Bone dysplasia families
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Abstract
Bone dysplasia families is a concept introduced by Juergen Spranger to group bone dysplasias with similar skeletal abnormalities. The concept is based on the recognition of patterns in bone dysplasias, which allows diagnosticians to reach a final diagnosis through the recognition of patterns and more careful analysis. The families of bone dysplasias may be the result of similar pathogenetic mechanisms.

Introduction
Bone dysplasias encompass a large number of genetic disorders with constitutional skeletal alterations. At first glance, the heterogeneity of bone dysplasias may look like total chaos. However, the pattern recognition of bone dysplasias is not a difficult task. Awareness of several prototypic patterns allows us to reach a definitive diagnosis in most affected individuals. In the mid 80's, Professor Juergen Spranger (Mainz, Germany; Fig. 1) proposed the concept termed ‘bone dysplasia families’. He stated: 1) different bone dysplasias that manifest themselves in similar patterns of skeletal abnormalities are grouped in ‘a family’; 2) based on the knowledge of the patterns, diagnosticians are able to reach a final diagnosis through provisional recognition of a pattern and more careful analysis of the pattern; 3) families of bone dysplasias may be
proteins (filaminopathies). Further molecular investigations on the genotype-phenotype correlation of bone dysplasias have added a number of new bone dysplasia families, such as TRPV4 group, ciliopathy group, the group of abnormal proteoglycan synthesis, the group of mitochondrial dysfunction, etc. In this review, the author attempts to outline the pattern-oriented approach to bone dysplasias (bone dysplasia families), and comments on the current understanding of their pathogenesis.

Dysostosis multiplex

Dysostosis multiplex is a skeletal phenotype seen in lysosomal storage diseases that are caused by abnormal lysosomal storage of oligosaccharides or glycosaminoglycans (GAGs), such as dermatan sulfate, heparan sulfate, and chondroitin sulfate. Regardless of the type of accumulated GAG, GAG-associated lysosomal storage diseases show the same pattern of skeletal alterations. The radiological hallmarks of dysostosis multiplex include a large cranium, dolichocephaly, J-shaped sella, canoe paddle-like ribs, hook-shaped vertebral bodies with posterior scalloping, comma-shaped ilia, coxa valga, diaphyseal broadening and metaphyseal constriction of the long bones, metacarpal pointing, and

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**Fig. 1** Photograph of Professors Juergen Spranger, Kazimierz Kozlowski, David Sillence (left, center, and right) at retirement ceremony of Professor Kozlowski, 1995

They were pioneers in establishing the fundamentals of skeletal dysplasias. Professor Spranger proposed the concept of bone dysplasia family. Professor Kozlowski first identified a number of novel entities, such as spondylometaphyseal dysplasia Kozlowski, and Professor Sillence contributed to development of the clinical classification and medical management of osteogenesis imperfecta.

**Fig. 2** A, D, G: Hurler syndrome; B, E, H: Hunter syndrome; C, F, I: Morquio syndrome

The manifestation of dysostosis multiplex is most severe in Hurler syndrome and milder in Hunter. Morquio syndrome shows not only severe dysostosis multiplex but also platyspondyly and epiphyseal dysplasia of the proximal femoral epiphyses. Diaphyseal broadening of the short tubular bones is milder than that of Hurler syndrome.
bullet-shaped phalanges (Fig. 2). Dysostosis multiplex variably manifests among disorders, i.e., it is severe in Hurler syndrome, moderate in Hunter syndrome, and mild in Sanfilippo syndrome. Morquio syndrome type A is associated with spondylar dysplasia (platyspondyly) and epiphyseal dysplasia as well as the common features of dysostosis multiplex. The phenotypic differences between Morquio A and other disorders are attributable to deposition of different GAGs (keratan sulfate in Morquio syndrome type A, heparan sulfate in Sanfilippo syndrome, and dermanan sulfate plus heparan sulfate in Hurler and Hunter syndromes). The pathogenic mechanism of dysostosis multiplex remains elusive.

In terms of radiological observation, however, the underlying pathogenesis is likely to be exaggeration of modeling process, i.e., increased endosteal bone resorption in the diaphysis (and equivalents) and increased periosteal bone resorption in the metaphyses (and equivalents). As a result, the metaphyses are constricted, while the diaphyses are expanded. The pathogenic process accounts for several other features of dysostosis multiplex, such as comma-shaped ilia, canoe-paddle ribs, metacarpal pointing, and bullet phalanges. Hook-shaped vertebral bodies are attributed to increased bone resorption along the paraspinal ligaments. Dural thickening secondary to GAG deposition is responsible for J-shaped sella and posterior scalloping of the vertebral bodies. Dolichocephaly and rarely brachycephaly are the result of craniosynostosis.

**Achondroplasia family (FGFR3-opathy)**

This group of disorders comprises the most severe thanatophoric dysplasia (TD), the prototypic achondroplasia (ACH), and the milder hypochondroplasia (HCH) (Fig. 3). The pathogenetic mechanism is gain-of-function mutations in the FGFR3 (fibroblast growth factor receptor 3) gene. It is interesting that the FGFs/FGFR3 signaling pathway is a positive regulator for fibroblast proliferation, but it is a negative regulator for chondrocyte proliferation. Increased FGFs/FGFR3 signaling impairs endochondral bone growth, and gives rise to hypoplasia of the skeletal segments that grow via endochondral ossification. In the fetal skeleton, endochondral bone growth occurs in the cancellous part of bone and skull base, while intramembranous bone growth progresses in the cortex of bone and calvarium. In the postnatal skeleton, endochondral bone growth occurs exclusively in the growth plate and its equivalents as well as epiphyses (secondary ossification centers). Endochondral bone formation of the growth plate plays a pivotal role in longitudi-
nal growth of the postnatal skeleton, while chondrocyte apposition from the perichondrial mesenchymal ring of the growth plate and diaphyseal intramembranous ossification contribute to transverse growth of the postnatal skeleton. Impairment of endochondral longitudinal growth due to increased FGFs/FGFr3 signaling is most conspicuous at the central part of the growth plate, while the signal aberration does not interfere with perichondrial transverse growth. The phenotypic consequence of the pathogenic process is metaphyseal cupping with metaphyseal corner spur (Fig. 4). Disturbance of endochondral growth at the iliac wing and triradiate cartilage creates stunted ilia, short greater sciatic notches, and horizontal acetabula. Central concavities and marginal spur of the triradi-
ate cartilage manifest as an appearance of trident pelvis. These skeletal alterations are more or less seen in TD, ACH, and HCH. Impaired growth of the skull base leads to narrowing of the foramen magnum (stenosis at the craniovertebral junction) that may be associated with apnea, sudden quadriplegia, and even sudden death in achondroplastic infants.

**Spondyloepiphyseal dysplasia congenita (SEDC) family (type 2 collagenopathy)**

Type 2 collagen is a homotrimer of type 2 procollegen alpha chains, which is a major component of the cartilage matrix. Mutations of COL2A1 (the gene encoding type 2 procollagen) create a heterogeneous group of skeletal dysplasias (type 2 collagenopathies). Missense mutations (and intragenic derangements) that do not undergo mRNA degradation cause a group of SEDC, ranging from the most severe achondrogenesis type 2 (ACG2) through the intermediate hypochondrogenesis (HCG) to the prototypic SEDC (Fig. 5). The pathogenesis of type 2 collagenopathies is complicated. Mutant procollagen chains not only disturb the property of the cartilage matrix, but also induce apoptosis of chondrocytes via their retention in the endoplasmic reticulum (ER stress). The phenotypic consequence is delayed endochondral ossification particularly prominent in the juxtatruncal bones. ACG2 shows very severe underossification and even absence of ossification of the vertebral bodies, ischia, and pubes. Delayed ossification of the tubular bones manifests as metaphyseal cupping. On the other hand, SEDC manifests with much milder retardation of juxtatruncal endochondral ossification. The radiological hallmarks of SEDC include moderate platyspondyly with pear-shaped vertebral bodies, delayed pubic ossification, and delayed epiphyseal ossification particularly in the proximal femoral epiphyses (Fig. 6). The short tubular bones are normal in length. Odontoid hypoplasia with atlantoaxial instability is an ominous association. The phenotype of HCG falls into the intermediate between ACG2 and SEDC. Type 2 collagen is a major component of the vitreous body and inner ear as well as the cartilage matrix. Thus, vitreoretinal degeneration and hearing impairment are common associations of type 2 collagenopathies.

**Stickler/Kniest dysplasia family, type 11 collagenopathy, perlecanopathy**

Haploinsufficiency (degradation of mutant mRNA) and exon skipping mutations (exon 12-24) of COL2A1 cause Stickler dysplasia type 1 and Kni-
The pathogenesis of these subsets of type 2 collagenopathies is more likely to be related to abnormal cartilage matrices than exaggerated apoptosis of chondrocytes. The major phenotypic consequence is increased transverse diameter of the growth plate, which gives rise to distinctive dumbbell deformity of the long bones (Fig. 7). As with SEDC group, retardation of enchondral ossification leads to spondylar dysplasia. Kniest dysplasia shows moderate platyspondyly with broad vertebral bodies, sometimes associated with coronal clefts of the vertebral bodies. Stickler dysplasia type 1 may show normal vertebral bodies or only mild spondylar changes.

Type 11 collagen is a heterotrimer that is composed of two kinds of type 11 procollagen alpha chains and a type 2 procollagen alpha chain. The skeletal phenotypes of disorders with COL11A1 or COL11A2 mutations (type 11 collagenopathies) resemble those of Stickler dysplasia type 1 or Kniest dysplasia, and they are variously termed Stickler dysplasia type 2, Stickler dysplasia type 3, oto-spondylo-megaepiphyseal dysplasia, and fibrochondrogenesis, according to the severity of the skeletal changes and extraskeletal manifestations. For example, Stickler dysplasia type 3 due to COL11A2 mutations is not associated with visual disability but with severe hearing impairment, while Stickler dysplasia type 2 due to COL11A1 mutations is accompanied by mild visual disability and severe hearing impairment. Meanwhile, Stickler dysplasia type 1 due to COL2A1 haploinsufficiency shows severe visual impairment and mild hearing impairment.

Schwartz-Jampel syndrome and dyssegmental dysplasia are caused by mutations in the HSPG2 gene encoding heparan sulfate proteoglycan 2, also known as perlecan. They are collectively termed...
perlecanopathies. Perlecan is a major proteoglycan of the basement membrane, which binds to various basement membrane proteins. Due to a yet unknown pathogenesis, the skeletal phenotypes of perlecanopathies are similar to those of type 2 and type 11 collagenopathies.

**Metatropic dysplasia group (TRPV4-pathy)**

*TRPV4* mutations are responsible for a group of disorders, including the prototype metatropic dysplasia, the intermediate spondylometataphyseal dysplasia (SMD) Kozlowski type, and the milder autosomal dominant brachyolmia (AD-BO). *TRPV4* encodes a calcium-permeable ion channel that acts as a mechanical sensor. Abnormal response to mechanical loading is deemed to cause hyperplasia of the epiphyseal cartilage and growth plates. By contrast, longitudinal endochondral growth is severely impaired. The radiological hallmarks of metatropic dysplasia include severe dumbbell deformity of the long bones, severe platyspondyly with increased width of the vertebral bodies, and broad ilia with concavity of the supraacetabular region termed halberd pelvis (Fig. 8). SMD Kozlowski type shows severe spondylar dysplasia identical with that of metatropic dysplasia, but does not have dumbbell deformity and instead does have conspicuous metaphyseal dysplasia (irregular ossification of the metaphyses) of the proximal femora. Spondylar dysplasia is much milder in AD-BO. *TRPV4* mutations also cause a spectrum of neuromuscular diseases that may occur alone or in combination with TRPV4-related skeletal dysplasias. Subclinical neuromuscular disorders may be responsible for progressive kyphoscoliosis that is commonly seen in metatropic dysplasia and SMD Kozlowski.

**Multiple epiphyseal dysplasia group**

Mutations in the genes encoding minor components in the cartilage matrix are responsible for a group of multiple epiphyseal dysplasia (MED). The best example is a group of disorders due to *COMP* mutations. The most severe phenotype termed pseudoachondroplasia manifests not only with epiphyseal dysplasia (delayed, irregular epiphyseal ossification), but also spondylar and metaphyseal dysplasia (Fig. 9). The milder phenotype was previously termed MED Fairbank type. The mildest end can be a familial osteoarthropathy. Other MEDs are caused by abnormalities of type 9 collagen and matrillin 3.

**Skeletal ciliopathy**

Recently, it has been known that a number of skeletal disorders are related to abnormalities of the primary cilia. The heterogeneous group of disorders is collectively named skeletal ciliopathies. The best examples are asphyxiating thoracic dysplasia (Jeune syndrome) and chondroectodermal dysplasia (Ellis-van Creveld syndrome). The skeletal hallmarks are thoracic hypoplasia with severely short ribs, absence of spondylar dysplasia, trident pelvis, disharmonic premature ossification of the proximal femoral and proximal humeral epiphyses, and severe brachydactyly with cone-shaped epiphyses (Fig. 10). Jeune syndrome may show mild metaphyseal dysplasia particularly in the proximal femora. Polydactyly is common in Ellis-van Creveld syndrome, while it is uncommon in Jeune syndrome. Congenital heart disease is an essential syndromic component of Ellis-van Creveld syndrome, while nephronophthisis is common in Jeune syndrome. The severer phenotypes are termed short rib polydactyly syndromes, which are heterogeneous in phenotypes, absolutely lethal, and may be associated with mild spondylar dysplasia and severe metaphyseal dysplasia. The phenotypic variations of skeletal ciliopathies are so diverse that they are not necessarily monogenic but digenic or even oligogenic in pathogeneses.
A, B, E: metatropic dysplasia; C, D, F: spondylometaphyseal dysplasia (SMD) Kozlowski type

Both disorders show severe platyspondyly with wide vertebral bodies. Metatropic dysplasia shows severe dumbbell deformity of the long bones, while SMD Kozlowski type exhibits metaphyseal dysplasia of the proximal femora.

A, D, G, J: pseudoachondroplasia; B, E, H, K: severe case with multiple epiphyseal dysplasia; C, F, I, L: mild case with multiple epiphyseal dysplasia

The three disorders show epi-metaphyseal dysplasias in variable severities. Pseudoachondroplasia is associated with spondylar dysplasia.
A, C: asphyxiating thoracic dysplasia; B, D: Ellis-van Creveld syndrome
Both disorders share thoracic hypoplasia, trident pelvis, and severe brachydactyly. Ellis-van Creveld syndrome is associated with polydactyly.

Fig. 10  

Scheme of proteoglycan synthesis (courtesy of Dr. Luisa Bonafe, Lausanne)
The complicated system comprises transport of UDP-sugar from the cytoplasm to endoplasmic reticulum (SLC35D1), disassembly of UDP-sugar with UDP recycling system (CANT1, etc.), transfer of sugar to core protein (B3GALT6, etc.), elongation of sugar chains (CHSY1), sulfation of sugars (CHST3), and sulfate transport system with recycling of PAP (DTDST and gPAPP).
A group of disorders due to abnormal synthesis of proteoglycans

Recently, a number of skeletal dysplasias that are related to abnormal synthesis of proteoglycans have been discovered. This group of disorders is characterized by congenital disarticulation (joint contracture/joint laxity) as well as generalized skeletal changes. Aggrecan is a major proteoglycan in the cartilage matrix. The complex process of proteoglycan synthesis comprises transport of UDP-sugar from the cytoplasm to endoplasmic reticulum, disassembly of UDP-sugar with UDP recycling system, transfer of sugar to core protein, elongation of sugar chains, sulfation of sugar, and sulfate transport system with recycling of PAP (Fig. 11). The prototype of this group is diastrophic dysplasia and allied disorders—atelosteogenesis type 2 (AO2) and achondrogenesis type 1B (ACB1B), which are caused by the defect of a sulfate transporter termed DTDST. The large joints show congenital contracture. However, laxity of the first carpometacarpal joint presents as distinctive hitchhiker thumbs. The major skeletal features include cervical kyphosis, distal tapering of the humerus, metaphyseal broadening, and abnormal patterning of the short tubular bones, such as proximal symphalangism, ovoid first metacarpal, and accelerated carpal ossification. In severe phenotypes, the distal femora are hypoplastic and ossification of the short tubular bones is severely disorganized (Fig. 12). Other subsets of abnormal proteoglycan synthesis include Desbu-
Desbuquois dysplasia and autosomal recessive Larsen syndrome. The former is attributed to impairment of UDP recycling as a result of CANT1 mutations, while the latter to abnormal sulfation as a result of CHST3 mutations. Both disorders, unlike diastrophic dysplasia, show dislocation of the large joints. However, the skeletal phenotype, including cervical kyphosis, distal tapering of the humerus, and abnormal patterning of the short tubular bones, overlaps with that of diastrophic dysplasia (Fig. 13). Coronal clefts of the thoracolumbar spine are commonly seen in Desbuquois dysplasia and autosomal recessive Larsen syndrome. A monkey wrench appearance of the proximal femora due to broadening of the femoral neck and prominence of the lesser trochanter is distinctive in Desbuquois dysplasia. GPAPP-related osteochondrodysplasia as a result of abnormal recycling of PAP is radiologically similar to Desbuquois dysplasia.

Filaminopathy

Filamins A, B, and C are cystoskeletal proteins that mediate interaction between actin-cytoskeleton and extracellular matrix-based transmembrane signaling complex (integrins, transmembrane receptor complexes, and second messengers). Mutations of FLNA and FLNB result in a group of skeletal dysplasias collectively termed filaminopathies; yet, it remains elusive how filamins regulate development of the bone and joint. There is striking phenotypic overlap between filaminopathy A (otopalatodigital syndrome type 1, otopalatodigital syndrome 2, frontometaphyseal dysplasia, and Melnick-Needles syndrome) and filaminopathy B (autosomal dominant Larsen syndrome, atelosteogenesis type 1, atelosteogenesis type 3, and boomerang dysplasia), such as modeling failure of the long bones and abnormal pattern formation of the short tubular bones (Fig. 14). These features overlap with those of a group of proteoglycan-related disorders as well (Fig. 15).
Skeletal dysplasias related to mitochondrial dysfunction

Recently, disorders that are caused by mutations in mitochondrial-related genes have attracted special attention. They include CODAS syndrome (LONP1 gene), EVEN-PLUS syndrome (HSPA9 gene), CAGSSS syndrome (IARS2 gene), and X-linked spondyloepimeta physeal dysplasia with mental retardation (AIFM1 gene). These disorders share common skeletal features, such as coronal clefts of the vertebral bodies and severe epiphyseal dysplasia, and show developmental delay (Fig. 16).

Summary

The author reviewed the clinical, radiological, and molecular aspects of several bone dysplasia families, but was not able to address other important groups of skeletal dysplasias, including the groups of metaphyseal dysplasias, acro-mesorhizomelic dysplasias, sclerosing bone dysplasias, and osteolysis syndromes. The reader should refer to more comprehensive review articles and textbooks. The diagnosis of skeletal dysplasias has been regarded as just diagnostic curiosities because of lack of medial intervention. However, advancements in understanding of the pathogenic mechanisms of skeletal dysplasias have recently geared therapeutic trials. Thus, accurate diagnosis is increasingly important.
These disorders share coronal clefts and severe epiphyseal dysplasia.

References