

Identification of the Molecular Defect in a Family With Spondyloepiphyseal Dysplasia

The problem of gene defects is of intense interest to geneticists and molecular biologists. The spondyloepiphyseal dysplasias (SED) are a heterogeneous group of inherited disorders characterized by disproportionately short stature and pleiotropic involvement of the skeletal and ocular systems. Recent investigations suggest an association between some forms of SED and a defect in type II collagen. In this study coarse scanning by Southern blot hybridization of the *COL2A1* gene, which encodes type II collagen, identified an abnormal restriction pattern in the DNA of one of the affected members of a relatively large family with SED. Analysis of selected genomic fragments localized the molecular defect, all affected family members carried the same heterozygous single-exon deletion.

The proband was a 3.5-year-old girl, apparently normal at birth, who had a history of ear infections, slowed growth, and genu valgum. She was short and had lordosis, mild kyphosis, and rhizomelic shortening of the extremities. Epiphyseal centers were affected with no metaphyseal involvement. The father,

four paternal aunts, and two nieces had kyphoscoliosis, retinal detachment, myopia, genu valgum, cervical instability, and dwarfism. Analysis of the proband's DNA yielded a novel 3.3-kb *EcoRI* fragment that was not seen in the control samples. This segment of *COL2A1* contains exons 45 to 52, which code for the C-terminal propeptide and the last 123 amino acid residues of the triple-helical domain. Amplification of *COL2A1* exons 47 to 52 from genomic DNA of unaffected family members produced a single 3.2-kb fragment. Analogous amplifications of DNA from affected family members produced the normal 3.2-kb fragment and a deleted 2.8-kb fragment. This finding established the segregation of the deleted *COL2A1* allele with the abnormal SED phenotype. The deletion accounts for the elimination of the whole of exon 48, including 36 amino acids of the type II triple-helical domain. The authors conclude that the *COL2A1* deletion is responsible for this type of dwarfism.

Lee B, Vissing H, Ramirez F, et al. *Science* 1989;244:978.

Editor's comment—*Chondrodysplasias are a highly heterogeneous group of disorders that includes endochondral ossifica-*

tion and simple abnormal skeletal growth. These entities are believed to result from mutations affecting either the structural integrity of cartilage matrix components or the regulatory pathways of chondrogenesis. COL2A1 has been linked to the Stickler syndrome by genetic analysis, and, as noted by the authors, biochemical analysis of small cartilage samples from chondrodysplastic individuals has recently suggested that some of these conditions, such as the spondyloepiphyseal dysplasias, Kniest dysplasia, and type II achondrogenesis-hypochondrogenesis, may be associated with type II collagen defects. The association seems to be confirmed for this particular family with SED.

Fibroblasts from patients with osteogenesis imperfecta have a type I collagen defect, and defects in type III collagen have been demonstrated in patients with Ehlers-Danlos syndrome. In these disorders, structural mutations in the type I and type III collagen subunits are believed to decrease the rate of helical assembly and expose greater regions of unassembled chains to overmodification. The location of a defect within the helical domain may affect directly the degree of collagen modification.

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