Multiple epiphyseal dysplasia: radiographic abnormalities correlated with genotype

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S. L. Unger · D. L. Rimoin ·
R. S. Lachman (✉) · D. H. Cohn
Ahmanson Department of Pediatrics,
Steven Spielberg Pediatric Research
Center, SSB-3,
Cedars-Sinai Research Institute,
8700 Beverly Blvd., Los Angeles,
CA 90048, USA
M. D. Briggs · P. Holden
Wellcome Trust Centre for Cell-Matrix
Research, School of Biological Sciences,
University of Manchester, Manchester,
England
B. Zabel
Children’s Hospital, University of Mainz,
Mainz, Germany
L. Ala-Kokko · P. Paassilta · J. Lohiniva
Collagen Research Unit,
Biocenter and Department of Medical
Biochemistry, University of Oulu, Oulu,
Finland
D. L. Rimoin · R. S. Lachman · D. H. Cohn
Department of Pediatrics, UCLA School
of Medicine, Los Angeles, California, USA
R. S. Lachman
Department of Radiology, UCLA School
of Medicine, Los Angeles, California, USA
D. H. Cohn
Department of Human Genetics, UCLA
School of Medicine, Los Angeles,
California, USA

Abstract Multiple epiphyseal dysplasia (MED) is an osteochondrodysplasia characterized clinically by mild short stature and early-onset degenerative joint disease and radiographically by epiphyseal hypoplasia/dysplasia. MED is genetically heterogeneous, with autosomal dominant cases resulting from mutations in at least three genes: the cartilage oligomeric matrix protein (COMP) gene (EDM1) and the COL9A2 (EDM2) and COL9A3 (EDM3) genes of type IX procollagen. We present here a comparison of the radiographic phenotypes of MED patients with type IX collagen gene mutations and those with COMP gene mutations. We reviewed radiographs from two patients with MED produced by COMP mutations, two families with COL9A2 mutations, and one family with a mutation in COL9A3. The data demonstrated that the patients with type IX collagen defects had more severe joint involvement at the knees and relative hip sparing, while the patients with COMP mutations had significant involvement at the capital femoral epiphyses and irregular acetabuli. This pattern of joint involvement was consistent regardless of overall degree of severity of the phenotype.
Introduction

Multiple epiphyseal dysplasia (MED) is a relatively mild osteochondrodysplasia phenotype. Most forms are inherited in an autosomal dominant manner [1], but at least one recessive form has been documented [2]. The most common symptoms are mild short stature and joint pain, which can be associated with joint stiffness. The joints most commonly affected are the large weight-bearing joints of the lower limbs. Patients may exhibit a waddling gait and genu varum/valgum deformity. In many patients, the secondary degenerative changes in the joints are severe enough to necessitate joint replacement in young adulthood. MED was formerly divided into two broad groups: Fairbank type (severe) and Ribbing type (mild), but it is now clear that MED represents a continuous spectrum of severity [3-6].

Dominatedly inherited forms of MED have been shown to result from mutations in the cartilage oligomeric matrix protein gene (COMP) and the *COL9A2* and *COL9A3* genes of type IX procollagen. COMP is a homopentameric glycoprotein predominantly expressed in cartilage but also found in tendon and ligament. COMP is a modular protein composed of a cysteine-rich amino-terminal domain, four epidermal growth-factorlike repeats, eight calmodulinlike (calcium binding) repeats, and a globular carboxyl terminal domain. Most COMP mutations have been localized to the calmodulinlike domains, with the remainder in the carboxyl terminal domain. Mutations in these regions of the molecule can also produce pseudoachondroplasia (PSACH), a more severe osteochondrodysplasia phenotype [5,7].

It has been suggested that COMP interacts with a variety of molecules in the extracellular matrix, including type IX collagen [8, 9]. Type IX collagen is a heterotrimERIC collagen primarily expressed in cartilage. Type IX collagen is located on the surface of cartilage collagen fibrils and is covalently cross-linked to type II collagen. It is composed of one chain each of the α1(IX), α2(IX), and α3(IX) collagen chains, which are each encoded by distinct genes (*COL9A1*, *COL9A2*, and *COL9A3*, respectively) on different chromosomes [10]. The type IX collagen molecule has three triple helical domains (*COL1,2,3*), which are separated by four non-collagenous domains (NC1,2,3,4). The MED families with documented *COL9A2* and *COL9A3* mutations all had exon skipping mutations, which caused a loss of exon three and a subsequent deletion of 12 amino acids in the COL3 domain, the most amino-terminal collagenous domain, of the protein product. To date, no mutations have been reported in *COL9A1*.

It has been observed that in families with MED due to type IX collagen abnormalities, there is early and severe degenerative joint disease and epiphyseal involvement at the knees with relative sparing of the hip joints [8, 11-14]. There has been speculation that this finding is sufficient to distinguish EDM2 and EDM3 from those with a COMP mutation (EDM1). In order to test this hypothesis, we reviewed radiographs and clinical information from families with a known molecular basis for their MED phenotype.

Materials and methods

We reviewed data on two patients with COMP mutations (patients A and B), two with *COL9A2* mutations (patients C and D), and one family with a *COL9A3* mutation (patient E). The mutations have been reported elsewhere [3, 5, 8, 13]. For the sake of clarity, the gene involved is listed in parentheses throughout the manuscript. Patient A (COMP) was the only affected member of his family. He came to medical attention at 13.5 years of age because of ankle pain. On physical examination his height was 142 cm (<5th %ile). His positive physical findings were crepitus in both ankles and decreased range of motion at the hips. Patient B (COMP) was noted to have a waddling gait at approximately 1 year of age. Her mother was similarly affected, as were her sister and a male half-sibling. The phenotype was remarkably consistent in all four individuals, with short stature, brachydactyly, and waddling gait. Patient B presented at 11 years of age with pain in her thighs and knees. Physical examination at 12.5 years of age revealed a height of 135 cm (<3rd %ile) along with brachydactyly and decreased range of motion at both elbows and the left hip. Patient C (*COL9A2*) was recognized as having MED because of a positive family history in his mother. He was late in walking and had an abnormal gait. Patient C had mild short stature and developed genu valgum that required surgical correction. Patient D (*COL9A2*) also had a positive family history of MED through his mother. His clinical features consisted of joint pain, particularly in both knees, and genu varum deformity. Patient D had average stature. Patient E (*COL9A3*) is part of a three-generation family with MED. The clinical phenotype among affected members was quite similar. Patient E first presented with joint stiffness and pain in his knees. He also had some pain in his elbows and ankles. On physical examination, he had normal stature, a waddling gait, and a genu varum deformity.

All radiographs of the MED patients were taken in late childhood/early adolescence (age range 10-16.5 years). For comparative purposes, radiographs of the knees, pelvis, and hands of a 6-year-old patient with typical PSACH due to the common deletion [4] and a lateral spine film of another patient with typical PSACH were included.

Results

Pelvis

AP films of the pelvis showing the capital femoral epiphyses were reviewed on all five probands. Radiographs of the two patients (A and B) with COMP mutations (Fig.1 b, c) are shown. Both patients had significant changes at the acetabuli and capital femoral epiphyses consisting of shallow irregular acetabular roofs and small, dysplastic appearing, capital femoral epiphyses. Patient B (COMP) had the most severe changes at the