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A Genetic Approach to the Diagnosis of Skeletal Dysplasia

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The skeletal dysplasias are a large and heterogeneous group of disorders. Currently, there are more than 100 recognized forms of skeletal dysplasia, which makes arriving at a specific diagnosis difficult. This process is additionally complicated by the rarity of the individual conditions. The establishment of a precise diagnosis is important for numerous reasons, including prediction of adult height, accurate recurrence risk, prenatal diagnosis in future pregnancies, and most importantly, for proper clinical treatment. When a child is referred for genetic evaluation of suspected skeletal dysplasia, clinical and radiographic indicators, and more specific biochemical and molecular tests, are used to try to arrive at the underlying diagnosis. Preferably, the clinical features and pattern of radiographic abnormalities are used to generate a differential diagnosis so that the appropriate confirmatory tests can be done. The current author will review this sequence of diagnostic steps. For geneticists, this process starts with history gathering including the prenatal and family history. This is followed by clinical examination with measurements and radiographs. Only once a limited differential diagnosis has been established, should molecular investigations be considered.

Glossary

COL9A1, COL9A2, COL9A3 = Type IX collagen is a heterotrimeric protein composed of one chain each of $\alpha1(1\times)$, $\alpha2(1\times)$, and $\alpha3(1\times)$. These three polypeptides are in turn encoded by three separate genes: COL9A1, COL9A2, and COL9A3.

COMP = The cartilage oligomeric matrix protein is a homopentameric structural protein and it is a part of the extracellular matrix of cartilage. The protein is encoded by the COMP gene.

DTDST = The DTDST gene codes for the diastrophic dysplasia sulphate transporter which is necessary for the sulfation of proteoglycans in the cartilage matrix.

FGFR3 = The fibroblast growth factor receptor 3 is a tyrosine kinase receptor that binds growth factors. Mutations in the FGFR3 gene that cause increased activation result in the FGFR3 family of skeletal dysplasias, which includes hypochondroplasia, achondroplasia, and thanatophoric dysplasia.

MATN3 = The matrilin-3 protein, which forms part of the extracellular matrix of cartilage, is encoded by the MATN3 gene.

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The original classification of skeletal dysplasias was simple but grossly inaccurate. Patients were categorized as either short-trunked (Morquio syndrome) or short-limbed (achondroplasia).[23] As the field expanded more than 200 different dysplasias were described and

this gave rise to an unwieldy and complicated nomenclature.[9,10,22] The advent of molecular testing has allowed the grouping of some dysplasias into families and a small trimming of numbers. For example, the Type II collagenopathies range from the perinatal lethal form (Achondrogenesis Type II) to precocious osteoarthritis.[1,13,26,30] This also was the first group of skeletal dysplasias for which the underlying genetic defect was found.[15] It was hoped that the molecular elucidation would lead to a far smaller number of skeletal dysplasias and a much easier clinical classification. Although grouping into molecularly related families has somewhat simplified the classification, there still remain a large number of skeletal dysplasias without a known genetic basis. The nomenclature continues to undergo revisions as new molecular genetic information becomes available.[21]

The spectrum of skeletal dysplasias ranges from the perinatal lethal to individuals with normal stature and survival but early onset osteoarthrosis.[10] The patients most likely to present to an orthopaedic surgeon are those who present in childhood with short stature. It sometimes is unclear whether the cause of growth failure is systemic or skeletal. Renal, endocrine, and cardiac abnormalities might need to be ruled out. However, patients with these conditions will present with proportionate short stature whereas the dysplasias most often cause disproportionate short stature. Also, some genetic syndromes cause primordial growth failure but should be easily distinguishable on the basis of associated features such as developmental delay, dysmorphic facies, and if necessary features seen on radiographs.[11]

History

When presented with a child with disproportionate short stature, a focused history can give invaluable clues as to the differential diagnosis. In genetics, this begins with prenatal history and includes birth length. Patients with some skeletal dysplasias, for example achondroplasia, present with short stature at birth[7] whereas others, such as those with pseudoachondroplasia have a normal birth length with subsequent failure of linear growth.[18] Increasingly, skeletal dysplasias, even the nonlethal varieties, are being detected on prenatal ultrasound and it is worthwhile to inquire whether any ultrasounds were done during pregnancy and whether any discrepancy was observed between fetal size and gestational dates.[8] Although the age at which growth failure is observed has some variability, it tends to be fairly constant and can be used in developing a differential diagnosis.

A family history also should be taken. Obviously, if there is another family member with a skeletal dysplasia, this will be important in assessing mode of inheritance. It also is important to note parental heights if considering that the child simply might have familial short stature.

Inquiry should be made for findings related to the skeletal system. Some of these are obvious, such as joint pain and scoliosis. Patients with some skeletal dysplasias present with multiple congenital joint dislocations, for example atelosteogenesis Type III.[25] Other findings that the family might have noticed include ligamentous laxity or conversely progressive finger contractures. Sometimes findings unrelated to the skeletal system can be most helpful in making the diagnosis, for instance, abnormal hair and susceptibility to infections in cartilage-hair hypoplasia (McKusick metaphyseal dysplasia).[16,17] Unfortunately, these additional findings are by no means constant. Parents may not consider other manifestations relevant to the diagnosis and a history will not be offered unless specifically asked for.

Physical Examination

On physical examination, growth parameters are essential information. It is important to note not only the height of the child but also weight and head circumference. This sometimes can establish a pattern, for example in achondroplasia, the head circumference is greater than normal whereas height is reduced dramatically compared with normal.[29] Determining proportions is done by measurement of the lower seg-

ment. The lower segment measurement is subtracted from the total height to determine the upper segment and therefore the upper segment to lower segment ratio. This ratio and the arm span to height ratio are used to document which is more severely shortened: spine or limbs. When there is limb shortening, it is helpful to classify it as rhizomelic, mesomelic, or acromelic depending on which segment is most affected.

As in other genetic syndromes, ancillary signs can be helpful in securing the diagnosis and therefore a general physical examination also is recommended. These would include such findings as congenital heart disease, polydactyly and dystrophic nails (Fig 1) in chondroectodermal dysplasia (Ellis-vanCreveld syndrome).[6] One finding never is present in 100% of patients with a syndrome but if present, can be instructive. A good example of this is the cystic ear swellings seen in children with diastrophic dysplasia, which are fairly specific for this disorder.[24]

Imaging Studies

The next step is obtaining good quality skeletal radiographs. A skeletal survey is necessary for diagnosis, because normal findings in a specific region can be important in making the differential diagnosis. The dysplasias generally are classified by which parts of the skeleton are involved. The patterns may include any or all of the following: spondylo-, epiphyseal, metaphyseal, and diaphyseal dysplasia. This system helps to narrow the differential to a group of dysplasias.[23] Pseudoachondroplasia is a classic example of a spondyloepimetaphyseal dysplasia. In childhood, children with pseudoachondroplasia have anterior beaking of their lumbar vertebrae (Fig 2), small irregular epiphyses, and metaphyseal flaring (Figs 3, 4). This pattern of features is specific to pseudoachondroplasia and sufficient for making the diagnosis.[3,14] This dysplasia also shows that the radiographic features of a dysplasia are not static. The diagnosis of pseudoachondroplasia is much more difficult on radiographs of adults when the epiphyses have fused and

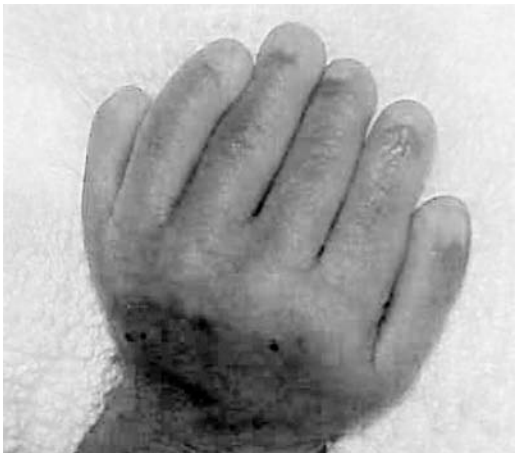

Fig 1. A photograph of the hand of a 1-month-old child with Ellis-vanCreveld syndrome shows polydactyly and dystrophic nails.

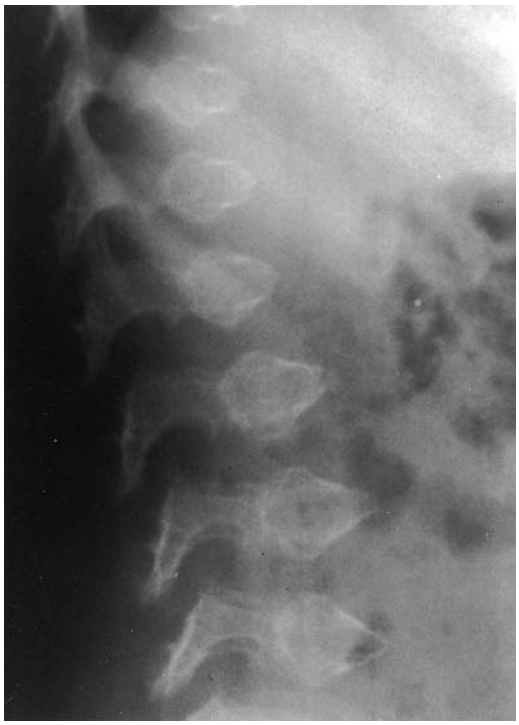

Fig 2. A radiograph of the lateral spine of a child with pseudoachondroplasia shows the platyspondyly with anterior beaking.

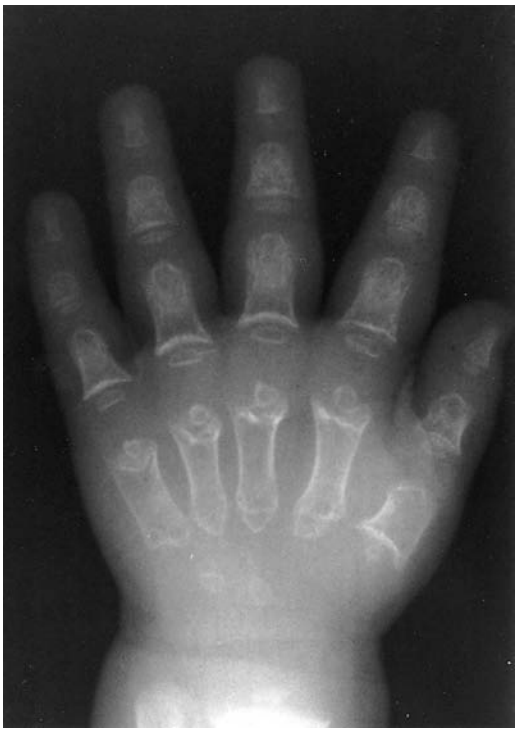

Fig 3. A radiograph of the hand of a child with pseudoachondroplasia shows the typical brachydactyly and the small irregularly etched carpal bones.

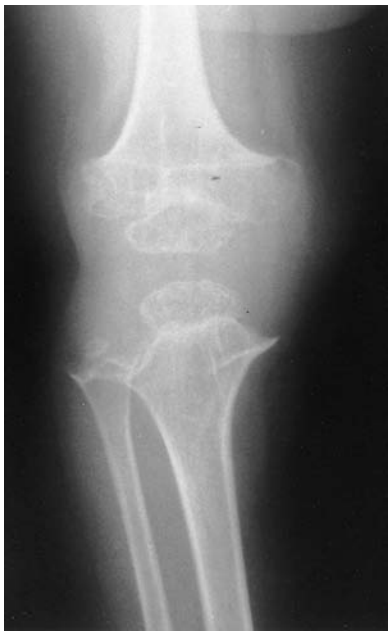

Fig 4. An anteroposterior radiograph of the knee of a child with pseudoachondroplasia shows metaphyseal flaring and small irregular epiphyses.

the anterior beaking of the vertebrae is replaced by nonspecific platyspondyly.

The most common form of skeletal dysplasia is achondroplasia. This is caused mutations in the FGFR3 gene. More than 80% of the time, it is caused by a new mutation and both parents are of average stature.[29] Although this diagnosis is most often made clinically on the basis of short limbs, increased head circumference, and midface hypoplasia, it should be confirmed on radiographs. The pattern of features is important but there is a key feature which is the narrowing of the interpediculate distance from L1 to L5[29] (Fig 5). This sign is not specific but is obligate to the diagnosis of achondroplasia.

In addition to the pattern of skeletal abnormalities, the region affected can be used to narrow the differential diagnosis. In the Type II collagenopathies, the pattern is of a spondyloepiphyseal dysplasia and there is relative sparing of the distal segments. This is seen in the radiograph of a child with spondyloepiphyseal dysplasia congenita (a Type II collagenopathy) which shows delayed epiphyseal ossification at the wrist and a large hand compared with the humerus (Fig 6). It is the pattern that is key to the diagnosis because there are few radiographic features that are specific. One notable exception is the finding of iliac horns (Fig 7) in nail-patella syndrome that essentially is pathognomonic.[12]

Molecular Diagnosis

The determination of a specific molecular diagnosis within one phenotypic entity can have clinical implications. Multiple epiphyseal dysplasia is one of the milder and more common dysplasias and probably the most genetically heterogeneous. It is caused by mutations in the COMP gene,[3] the genes for Type IX collagen

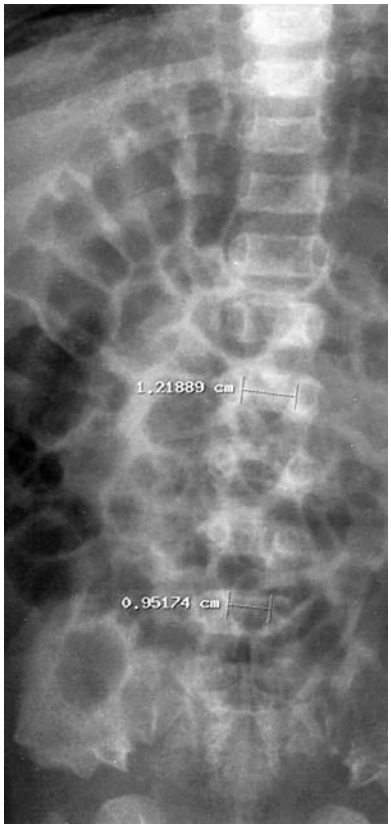

Fig 5. An anteroposterior radiograph of the lumbar spine of a child with achondroplasia is shown. The characteristic narrowing of the interpediculate distance from L1 to L5 (widening is the normal pattern) can be seen. The small rounded iliac wings and narrow sacrosciatic notches also typical of achondroplasia can be seen.

(COL9A1, COL9A2, COL9A3),[2,5,19,20] the MATN3 gene,[4] the DTDST gene,[27] and other as yet unidentified genes. In multiple epiphyseal dysplasia caused by COMP mutations, the hips are the most severely affected joints whereas in patients with COL9A2 or COL9A3 mutations, the knees are the most severely affected joints.[28] It also is important to distinguish the diastrophic dysplasia sulfate transporter form of multiple epiphyseal dysplasia because this is inherited in a recessive manner and therefore the recurrence risk for the parents is 25%.[24,27] The other forms are dominant

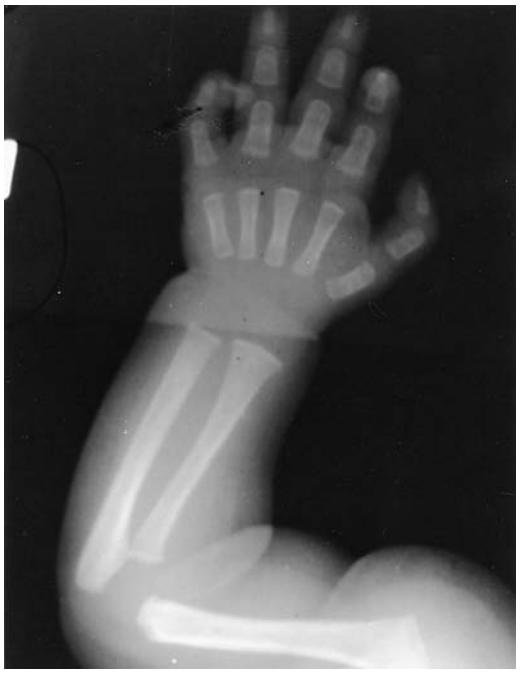

Fig 6. A radiograph of the arm of a child with spondyloepiphyseal dysplasia congenita shows the relative sparing of hand size compared with rhizomelia and mesomelia. The delay in epiphyseal ossification typical of spondyloepiphyseal dysplasia congenita and the other Type II collagenopathies also can be seen.

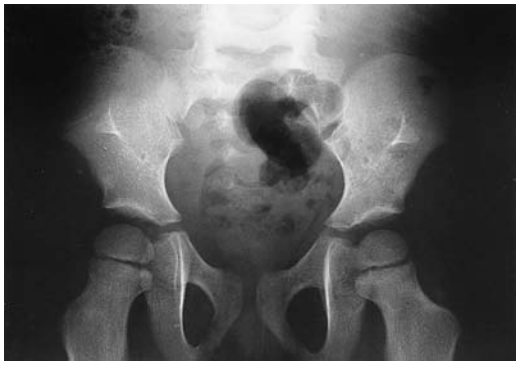

Fig 7. This radiograph of the pelvis of a 3.5-year-old girl with nail-patella syndrome shows the iliac horns characteristic of this dysplasia.

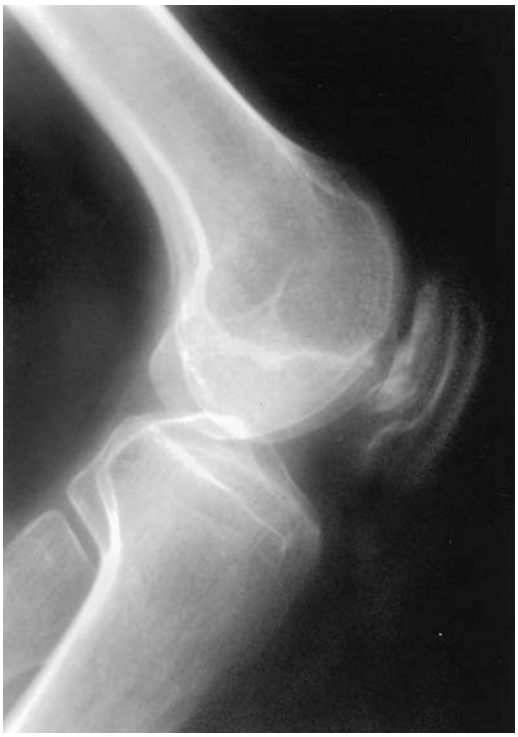

Fig 8. This is a lateral radiograph of the knee in a patient with multiple epiphyseal dysplasia (recessive form). The double layer patella is easily visible.

and have a negligible recurrence risk for the parents and a 50% recurrence risk for the affected child. The finding of a double layer patella on a lateral radiograph of the knee is suggestive of a diastrophic dysplasia sulfate transporter defect[27] (Fig 8).

The diagnosis of skeletal dysplasias is not difficult but remains complicated. It demands a familiarity with numerous rare conditions and good pattern recognition skills. The sequence of steps in this article provides a framework for establishing a differential diagnosis but consultation with an expert in the field of skeletal dysplasia remains a valuable tool.

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