

Genetic Heterogeneity in Multiple Epiphyseal Dysplasia

Multiple epiphyseal dysplasia (MED) is an autosomal dominant chondrodysplasia characterized by mild to moderate shortness of the limbs, waddling gait, genu valgum, and early onset osteoarthritis. Two autosomal dominant types have been described: the severe Fairbank type and the milder Ribbing type. Although previously it was suspected that variability occurred within the same disorder, ie, allelic disorders, linkage analysis has shown that there are at least 2 forms: Fairbank-type MED maps to chromosome 19, which may be allelic with pseudoachondroplasia; Ribbing-type MED maps to chromosome 1 near the locus for the alpha 2 chain of type IX collagen (COL9A2). These have been designated EDM1 and EDM2, respectively.

The current report describes 2 intriguing families with clinically similar findings in certain respects and dissimilar findings in others—particularly stature and mode of inheritance.

In family 1, the proband (a 5-year-old female) and 2 siblings (an 8-year-old sister and a 12-year-old brother) presented for genetic evaluation because of painful hips and waddling gait. The heights of these children were not short (35th through 70th percentiles). None were disproportionate since the arm spans approximated the heights. Radiographic findings for all 3 subjects showed typical features of Fairbank-type MED, as the epiphyses were small, irregular, and flat, especially at the knees. The femoral necks were short and broad and the capital femoral epiphyses were small and round. The bones of the hand were normal, but with delayed ossification of the distal ulnar epiphyses and carpal bones. An autosomal dominant inheritance pattern was unequivocal. The authors demonstrated that this family had Fairbank-type MED, with linkage to chromosome 19. All affected individuals had heights within ± 2 standard deviations (SD).

The 43-year-old white female proband in family 2 was evaluated because of short stature, which was disproportionate in type, and joint pain. The proband was < 2 SD in height, and the arm span was short for the length (length = 151.cm; span =

143.5 cm). Two siblings had joint pain and short stature. The parents had no symptoms of MED and were not short. A recessive inheritance or possibly autosomal dominant inheritance with germline mosaicism was responsible. No abnormalities associated with chromosome 19 or with the cartilage-specific candidate collagen genes (COL) were demonstrable. COL9A2 has recently been reported to be linked in one family with autosomal dominant MED.

In summary, the authors confirm that autosomal dominant Fairbank-type MED maps to chromosome 19. However, they also studied another large MED family in which linkage to the chromosome 19 locus was excluded. They further excluded linkage of MED in this family to the chromosome 1 (EDM2) locus using markers for COL9A2. Thus, at least 1 additional genetic locus remains to be identified for conditions having the clinical and radiographic criteria of MED.

Deere M, et al. *Am J Hum Genet* 1995;56:698-704.

Editor's comment: *With the recent identification of genes and mutations associated with multiple chondrodysplasias and similar disorders, a trend seems to be emerging. Disorders with similar clinical phenotypes involving genes that encode extracellular matrix proteins exhibit considerable genetic heterogeneity. Mutations tend to occur in different genes and at different sites within the same gene. This is not a new observation. Disorders manifesting spondyloepiphyseal dysplasia and MED phenotypes are good examples.*

In contrast, disorders due to mutations of growth factor receptors, such as fibroblast growth factor receptors, exhibit much less heterogeneity. Mutations tend to cluster in relatively few sites, as in achondroplasia, where almost all patients have the same mutation. Time will tell if these impressions are correct.

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