families are briefly described here.

The metatropic dysplasia family includes metatropic dysplasia and spondylometaphyseal dysplasia type Kozlowski. Neither a causative gene nor a gene locus has been elucidated in this group. The skeletal changes in this family superficially resemble those in the Kniest-Stickler dysplasia family: metaphyseal splaying of the tubular bones is so striking that it creates dumbbell deformity; short and broad ilia manifest as halberd pelvis; elongated and severely flattened vertebral bodies present as "open staircase" vertebrae; and progressive kyphoscoliosis gives rise to a unique evolution of body proportion, changing from micromelia at birth to short trunk in childhood, particularly in metatropic dysplasia. Several lethal bone dysplasias, including Schneckenbecken dysplasia and fibrochondrogenesis, are also presumed to belong to this family.

The short rib dysplasia family comprises asphyxiating thoracic dysplasia, chondroectodermal dysplasia (Ellis van Creveld syndrome), and a group of short rib polydactyly dysplasias. This group of disorders is associated with a variety of visceral anomalies, for example, renal dysplasia in asphyxiating thoracic dysplasia and congenital heart disease in chondroectodermal dysplasia. The radiologic hallmarks consist of brachydactyly with cone-shaped epiphyses, acromesomelic shortening of the limbs, premature ossification of the proximal femoral epiphyses, and extremely short ribs leading to respiratory distress. The axial skeleton exhibits various findings, ranging from overt platyspondyly in short rib dysplasia Saldino-Noonan type to normal spine in short rib dysplasia Majewski type. Most disorders in
this family show trident pelvis, whereas the pelvis appears normal in short rib dysplasia Majewski type and Beemer type. Despite these variations, the disorders in this family share phenotypic overlap great enough to represent allelic disorders. The etiology remains unknown, but there have been several cases of short rib dysplasia with chromosomal aberration, which may allow positional cloning of this family.

The Larsen-OPD dysplasia family consists of Larsen syndrome, boomerang dysplasia, atelosteogenesis type I and III, otopalatodigital syndrome type I and II, frontometaphyseal dysplasia, and Melnick-Needles syndrome. This group of disorders is genetically heterogeneous. Most cases of Larsen syndrome are inherited as an autosomal dominant trait and the gene locus is mapped to 3p21.1-p14.1 (11). All individuals with boomerang dysplasia and atelosteogenesis type I and III reported to date have been sporadic cases, suggesting a dominant new mutation. The other disorders are inherited as an X-linked trait: otopalatodigital syndrome type I and II and frontometaphyseal dysplasia are transmitted as an X-linked recessive trait with partial manifestation in affected females, but Melnick-Needles syndrome as an X-linked dominant trait with male lethality. This group of disorders is clinically characterized by multiple joint abnormalities, including joint dislocations, joint contractures, club feet, and abnormalities in spinal curvature. Older children and adults affected with this group of disorders share common facial dysmorphism, including prominent supraorbital ridges, a broad nasal bridge, ocular hypertelorism and micrognathia. Undertubulation of the short tubular bones radiologically signifies this group of disorders. Stubby digits and toes are common features in this group, particularly in the lethal varieties, including boomerang dysplasia, atelosteogenesis type I and III, and otopalatodigital syndrome type II. But arachnodactyly is an essential feature in frontometaphyseal dysplasia, and occasionally occurs in Melnick-Needles syndrome. The long bones are bowed and undertubulated. Unlike sclerosing bone dysplasias, the undertubulation does not relate to impairment of bone modeling, but represents malformation of the cartilaginous anlage, because abnormal development of the growth plates reminiscent of delta phalanx is known in boomerang dysplasia. Advanced and/or supernumerary carpal ossification is another hallmark of this group of disorders, excepting the lethal varieties.

The chondrodysplasia punctata (CDP) family, characterized by epiphyseal and juxtaepiphyseal stippled calcifications, encompasses a heterogeneous group of disorders, including rhizomelic due to peroxisomal enzyme defects, X-linked recessive form (brachytelephalangic type) due to arylsulfatase E deficiency (12), X-linked dominant form mapped to Xq28 (11), and a large number of unclassified cases. Warfarin has been elucidated to impair arylsulfatase activity, which creates a phenocopy of CDP (Warfarin embryopathy).

A group of bone fragile syndromes have been termed osteogenesis imperfecta and currently subdivided into benign types I and IV, severe type III, and lethal type II. The affected individuals are almost exclusively, if not all, related to a mutation of type I collagen gene, so that osteogenesis imperfecta is currently called type I collagenopathy. The biochemical and molecular investigation on type I collagen has brought about a new understanding of bone dysplasias. For example, in contrast to the traditional concept, most cases of "osteogenesis imperfecta congenita" result from a dominant new mutation, and intrafamilial recurrence, ranging up to 7-8% in type IIb, has been clarified as being caused by germlinal mosaicism, which has also been discovered in other bone dysplasias.

Other Common Bone Dysplasias

Finally, a heterogeneous group of common bone dysplasias that do not constitute a family
but reflect a single disorder are addressed. These disorders includes spondyloepiphyseal dysplasia tarda, cleidocranial dysplasia, and campomelic dysplasia.

Spondyloepiphyseal dysplasia tarda is the most common, late-onset, short-trunked dwarfism inherited as an X-linked recessive trait. The causative gene is mapped to Xp22.2-p21.3 (11). Short stature generally ensues in late childhood, but occasionally becomes evident in early childhood. A posterior hump in the thoracolumbar spine, which represents an osseous mound in the posterior aspects of both superior and inferior endplates of the thoracolumbar spine, typifies this entity; nevertheless this finding does not develop until late childhood and only mild platyspondyly is found in early childhood.

Cleidocranial dysplasia is a disorder inherited as an autosomal dominant trait. The causative gene is mapped to 6p21, but genetic heterogeneity apparently exists (11). The radiologic features include large fontanelles, hypoplastic clavicles, and delayed ossification of the pubic symphysis. The epiphyses of the tubular bones appear round and large (megaepiphyses), particularly in the proximal femora and short tubular bones. Brachytelephalangy is another diagnostic feature. Generalized osteosclerosis is rarely evident.

Despite the traditional proposal of an autosomal recessive trait, campomelic dysplasia has been elucidated to be caused by heterogeneous mutations of the SOX9 gene, whose homology to SRY gene accounts for the presence of sex reversal in this disorder (13). In addition to bending of the long bones, a variety of features, including hypoplasia of the scapular wings, narrow ilia with vertically oriented pubii and ischiae, hypoplastic fibulae, and the absence of ossification of the talus, help to distinguish campomelic dysplasia from other bone dysplasias with bending bones, such as kypohemic dysplasia, Antley-Bixler syndrome and a severe form of Schwartz-Jampel syndrome.

In summary, bone dysplasia family concept that was postulated on clinical grounds eventually plays an important role in candidate gene approach to molecular investigations on a multiplicity of constitutional bone diseases. Even in this molecular era, the efforts of meticulous clinical observations and nosologic investigations should be a fundamental of fruitful researches that would be beneficial to the medical service for affected individuals and families.

References


