Skeletal Dysplasias

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KEYWORDS

• Osteochondrodysplasias • Skeletal dysplasias • Nonassortive mating
• Achondroplasia • Type II collagenopathies • Osteogenesis imperfecta

KEY POINTS

- Approximately 5% of children with congenital birth defects have skeletal dysplasias.
- Lethality usually results from small chest, pulmonary hypoplasia, and respiratory compromise.
- Diagnosis is made based on clinical and radiographic findings, including molecular diagnosis when possible.
- Nonlethal skeletal dysplasias are associated with short stature, but overall affected individuals are cognitively normal and have a good quality of life.

The skeletal dysplasias or osteochondrodysplasias are a heritable group of more than 450 well-delineated disorders that affect primarily bone and cartilage, but also can have significant effects on muscle, tendons, and ligaments.[1] By definition, skeletal dysplasias are heritable diseases that have generalized abnormalities in cartilage and bone, whereas dysostoses are genetic disorders characterized by abnormalities in a single or group of bones.[2] Over time, the distinction between these disorders has become blurred, as the field has recognized that there is radiographic, clinical, and molecular overlap. Recent advances in genetic technologies have identified the molecular basis in more than 350 of these disorders, providing us with the opportunity to translate research findings into clinical service. Understanding the genes that

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produce these disorders allows us to delineate the extent of spectrum of disease associated with a particular disorder, provides diagnostic service for families at risk for recurrence based on mode of inheritance, as well as furthering our understanding of pathways involved in the development and maintenance of the skeleton.

EMBRYOLOGY

The skeleton forms under 2 distinct processes; endochondral and membranous ossification. Endochondral ossification is responsible for the formation of most of the mammalian appendicular skeleton and it involves a sequence of carefully orchestrated developmental processes. These include embryonic limb bud initiation and its outgrowth from lateral plate mesoderm, specification of mesenchymal cells for the future limb elements, mesenchymal condensations triggering cartilage differentiation, ossification of developing bones, and, finally, their proper growth and maturation in the postnatal period.[3,4] Membraneous ossification is the developmental event in which condensing mesenchymal cells progress almost directly to bone cells. The bones of the skull, lateral clavicle, and pubis form via mesenchymal ossification. Postnatally, growth continues through the cartilage growth plate in which resting chondrocytes proliferate, undergo hypertrophy, then apoptosis, becoming the growing scaffold of bone.[5] Multiple molecular mechanisms (genes) underlie skeleton formation and perturbations to these highly orchestrated processes can lead to skeletal dysplasias.[6]

GENETICS

Best Practices

Determine the diagnosis either through clinical, radiographic, and molecular testing to determine the mode of inheritance and recurrence risk.

Be aware of nonassortive mating in the short-stature community and that outcomes for children with compound heterozygosity for autosomal disorders can be guarded and variable.

The skeletal dysplasias are inherited in an autosomal-recessive, autosomal-dominant, X-linked recessive, X-linked dominant, and Y-linked manner.[1] Appreciation of the mode of inheritance is important because it imparts information to families regarding future recurrences. Family history, including parental and familial heights and growth patterns, should be obtained from the parents of any affected child to determine if there are similarly affected siblings, or other family members, which can lead to a diagnosis or establish the mode of inheritance. There are several X-linked skeletal disorders that recur in male family members and carrier females are either unaffected or only mildly affected (eg, X-linked spondyloepiphyseal tarda).[7] **Table 1** lists some of these more commonly seen disorders seen in the neonatal period with their respective inheritance pattern. The Nosology and Classification of Genetic Skeletal Disorders[1] and Online Mendelian Inheritance in Man (OMIM:www.omim.org/) are sources that include information on these disorders and include data on their patterns of inheritance. There are some uncommonly seen patterns of inheritance in the skeletal dysplasias. These include somatic mosaicism, in which one of the parents is mildly affected and their offspring is more severely affected.[8] Evaluation of the parents should be considered if there is any question that one of the parents could have a mild skeletal disorder. Gonadal mosaicism is characterized by familial recurrence of