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Genetic Mapping of a Locus for Multiple Epiphyseal Dysplasia (EDM2) to a Region of Chromosome 1 Containing a Type IX Collagen Gene

Michael D. Briggs,[1,3] HiChang Choi,[1] Matthew L. Warman,[5] John A. Loughlin,[6] Paul Wordsworth,[7] Bryan C. Sykes,[6] Catherine M. M. Irven,[6] Michael Smith,[9] Ruth Wynne-Davies,[8] Mark H. Lipson,[10] Leslie G. Biesecker,[11] Ann P. Garber,[1,2] Ralph Lachman,[1,3,4] Bjorn R. Olsen,[5] David L. Rimoin,[1,3] and Daniel H. Cohn[1,3]

[1]Ahmanson Department of Pediatrics, Steven Spielberg Pediatric Research Center, [2]Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, and Departments of [3]Pediatrics and [4]Radiology, University of California, Los Angeles, School of Medicine, Los Angeles; [5]Department of Cell Biology, Harvard Medical School, Boston; [6]Institute of Molecular Medicine, University of Oxford, [7]Nuffield Department of Clinical Medicine, John Radcliffe Hospital, and [8]St. Ebbe's, Oxford; [9]Department of Orthopaedic Surgery, St. Thomas Hospital, London; [10]Permanente Medical Group, Sacramento; and [11]National Institutes of Health/National Center for Human Genome Research, Bethesda

Summary

Multiple epiphyseal dysplasia (MED) is a dominantly inherited chondrodysplasia characterized by mild short stature and early-onset osteoarthrosis. Some forms of MED clinically resemble another chondrodysplasia phenotype, the mild form of pseudoachondroplasia (PSACH). On the basis of their clinical similarities as well as similar ultrastructural and biochemical features in cartilage from some patients, it has been proposed that MED and PSACH belong to a single bone-dysplasia family. Recently, both mild and severe PSACH as well as a form of MED have been linked to the same interval on chromosome 19, suggesting that they may be allelic disorders. Linkage studies with the chromosome 19 markers were carried out in a large family with MED and excluded the previously identified interval. Using this family, we have identified an MED locus on the short arm of chromosome 1, in a region containing the gene (COL9A2) that encodes the α2 chain of type IX collagen, a structural component of the cartilage extracellular matrix.

Introduction

Multiple epiphyseal dysplasia (MED) is an autosomal dominant disorder characterized by mild short stature and early-onset osteoarthropathy (International Working Group on Constitutional Diseases of Bone 1992). There is clinical variability in MED, with the severe Fairbank type and the milder Ribbing type defining the ends of the spectrum (Ribbing 1937; Fairbank 1947). The earliest symptom may be pain and stiffness of the large joints and/or short-limbed short stature. In severe cases, the onset of symptoms may be in early childhood, but in mild cases onset is more typical in midchildhood to adolescence. Mild forms may simply present as precocious osteoarthropathy of the hips with mild short stature.

The mild form of pseudoachondroplasia (PSACH) has some similarity to MED (Maroteaux et al. 1980). Diagnosis can be made at the onset of walking, with the recognition of a waddling gait, and short stature becomes apparent by 2–3 years of age. Short hands with stubby fingers and loose joints characterize PSACH, but not MED. As with MED, early-onset osteoarthrosis is a major feature of PSACH.

In childhood, the MED and PSACH phenotypes can be distinguished radiographically (Taybi and Lachman 1990). Skeletal radiographs in both conditions appear normal at birth, but abnormalities develop within the first few years of life. PSACH is associated with irregular dysplastic metaphyses and small dysplastic epiphyses of the hands and long bones, whereas in MED the radiographic abnormalities are primarily limited to the epiphyses, including the knees, hands, shoulders, and hips. In MED, the vertebrae are relatively normal throughout life, while in PSACH there is anterior beaking of the vertebrae in childhood, which resolves in adolescence (Rimoin et al. 1994). The early-onset osteoarthrosis that characterizes both conditions results from degeneration of the epiphyses of the long bones and can eventually require hip replacement.

Ultrastructural studies on cartilage from individuals affected with PSACH and some with MED show the accumulation of material within the rough endoplasmic reticulum of chondrocytes (Maynard et al. 1972; Stanescu et al. 1977, 1993). In PSACH and one reported case of MED, the retained material forms a unique lamellar structure (Maynard et al. 1972; Stanescu et al. 1977, 1982, 1993), which stains with antibodies to chondroitin sulfate proteoglycan 1 (also called *aggrecan*), a large aggregating proteoglycan found in cartilage extracellular matrix (Doege et al. 1991). Their clinical and biochemical similarities led to

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Address for correspondence and reprints: Dr. Daniel H. Cohn, Medical Genetics, SSB-3, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, CA 90048.

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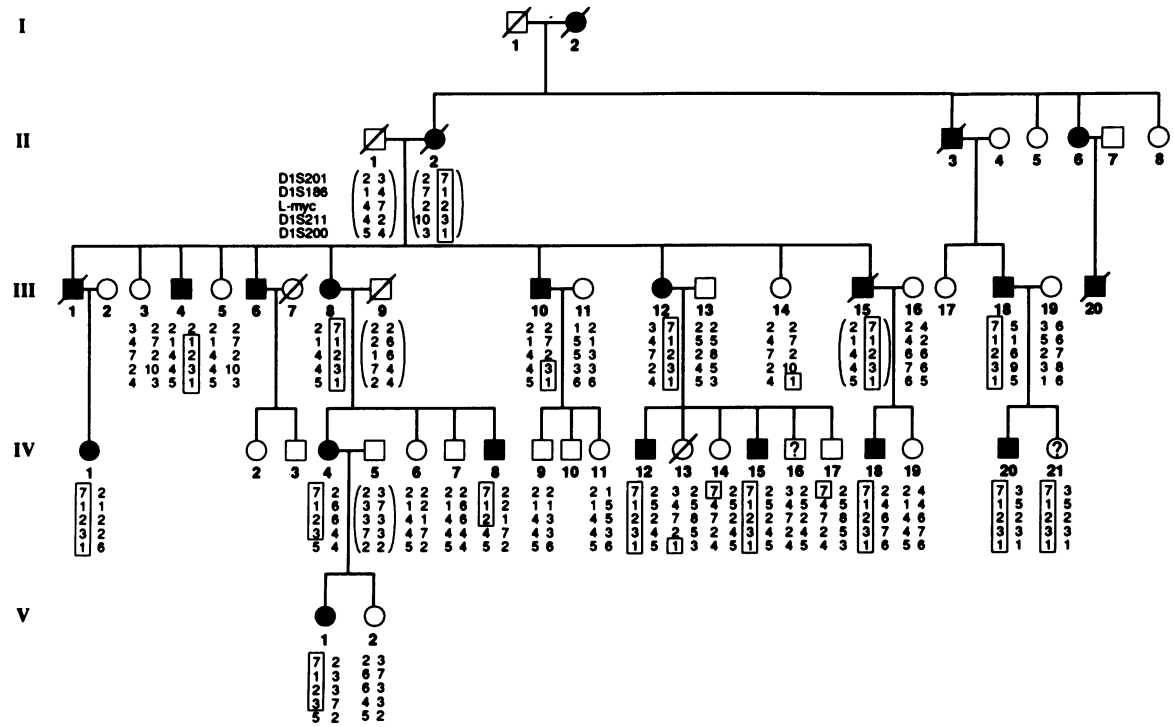

Figure 1 Pedigree of the MED family, R93-319. The uncertain clinical status of individuals IV-16 and IV-21 is indicated by the question mark within the symbol, and their genotypes were not used in linkage calculations. Genotypes for the haplotype that cosegregated with the disease gene are boxed. The genotypes of II-1, II-2, III-9, III-15, and IV-5 are in parentheses because they were deduced from the genotypes of their offspring. The inferred genotypes were not used in linkage calculations.

the hypothesis that MED and PSACH are part of the same bone dysplasia family (Stanescu et al. 1993). Recent studies have demonstrated linkage of mild and severe PSACH to a common 6.6-cM region on chromosome 19 (Briggs et al. 1993; Hecht et al. 1993), suggesting that these are allelic disorders resulting from different mutations in the same gene. A form of MED has been genetically mapped to a 1.7-cM region within the 6.6-cM interval (Oehlmann et al. 1994), suggesting that the disease in this family is likely to be allelic to PSACH but not excluding the possibility that the two disorders result from mutations in distinct, tightly linked genes.

We have carried out additional genetic mapping studies in a large MED family. When markers on chromosome 19 were used, the PSACH region was excluded. A lod score of 4.94 at zero recombination was obtained with a marker near the L-myc gene (Mäkelä et al. 1992), which is located on the short arm of chromosome 1 (Nau et al. 1985). This region contains the gene (COL9A2) that encodes the α2 chain of type IX collagen (Warman et al., in press), a cartilage-specific extracellular-matrix structural protein that is now the leading candidate for defects in this disorder.

Patients and Methods

Clinical summary

This family (International Skeletal Dysplasia Registry reference no. R93-319) was clinically described in a previous publication (Barrie et al. 1958). Affected individuals typically presented at 2.5–6 years of age, with pain in the knees. Knee and ankle pain was present throughout childhood. Bilateral osteotomies were required for gross varus deformities of the knees in some individuals. The hands were mildly short and the joints prominent. There were no abnormalities of the spine or chest. Examination of X-rays revealed flattened, irregular epiphyses in most joints, particularly the knees. Childhood X-rays showed small epiphyses with a large physeal space. The vertebrae appeared normal in adulthood, but there were some anterior defects at earlier ages.

Microsatellite Analysis

Blood samples were collected from family members, and genomic DNA was prepared by standard methods. PCR amplification of markers was performed as published elsewhere (Weber et al. 1993). In brief, 25-μl PCR reactions contained 1.5–2.5 mM $MgCl_2$; 10 mM Tris-HCl pH 8.3; 50 mM KCl; 200 μM each of TTP, dCTP, and dGTP; 2.5 μM dATP; 2.5 pmol of each primer; 2 μCi of [^{35}S dATP]; and 80 ng of genomic DNA. Cycling conditions usually consisted of 35 cycles of 94°C for 1 min, 55°C for 1 min, and 70°C for 1 min, with a final elongation step of 70°C for 5 min. Reactions were carried out either in microcentrifuge tubes by using a Perkin-Elmer DNA Ther-

Table 1

Two-point Lod Scores Calculated Between MED (Family R93-319) and Markers Flanking the PSACH-EDM1 Locus on Chromosome 19

Locus	θ = .00	.001	.05	.10	.20	.30	.40	Exclusion[a] (cM)
D19S199	−∞	−18.25	−4.94	−2.84	−1.09	−.39	−.12	14
D19S215	−∞	−14.12	−4.05	−2.31	−.74	−.09	.10	11

[a] The excluded distance is calculated with odds of 100:1 against linkage. The genetic distance between D19S199 and D19S215 is 4.4 cM.

mocycler or in 96-well microtiter plates by using a Stratagene SCS-96 thermocycler. Products were resolved by electrophoresis through 6% polyacrylamide/7 M urea gels and were sized by comparison to a DNA sequence ladder (M13mp18).

The anonymous markers used were primarily derived from the framework and skeletal maps constructed by the Cooperative Human Linkage Center (CHLC) at the University of Iowa (Buetow et al. 1994). The maps and primer sequences were accessed through the CHLC Gopher server (gopher.chlc.org). Additional markers were selected from the Genethon genetic maps (Weissenbach et al. 1992), and primer sequences were obtained from the Genome Database. Primers either were synthesized within the core facility at Cedars-Sinai Medical Center or were purchased from Research Genetics.

Linkage Analysis

Two-point LOD scores were generated using MLINK, and multipoint analysis used LINKMAP, both within LINKAGE version 5.10 (Lathrop et al. 1985). MED was defined as an autosomal dominant disorder with complete penetrance. Individuals with an uncertain clinical phenotype were not used in linkage calculations. Because of computational limitations, multipoint analysis was performed with only three markers: D1S211, L-myc, and D1S186.

Results

The pedigree for the MED family studied is shown in figure 1. Genotypes were determined for the markers at loci D19S199 and D19S215, which flank the previously defined PSACH/EDM1 locus on chromosome 19 (Briggs et al. 1993; Hecht et al. 1993; Oehlmann et al. 1994). Linkage of the disease phenotype to this interval was excluded. The two-point LOD scores are presented in table 1.

To identify the chromosomal location of the disease gene, we carried out linkage studies with PCR-based polymorphic markers by using two complementary approaches. The first approach used markers within or tightly linked to candidate genes. These were defined as genes whose products are expressed in the cartilage extracellular matrix. In the second approach, a panel of anonymous markers was used to systematically exclude the genome.

For the candidate-gene approach, in which intragenic markers were used, the genes that encode the α1 chain of type IX collagen (COL9A1) and the α1 chain of type XI collagen (COL11A1) were excluded. The two-point LOD scores for these markers are shown in table 2. The genes that encode type II collagen, cartilage matrix protein, and cartilage link protein had already been excluded in this family (Wordsworth et al. 1988; Loughlin et al., in press). When an intragenic marker was not available, we used anonymous markers to exclude the genomic region to

Table 2

Two-point Lod Scores Calculated between MED (Family R93-319) and Markers in Two Cartilage-specific Candidate Genes

Locus	θ = .00	.001	.05	.10	.20	.30	.40	Exclusion[a] (cM)
COL11A1	−∞	−22.49	−5.86	−3.23	−1.04	−.20	.05	14
COL9A1	−∞	−26.50	−8.04	−4.98	−2.26	−.98	−.31	21

[a] The excluded distance is calculated with odds of 100:1 against linkage.

which a candidate gene was mapped. By excluding the whole of chromosome 6 and the long arm of chromosome 15, we indirectly excluded the genes coding for the α1 chain of type X collagen (COL10A1) (Apte et al. 1991), the α2 chain of type XI collagen (COL11A2) (Vuorio and de Crombrugghe 1990), and chondroitin sulfate proteoglycan 1 (Korenberg et al. 1993) (data not shown).

For the genomewide search, anonymous markers that have high heterozygosity (≥70%) and have been stringently mapped (Buetow et al. 1994) were selected. We used an average spacing of ~40 cM between anonymous markers. For the 25 markers of this type, for which complete genotypes were determined, the average exclusion (defined as the maximum distance at which the lod score was < -2) was 16 cM. At 20 cM, halfway between adjacent markers, the average lod score was −1.51.

Linkage analysis using an AluVpA repeat marker 16 kb upstream from the L-myc gene (Mäkelä et al. 1992), which was known to be located at 1p32 (Warman et al., in press) ~200 kb from the COL9A2 gene of type IX collagen (E. Hellsten, J. Vesa, T. P. Mäkelä, M. Heiskanen, J. K. Cowell, S. Mead, K. Alitalo, et al., personal communication), gave the first indication of linkage, with a maximum lod score of 4.94 at a recombination fraction (θ) of 0. An additional five markers at loci flanking L-myc were analyzed. The genomic region represented by the markers used is shown in figure 2. Two-point lod scores between each marker and the phenotype are shown in table 3. The highest lod score was achieved with D1S211 (Z_{max} = 5.41 at θ = .04). Multipoint analysis (fig. 3) gave a maximum location score of 36.15 for the interval between D1S186 and D1S211, which supports a gene location within the interval containing the L-myc gene.

Analysis of recombinant haplotypes also supported a gene location in the D1S186–D1S211 interval (fig. 1). Individual III-10, who is affected, inherited cosegregating alleles for the markers at loci D1S200 and D1S211 but not at locus D1S186, placing the most likely disease gene location centromeric to D1S186. Similarly, individual IV-8, who is also affected, inherited cosegregating alleles for the markers at loci D1S201, D1S186, and L-myc, but not at D1S211 and D1S200, placing the disease gene telomeric to D1S211. The clinical status of individuals IV-16 and IV-21 is unknown. However, both individuals inherited from their affected parents nonrecombinant haplotypes that predict IV-16 to be unaffected and IV-21 to be affected.

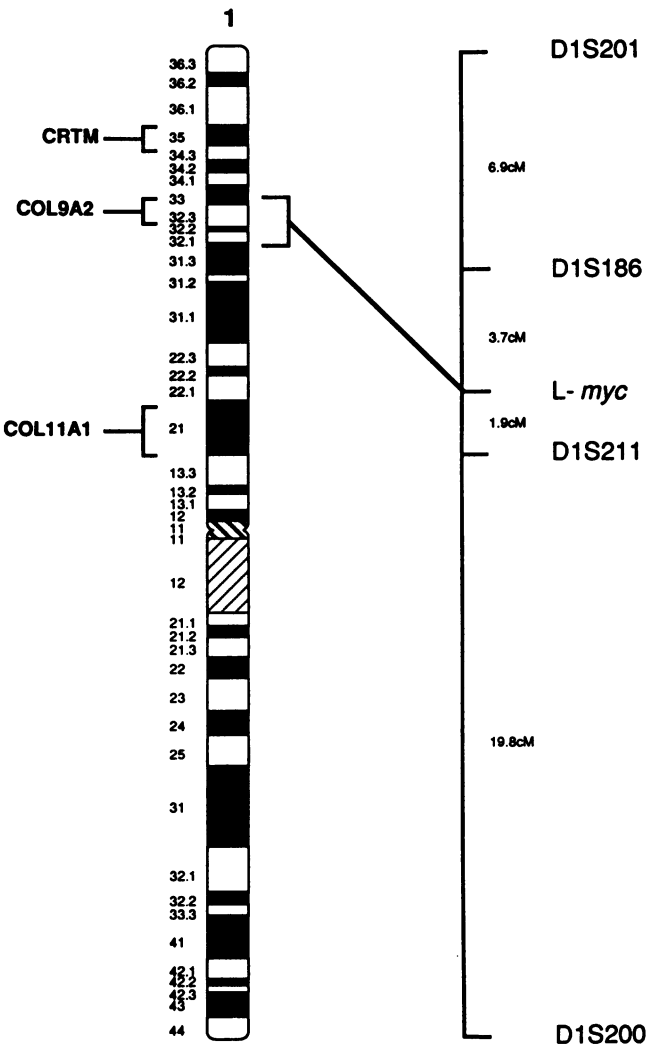

Figure 2 Ideogram of chromosome 1 and sex-averaged genetic distances between five of the markers used in this study. With the exception of D1S211, the order and genetic distances between markers have been determined by the CHLC (Buetow et al. 1994). D1S211 was placed below L-myc on the basis of its placement below D1S193 (Weissenbach et al. 1992), which is below L-myc on the CHLC map. D1S255 (see table 3) could not be placed relative to D1S186 and therefore is not shown. Indicated on the left are the chromosomal locations of the COL11A1, COL9A2, and CRTM genes, all of which are specifically expressed in cartilage.

Discussion

These studies demonstrate genetic heterogeneity within phenotypes in the MED clinical spectrum and identify a new locus (EDM2) for MED, on chromosome 1. The short arm of chromosome 1 contains three known genes that encode components of the cartilage extracellular matrix. The COL11A1 gene, which encodes the α1 chain of type XI collagen, is located at 1p21 (Henry et al. 1988), the cartilage matrix protein gene (CRTM) has been localized to 1p35 (Jenkins et al. 1990; Collins et al. 1992), and the COL9A2 gene, which encodes the α2 chain of type IX collagen, is located at 1p32 (Warman et al., in press). Both COL11A1 (table 2) and CRTM (Loughlin et al., in press) have been excluded as disease-gene candidates in this family, by linkage studies using intragenic polymorphic markers. Like the COL9A2 gene (Warman et al., in press), the L-myc gene has been localized by in situ hybridization to 1p32 (Nau et al. 1985), and physical mapping studies (E.

Table 3

Two-point Lod Scores Between MED and Chromosome 1 Markers

		θ =							
Locus	0	.001	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D1S201	−∞	−5.73	.64	1.38	1.60	1.24	.60	1.62	.17
D1S186	−∞	2.13	3.41	3.26	2.61	1.73	.70	3.41	.05
D1S255	−∞	4.26	5.38	5.07	4.06	2.81	1.36	5.40	.04
L-myc	4.94	4.93	4.54	4.12	3.24	2.67	1.78	4.94	.00
D1S211	−∞	4.26	5.39	5.08	4.08	2.82	1.34	5.41	.04
D1S200	−∞	−7.38	.60	1.56	1.89	1.46	.64	1.90	.18

Hellsten, J. Vesa, T. P. Mäkelä, M. Heiskanen, J. K. Cowell, S. Mead, K. Alitalo, et al., personal communication) place COL9A2 and L-myc within ~200 kb of each other.

Type IX collagen is a heterotrimer of the α1(IX), α2(IX), and α3(IX) chains (van der Rest et al. 1985), which are encoded by the COL9A1, COL9A2, and COL9A3 genes, respectively (Shaw and Olsen 1990; Vuorio and de Crombrugghe 1990). Type IX collagen constitutes a minor proportion of the collagen in cartilage, where it binds laterally to type II collagen fibrils via lysine-derived cross-links (van der Rest and Mayne 1988; Wu et al. 1992). The precise role of type IX collagen is not known; however, both its localization to the surface of type II collagen–containing fibrils and the projection of its large amino-terminal globular domain into the perifibrillar space (Vaughan et al. 1988) suggest a role in mediating the interaction between collagen fibrils and other extracellular-matrix components.

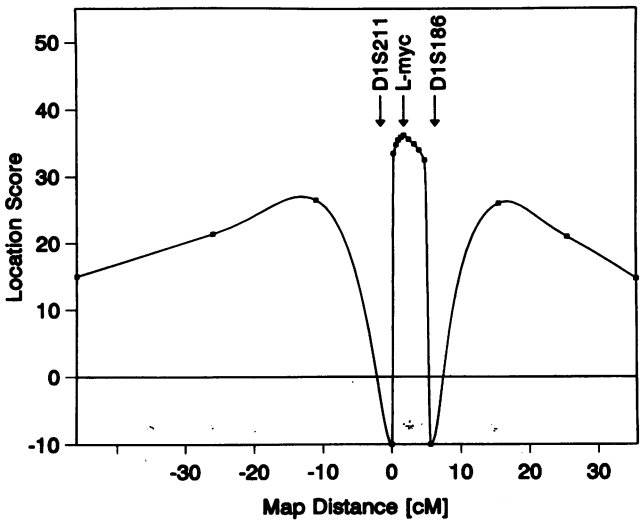

Figure 3 Multipoint linkage map generated with LINKMAP using markers D1S211, L-myc, and D1S186. The Haldane mapping function was used to calculate map distance from D1S211, which was arbitrarily placed at 0 cM. A maximum location score of 36.15 was obtained at L-myc (between markers D1S211 and D1S186). The odds calculated against a gene location either centromeric to D1S211 or telomeric to D1S186 were 130:1 and 160:1, respectively.

The major morbidity associated with MED is early-onset osteoarthrosis. Transgenic mice bearing a defective COL9A1 gene develop a mild chondrodysplasia with early-onset osteoarthrosis (Nakata et al. 1993), as do mice homozygous for a CoL9a1 null allele (Fassler et al., in press). Taken together, the cartilage specificity of the abnormalities in MED, the chromosomal location of the disease gene, the chondrodysplasia phenotype of the transgenic mice, and the central role that type IX collagen plays in determining the architecture of the cartilage extracellular matrix suggest the COL9A2 gene as the leading candidate for the disease gene in this family.

The COL9A1 gene, located on chromosome 6q13 (Kimura et al. 1989; Warman et al. 1993), and the COL9A3 gene, which has yet to be isolated and mapped, may be additional targets for mutations that produce MED. The definition of the chromosome 1 locus will allow other MED families to be tested to determine if there is further genetic heterogeneity within this disease phenotype. It is also possible that type IX collagen defects will be identified in sporadic forms of early-onset osteoarthrosis.

The chondrodysplasias are a clinically and genetically diverse group of dwarfing conditions. Classification of these disorders into bone-dysplasia families is mainly based on clinical features and radiographic presentation. A more complete classification, which will include recent molecular genetic data such as those presented here, will provide a chromosomal location and, in time, a defective gene product with which to associate each phenotype. Identification of the molecular defects in the components of the cartilage extracellular matrix will define how these components interact with each other and will suggest mechanisms by which this spectrum of disease phenotypes is produced.

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