Precocious Osteoarthritis in a Family with Recurrent COL2A1 Mutation

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ABSTRACT. ***Objective.*** To examine the genotypic and phenotypic characteristics of a Micronesian kindred with autosomal dominant precocious osteoarthritis (OA).

Methods. We reviewed records and radiographs of 3 index patients and their parents, administered questionnaires to 16 additional kindred members, performed whole-genome scans of 24 family members, and sequenced relevant genes from 16 family members.

Results. The kindred displayed early onset OA, enlarged epiphyses, platyspondyly, and brachydactyly with dysplastic findings consistent with mild spondyloepiphyseal dysplasia. Genetic analysis revealed an arginine to cysteine substitution at position 75 of the collagen 2A1 gene, a mutation that has been described in 4 other geographically distinct families. The major phenotypic differences among the families were in height (ranging from short to tall) and hearing loss noted in 3 of the 5 families.

Conclusion. The presence of the COL2A1 Arg75Cys mutation in 5 geographically distinct areas helps to confirm a potential mutational hotspot. The diverse phenotypic spectrum suggests that modifier genes and environmental factors play a role in the expression of this mutation. (J Rheumatol 2006;33:1133–6)

Key Indexing Terms:
COLLAGEN OSTEOARTHRITIS DYSPLASIA COL2A1

Spondyloepiphyseal dysplasia associated with the early destruction of weight-bearing joints has been reported[1]. It is characterized by considerable phenotypic and genetic heterogeneity. We identified a large Micronesian kindred presenting with severe precocious arthritis, and investigated the mutation causing the affliction.

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MATERIALS AND METHODS

All phases of this study were approved by institutional review boards for human studies. Chart and radiologic reviews were performed for 3 index patients and the affected parent. Sixteen family members completed clinical questionnaires and blood was obtained from 24 family members, including the 3 index patients. Whole-genome linkage analysis was done using over 400 microsatellite markers (available from: Australian Genome Research Facility, http://www.agrf.org.au/) and analyzed by Fastlink 3.0[2]. Exons 11 and 33 of the COL2A1 gene were amplified by polymerase chain reaction[3].

RESULTS

Clinical findings. The most common joints involved in the 19 affected family members were the hips and knees. Other sites included the spine, other large joints, and the small joints of the hands and feet. Osteoarthritis (OA) was observed as early as age 2.5 years. Eight patients had 25 orthopedic surgeries, primarily involving the hip and knee. Degeneration and fissuring of the articular surface were seen at surgery. Pathology revealed degenerated hyaline cartilage and hyperplastic synovial lining with focal mild chronic inflammation. Radiographic findings from 6 patients showed epiphyseal enlargement, widened intercondylar femoral notch, coxavalga with flattened acetabula, brachydactyly, and platyspondyly with anterior vertebral beaking. Illustrative radiographs of the hip and knee of a patient (Figure 1A, 1B) and father (Figure 1C, 1D) are shown.

Compared to United States norms, a mild decrease in height was noted, but no differences between affected and unaffected family members were found. Hearing loss in affected individuals was also reported.

Linkage and molecular analysis. The kindred exhibited a fully penetrant, autosomal dominant pattern of segregation of the

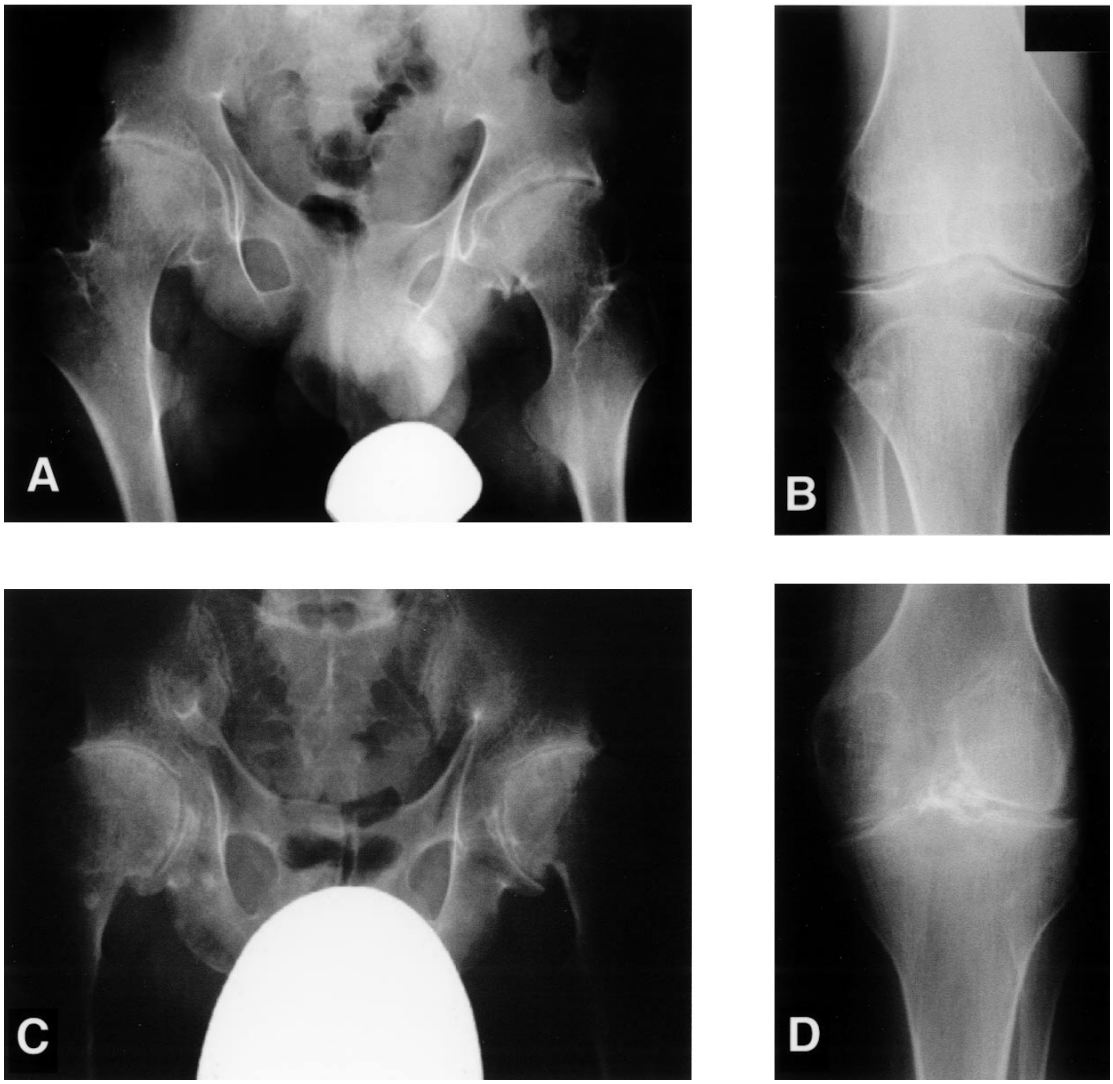

Figure 1. A. Anteroposterior (AP) radiographs of the hips of a representative patient reveal flattening of the femoral head and destructive changes. B. AP radiographs of the knee of a representative patient show flattening of the femoral condyles and destructive changes. C. AP radiographs of the hips of the patient's father, who had more advanced arthritic changes. D. AP radiographs of the knee of the patient's father, with more advanced changes.

OA phenotype (Figure 2). After whole-genome scanning, a single marker located 1.03 Mb from COL2A1 was linked to the phenotype (LOD = 4.04). Direct sequencing of COL2A1 exon 11 revealed heterozygosity for a C to T transition resulting in an R75C mutation. This mutation cosegregated with the OA phenotype in the family (Figure 2).

DISCUSSION

The R75C mutation in COL2A1 found in this Micronesian kindred with precocious, generalized OA and mild, late onset spondyloepiphyseal dysplasia is the fifth report of the R75C mutation[4-7]. The 5 families were found in distinct geographical regions (Chiloe Islands, France, Utah, Finland, and Micronesia) and likely represent 5 independent occurrences of the same mutation.

Phenotypic variability was noted in height and hearing loss. Our patients were the same height as their unaffected kindred members, whereas tall stature was noted in 3 of the 4 previously reported families[5-7], and the Chiloe kindred was specifically described as being short[4]. Hearing loss was reported in the Micronesian, French[6], and Finnish kindreds[7], whereas hearing loss was not reported in the Chiloe family.

Significant similarities of this Micronesian kindred to each of the previously described kindreds with the R75C mutation in COL2A1 include the onset of arthritis in the first or second decade of life with involvement of several large joints, small joints, and the spine. Brachydactyly and platyspondyly with endplate irregularities similar to Schmorl's nodes[4-7] are evident. Table 1 summarizes the clinical features of the 5 families with the R75C mutation.

Table 1. Comparison of 5 families with Arg 75 →Cys mutation in COL2A1.

Feature	Chiloe[4]	Utah[5]	France[6]	Finland[7]	Micronesia
Onset of OA	1st and 2nd decade	2nd decade	2nd decade	2nd decade	1st and 2nd decade
Stature	Short	Average or above average	Tall	Tall	Average
Moderate deafness	None	Not reported	Yes	Yes	Yes
Hips	Flexion contractures	Coxa vara, protrusio acetabulae, flattening of the femoral epiphysis	Enlarged epiphyses, osteochondromatosis; irregular, enlarged femoral heads	Intraarticular soft tissue calcification, periosteal calcification	Flat acetabulae, coxa valga
Knees	Fibrous ankylosis of knees	Periarticular calcification	Enlarged epiphyses with exuberant osteochondromatosis	Narrow joint spaces, osteophytes	Flattened femoral condyles, widened intercondylar notch
Spine	Platyspondyly endplate irregularity, Schmorl's nodes	Platyspondyly	Platyspondyly, endplate irregularity	Platyspondyly, endplate irregularity, Schmorl's nodes, kyphoscoliosis	Platyspondyly, endplate irregularity
Shoulders	Dysplastic epiphyses, juxtaarticular calcified deposits	Not reported	Enlarged epiphyses with exuberant osteochondromatosis	Not reported	Enlarged dysplastic epiphyses
Hands and feet	Wide epiphyses, brachymetatarsia of 4th and 5th metatarsal bones	Metacarpals and metatarsal shortened and flattened	Short 4th metatarsal bones (case 1)	Brachymetatarsia of 3rd and 4th toes	Enlarged epiphyses, brachydactyly

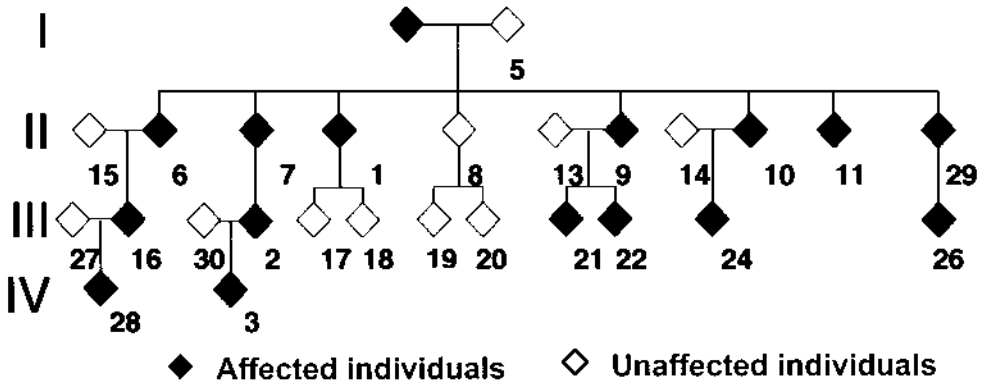

Figure 2. The pedigree of the Micronesian family; gender-neutral symbols have been used to protect family identity. Numbers represent individuals who completed questionnaires and donated blood samples. Roman numerals indicate generations. Sequencing of COL2A1 exon 11 showed the following unaffected individuals (numbers from top to bottom) carried homozygous cytosine at both alleles: 5, 27, 17, 18, 19, and 20. Affected individuals carrying the heterozygous cytosine to thymidine mutations were (top to bottom) 6, 9, 11, 16, 2, 21, 22, 24, 28, and 3.

It is intriguing that the identical mutation has now been identified in 5 distinct and apparently unrelated families. This site appears to be a mutational hotspot in the COL2A1 gene[5]. Cytosine to thymidine nucleotide substitutions are commonly found at the cytosine position of CpG dinucleotides[8]. The amino acid substitution at this residue is critical for protein function. The R75C mutation alters the Y position of the Gly-X-Y repeat motif. Cysteine residues are absent in either the X or Y position in any identified collagen triple helical repeat[9]. To date, 3 different mutations have been reported resulting in an arginine to cysteine substitution at the Y position in COL2A1: R75C[4–7], R519C[3,10], and R789C[11].

Identification of a fifth family with R75C mutation supports the theory of a mutational hotspot in the COL2A1 gene[5]. The unique clinical phenotype observed in this Micronesian family expands the phenotypic spectrum associated with this specific COL2A1 mutation, and lends support to the hypothesis that both genetic modifiers and environmental factors may contribute to the pathogenesis associated with the R75C mutation in COL2A1.

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