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Refinement of the Chromosome 5p Locus for Familial Calcium Pyrophosphate Dihydrate Deposition Disease

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Summary

Familial calcium pyrophosphate dihydrate deposition disease (CPPDD) is a disease of articular cartilage that is radiographically characterized by chondrocalcinosis due to the deposition of calcium-containing crystals in affected joints. We have documented the disease in an Argentinean kindred of northern Italian ancestry and in a French kindred from the Alsace region. Both families presented with a common phenotype including early age at onset and deposition of crystals of calcium pyrophosphate dihydrate in a similar pattern of affected joints. Affected family members were karyotypically normal. Linkage to the short arm of chromosome 5 was observed, consistent with a previous report of linkage of the CPPDD phenotype in a large British kindred to the 5p15 region. However, recombinants in the Argentinean kindred have enabled us to designate a region <1 cM in length between the markers D5S416 and D5S2114 as the CPPDD locus.

Introduction

Zitnan and Sitaj (1958, 1963) presented case studies of 27 patients with what they referred to as "articular chondrocalcinosis." The fact that most of the patients were members of five families suggested that the disease has a strong hereditary component. McCarty and Hollander (1961) reported on two cases of non–urate-associated crystal deposition in the joints of patients thought to have gout. Radiographic examination of the joints in these and other patients revealed distinctive and abnormal calcifications in and around articular hyaline cartilage and fibrocartilage of numerous joints. Following the initial description of calcium pyrophosphate dihydrate deposition disease (CPPDD) in the five Czech families, multiple ethnic series were reported from throughout the world (Louyot et al. 1964; Moskowitz and Katz 1964; van der Korst et al. 1974; Reginato et al. 1975; Gaucher et al. 1977; Gaudreau et al. 1981; Bjelle 1982; Sakaguchi et al. 1982; Richardson et al. 1983; Fernández-Dapica and Gómez-Reino 1986; Rodríguez-Valverde et al. 1988; Balsa et al. 1990; Eshel et al. 1990; Doherty et al. 1991; Hamza et al. 1992). Most familial cases appeared to be inherited in an autosomal dominant manner, with precocious onset and variable clinical expression; deposition of calcium pyrophosphate dihydrate (CPPD) crystals frequently preceded the development of arthropathy. The radiographic features included crystal deposition in the knee, symphysis pubis, and triangular fibrocartilage of the wrist (Riestra et al. 1988; Ryan and McCarty 1993). A peculiar type of osteoarthritis with numerous and large subchondral cysts was also observed.

In primary familial cases of chondrocalcinosis, crystal deposition prior to the onset of degenerative joint disease is observed. The disorder may also be sporadic or associated with several metabolic disorders, such as hypophosphatasia, hypomagnesemia, hemochromatosis, and hyperparathyroidism. The mechanisms responsible for the deposition of the CPPD crystals are not known, although some studies have reported that structural changes in the articular cartilage extracellular matrix might promote crystal formation (Bjelle 1972, 1981). In light of these reports, genes encoding cartilage extracellular-matrix proteins have been considered as candidate genes for chondrocalcinosis. In a large family from the Chiloe Islands, with a clinical phenotype of severe, pre-

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cocious osteoarthritis with ankylosis, late-onset spondyloepiphyseal dysplasia, and chondrocalcinosis in multiple joints and fibrocartilages, a heterozygous mutation in the *COL2A1* gene that resulted in an R75C substitution in the gene product was identified (Williams et al. 1993; Reginato et al. 1994). However, it appears that in this family the chondrocalcinosis phenotype was a secondary consequence of the advanced and severe osteoarthritis. It has also been suggested that the inorganic composition of the matrix may affect crystal deposition. A chondrocyte nucleoside triphosphate pyrophosphohydrolase (NTPPPH) that may play a role in the extracellular generation of inorganic pyrophosphate at the site of crystal deposition has been characterized (Howell et al. 1984; Muniz et al. 1984; Ryan et al. 1984, 1985). The activity of this enzyme was elevated in sporadic cases of CPPDD; however, elevated levels of NTPPPH activity were not observed in the familial form of the disease (Ryan et al. 1986). Nonetheless, increased levels of inorganic pyrophosphate have been observed in cultured fibroblasts and lymphoblasts of patients affected with familial CPPDD (Lust et al. 1981*a,* 1981*b*), which thus perpetuates the suspicion that abnormalities in pyrophosphate metabolism may give rise to abnormal crystal deposition in these families.

In recent years, genetic linkage analysis has been undertaken to map the disease gene(s) for familial CPPDD. A study of a large family from Maine, in which the CPPDD phenotype appeared to occur as a secondary consequence of severe, nondysplastic osteoarthritis, excluded linkage to the *COL2A1* locus; in this family, genetic linkage was demonstrated between the disease phenotype and a locus on the long arm of chromosome 8 (MIM 600668; Baldwin et al. 1995). A study of a British family with a phenotype of primary chondrocalcinosis and childhood seizures demonstrated genetic linkage to a chromosomal interval in the region of 5p15 (MIM 118600; gene symbol *CCAL1*; Hughes et al. 1995). In this report we document linkage of the primary CPPDD phenotype to the short arm of chromosome 5 in two unrelated families, one from Argentina and the other from France. Recombination events in the Argentinean kindred assign the CPPDD locus to a 1-cM region just centromeric to the locus reported for the British kindred. The results of all these studies indicate that familial CPPDD is a clinically and genetically heterogeneous disease and that mutations in at least three different genes may eventually lead to the expression of the disease.

Subjects, Material, and Methods

Family Studies and Collection of Material

The subjects of this study were from two families: an Argentinean kindred of northern Italian (Cuneo, Piamonte) ancestry and a French kindred from the Alsace region. Among the Argentinean kindred, 77 members from four generations, with 27 affected individuals, were analyzed in the study. In the French kindred, 41 members from three generations, with 25 affected individuals, provided DNA for genotype analyses. The CPPDD phenotype in both families displayed an autosomal dominant mode of inheritance. Affected members were initially evaluated by clinical examination. Follow-up evaluations with detailed radiographs were obtained as indicated. When there was evidence of effusion, we obtained synovial fluid for analysis by compensated polarized microscopy (seven members of the Argentinean family and three members of the French family provided aspirated synovial fluid for analysis). Both families displayed very similar phenotypes, with early age at onset in the youngest affected members (3d decade of life) and radiographic evidence of fibrocartilage and hyaline cartilage calcifications typical of CPPD deposition without dysplasia or precocious osteoarthritis. The most commonly affected joints included knees and wrists; fibrocartilage tissues, including menisci, pubic symphysis, and intervertebral disks, were also affected (Gaucher et al. 1977). In both families, laboratory studies of affected individuals yielded no metabolic alterations: serum and urinary calcium and magnesium and inorganic phosphates, alkaline phosphates, iron, iron-binding capacity, and serum copper levels were normal. In the Argentinean family, parathyroid-hormone levels were determined in 18 affected members and were normal. This study was approved by the Institutional Review Board of Thomas Jefferson University, Philadelphia, and by the Comité Consultatif de Protection des Personnes dans la Recherche Biomedicale de Nancy.

DNA Microsatellite Marker Analyses

We extracted DNA from whole blood, with an automated nucleic acid extractor (ABI model 341, Genepure), under conditions specified by the manufacturer. Polymorphic dinucleotide-repeat markers from several candidate loci, including a variety of extracellular-matrix genes as well as the loci at 8q and 5p (Baldwin et al. 1995; Hughes et al. 1995), which have been reported elsewhere to be linked to the chondrocalcinosis phenotype, were genotyped in all participating family members. Markers (Weber et al. 1991; Gersh et al. 1994) were analyzed following PCR amplification (Saiki et al. 1985) of 30 ng of genomic DNA in a 10–20-μl reaction containing 5 pmol of each primer. Optimal magnesium concentrations were determined for each primer pair. For automated genotype analyses, fluorescently labeled PCR products were visualized on an ABI model 373 sequencer (Genepure) and analyzed with GENESCAN software

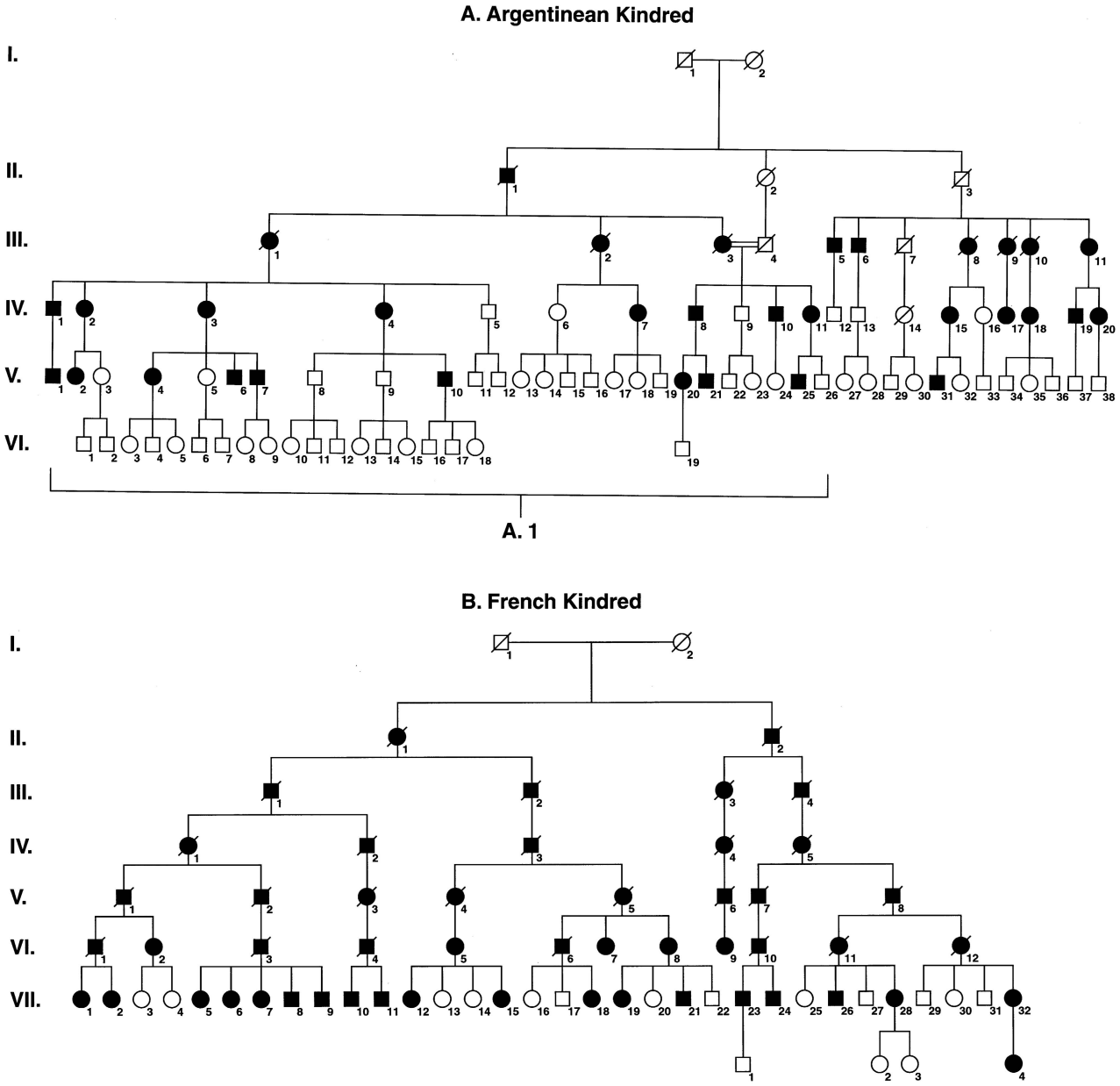

Figure 1 *A,* Pedigree of Argentinean kindred. Member III-10 died during the course of the study, but two separate DNA samples were obtained prior to her death. The subfamily denoted by "A.1" underwent linkage analysis; members of subfamily A.1 participating in genotype analysis and used in linkage analysis included all living relatives except members IV-9 and IV-10. *B,* Pedigree of French kindred. Members participating in genotype analysis and used for linkage analysis included all living relatives depicted.

(Applied Biosystems). For radioactive genotype analyses, [^{33}P]–end-labeled PCR products were resolved on a 6% denaturing polyacrylamide gel and visualized by autoradiography (Maniatis et al. 1982).

Linkage Analyses

We performed two-point linkage analysis with the FASTLINK 3.0P version of MLINK (Cottingham et al. 1993; Schäffer et al. 1994). The disease was modeled as an autosomal dominant trait with a reduced penetrance of .9, since some asymptomatic individuals of the last generation were still too young for the disease to be detected either clinically or radiologically. Moreover, since the phenotype being analyzed could, in a small proportion of cases, also result from various factors apart from the genetic component, we took into account a phenocopy rate for affected individuals. Because

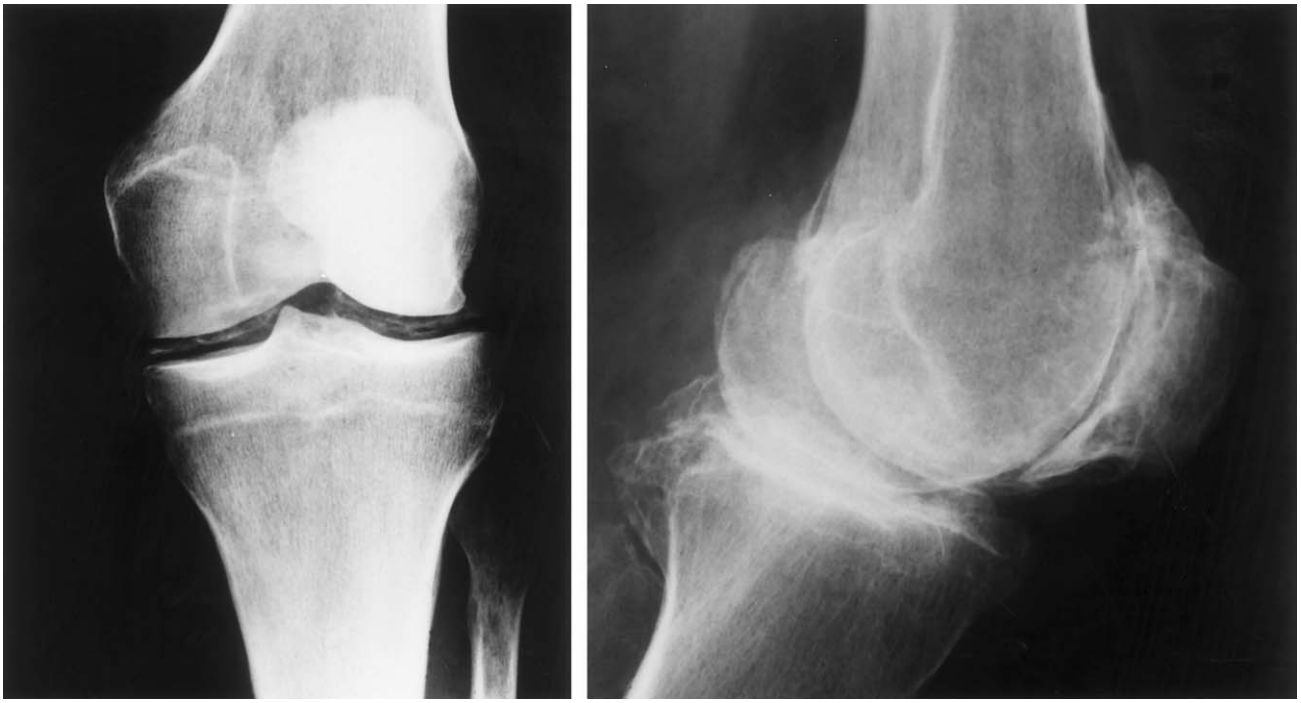

Figure 2 *Left,* Radiograph of knee of member V-2 (aged 42 years) of the Argentinean kindred, showing calcific deposits in the knee meniscus. Note that there is no evidence of osteoarthritis at this early stage of the disease; joint space, tibial plateau, and femoral condyle are normal and uncompromised. *Right,* Lateral radiograph of knee of member IV-2 (proband, aged 77 years) showing late-stage disease progression. Note severe osteoarthritis with narrowing of joint space and bone remodeling of patella, tibial plateau, and femoral condyle.

CPPDD mimics other rheumatic disorders (McCarty 1975), especially rheumatoid arthritis, we used annual incidence values for rheumatoid arthritis in a general population >18 years of age, which yielded phenocopy rates of .0006 and .00022 for women and men, respectively (Chan et al. 1993). The disease-allele frequency was assumed to be .0001. We estimated marker-allele frequencies with the FASTLINK 3.0P version of the ILINK program, after breaking the only loop of the Argentinean family (see fig. 1*A,* members III-3 and III-4) to hasten the analyses. Since the familial form of CPPDD is rare, we designated married-in individuals as being unaffected; individuals for whom no clinical or radiological evaluation was performed were designated as unaffected in the same liability classes as the affected members. A multipoint linkage analysis was also performed when marker orders and intermarker distances were recovered from various genome databases. We used the VITESSE program (O'Connell and Weeks 1995) to generate multipoint LOD scores.

Results

The detailed pedigrees of the two families analyzed in this study are shown in figure 1*A* and *B*. The extended history of the Argentinean family spanned seven generations. Confirmation of affected status was available for a total of 162 members (143 living and 19 deceased) from generations III–VI. Blood samples were obtained from 77 members, from four generations, for genotype analysis, as shown in figure 1*A*. All individuals who donated blood underwent genotype analyses; however, only members of subfamily A.1 (with the exception of members IV-9 and IV-10, who declined to participate in the study) underwent two-point linkage analysis (see below). The French family could be traced through nine generations; a detailed genealogy of the entire family, through seven generations, has been published elsewhere (Gaucher et al. 1977). Blood samples were available from all living family members shown in figure 1*B,* and all individuals underwent genotype and linkage analyses.

Clinical Features of Chondrocalcinosis in the Two Families

Articular chondrocalcinosis was observed on joint radiographs of 27 living members, and CPPD crystals were identified by compensated polarized light microscopy of the synovial fluids of seven patients from the Argentinean kindred. For two of these patients, x-ray diffraction and infrared spectroscopic analyses of calcified tissues

Table 1

Two-Point LOD Scores for Argentinean and French Families

Marker and Family	LOD Score at θ =						
	.00	.01	.05	.10	.20	.30	.40
D5S432	1.66	1.67	1.62	1.47	1.04	0.63	0.27
A.1	0.41	0.47	0.62	0.69	0.63	0.43	0.20
B	1.25	1.20	1.01	0.78	0.42	0.19	0.06
D5S817	6.02	8.10	8.26	7.67	5.73	3.42	1.28
A.1	3.95	3.96	3.92	3.72	3.01	2.04	0.91
B	2.07	4.14	4.34	3.95	2.72	1.39	0.37
D5S810	−2.40	−0.12	0.72	0.93	0.79	0.43	0.11
A.1	0.45	0.56	0.76	0.81	0.64	0.35	0.06
B	−2.85	−0.67	−0.04	0.13	0.14	0.09	0.04
D5S2081	−1.99	1.84	3.18	3.51	3.17	2.27	1.09
A.1	0.78	2.46	3.21	3.38	3.02	2.18	1.05
B	−2.78	−0.62	−0.03	0.13	0.15	0.09	0.04
D5S1991	3.27	4.95	5.63	5.58	4.54	2.96	1.22
A.1	0.37	2.05	2.82	3.02	2.69	1.89	0.83
B	2.90	2.90	2.81	2.56	1.85	1.06	0.38
D5S1954	0.99	2.63	3.17	3.04	2.15	1.06	0.20
A.1	0.37	1.93	2.36	2.27	1.69	0.90	0.19
B	0.62	0.69	0.80	0.76	0.46	0.16	0.01
D5S1963	10.10	11.60	11.90	11.30	9.00	6.00	2.70
A.1	2.07	3.65	4.09	3.99	3.28	2.26	1.06
B	7.99	8.00	7.81	7.28	5.71	3.75	1.69
D5S416	1.67	3.41	4.27	4.39	3.70	2.50	1.14
A.1	0.65	2.33	3.10	3.28	2.94	2.12	1.02
B	1.01	1.08	1.17	1.11	0.75	0.38	0.12
D5S2114	0.50	4.20	5.80	6.00	5.00	3.20	1.30
A.1	−6.67	−2.89	−0.78	0.11	0.63	0.51	0.19
B	7.17	7.06	6.56	5.88	4.37	2.73	1.14
D5S1997	2.79	7.96	8.24	7.74	5.93	3.71	1.59
A.1	−3.51	1.75	2.47	2.63	2.33	1.65	0.79
B	6.29	6.20	5.77	5.11	3.59	2.06	0.79
D5S268	−2.56	2.77	3.66	3.87	3.40	2.37	1.11
A.1	−5.19	0.17	1.25	1.73	1.86	1.46	0.75
B	2.63	2.59	2.41	2.14	1.54	0.91	0.35
D5S486	−3.23	1.92	2.34	2.29	1.85	1.25	0.58
A.1	−3.23	1.93	2.35	2.29	1.85	1.26	0.59
B	ND	ND	ND	ND	ND	ND	ND

Note.—Values in lines beginning with marker names are combined LOD scores for family A.1 and family B. The highest LOD scores obtained are underlined. ND = not done.

confirmed the presence of CPPD crystals. Clinical patterns in affected members comprised pseudogout alone (19%), pseudogout plus osteoarthritis (44%), pseudo-osteoarthritis alone (22%), and pseudo–rheumatoid arthritis (15%). One member demonstrated radiographic evidence of CPPDD but was clinically asymptomatic. The mean age at onset was 29 years (range 17–60 years). Among affected members, 93% had radiographic evidence of chondrocalcinosis in the knees, 67% had involvement of the pubis symphysis, and 59% and 52% showed involvement of the wrists and hips, respectively. Eight affected members had severe, destructive arthropathy of the hips, knees, and shoulders; six of them had required total hip replacement (bilateral for two of the six members), and knee replacement had been performed on two members. The lumbar spine was also affected in some members.

Clinical as well as biochemical profiles of the French CPPDD family have been extensively characterized. Details of the clinical phenotype were described by Gaucher et al. (1977); in brief, affected family members had a diffuse form of the disease. CPPD deposits were observed in cartilage linings and fibrocartilages, including menisci, glenoidal and cotyloid labra, pubis symphysis, and intervertebral disks. Calcifications were also detected in joint capsules and ligaments. The crystals obtained from joints of three affected members were identified, by x-ray diffraction analysis, as CPPD in the triclinic crystalline form (Lust et al. 1981*b*). A study of lymphoblasts and fibroblasts from members of the family demonstrated a mean concentration of intracellular pyrophosphate that was two times higher than that observed in cells from unaffected family members and from other, unrelated controls (Lust et al. 1981*a,* 1981*b*). Finally, no association with or linkage to any human leukocyte antigen was observed in this kindred (Gaucher et al. 1977).

Figure 2 shows knee radiographs of members V-2 (*left panel*) and IV-2 (*right panel*) of the Argentinean kindred. Member V-2 was a 42-year-old woman who developed CPPDD in her mid 30s. Her mother (member IV-2), the proband, underwent hip replacement at the age of 50 years; her age at onset was 30 years.

Two-Point Linkage Analyses

The first family from whom samples were collected and analyzed was the Argentinean kindred. Because of reported locus heterogeneity for chondrocalcinosis, we tested a number of candidate loci, including several cartilage extracellular-matrix genes and the locus on chromosome 8q (Baldwin et al. 1995), through two-point linkage analysis by means of an affecteds-only dominant model that considered only affected individuals to be in a liability class with complete penetrance. The family showed no linkage to all the loci considered, with the exception of a locus on the short arm of chromosome 5, where there was evidence for linkage but at a recombination fraction (θ) >0 (data not shown). On the basis of haplotype analysis, two individuals (member III-10 and her daughter, member IV-18) who were scored as affected did not exhibit the disease haplotype as defined for 25 other affected members in the kindred. Unfortunately, the clinical profiles of these two members were entirely consistent with those described for other affected members of the family, including a clinical presentation of pseudogout and chondrocalcinosis of the wrists, pubis symphysis, and knees; thus, it was impossible to distinguish these individuals from other affected members, on the basis of their phenotype. Since CPPDD is a condition

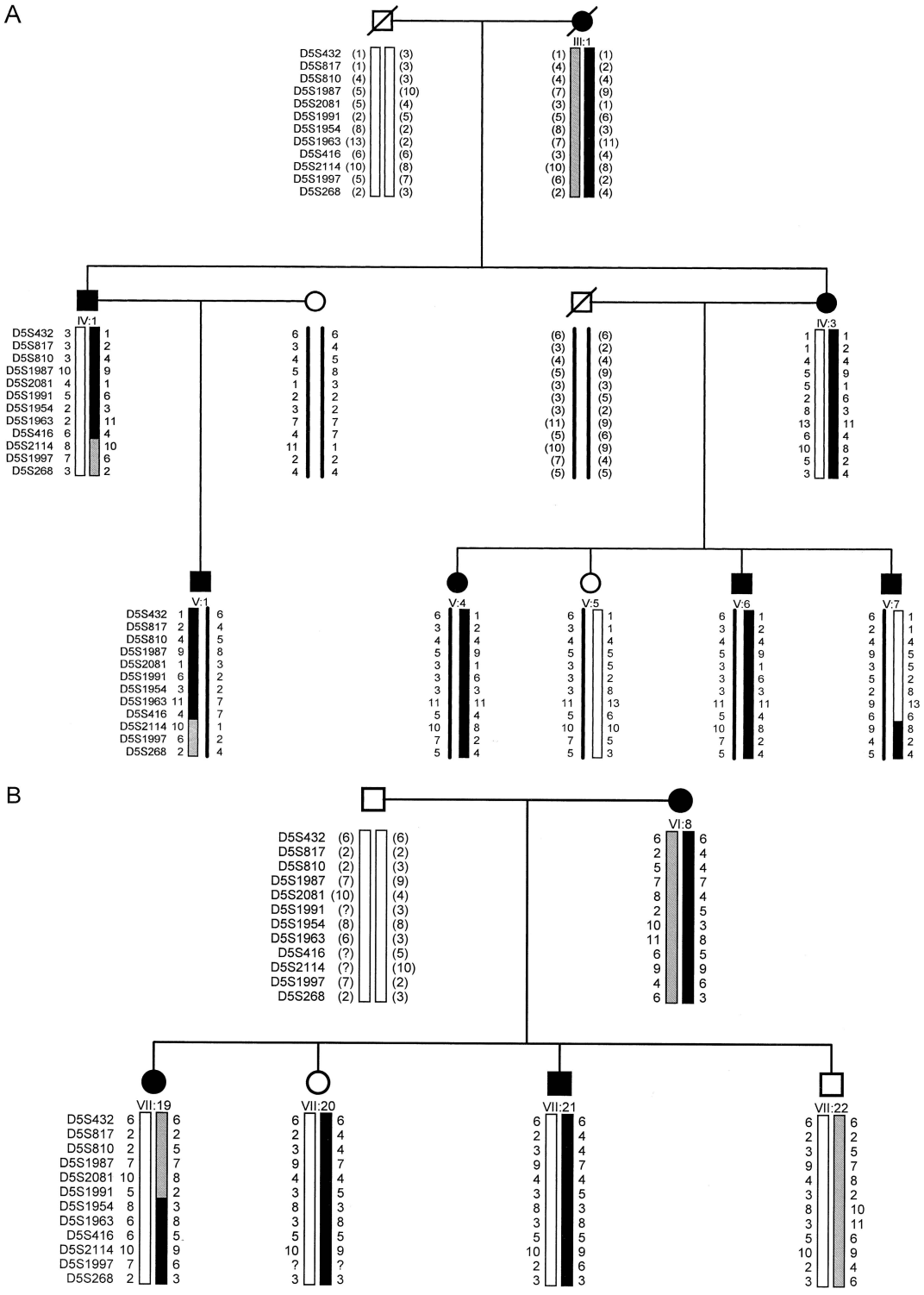

Figure 3 Recombination analysis of genotypes for relevant nuclear families in the Argentinean and French kindreds. Marker order is indicated to the left of the first individual in each generation. Alleles transmitted by the spouses of members of the top generation for each family are shown as unblackened boxes; alleles transmitted by spouses of subsequent generations in the Argentinean family are shown as black lines. Pedigree numbers correspond to the pedigree positions shown in fig. 1*A* and *B*. The haplotype linked to the disease gene is shown in black. *A*, Recombinants in the Argentinean kindred. *B*, Recombinants in the French kindred. Member VII-20 (aged 31 years) was still unaffected at the time of this study.

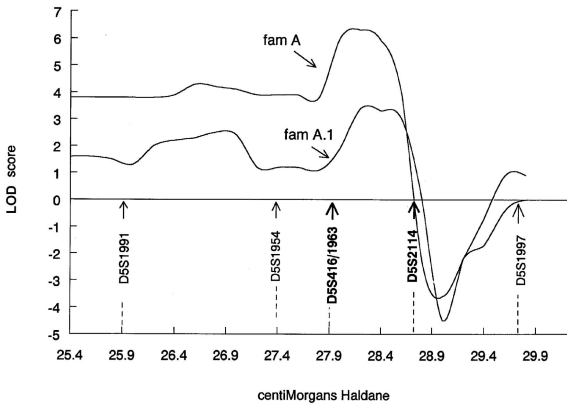

Figure 4 Multipoint linkage analysis for the Argentinean kindred. Multipoint plots for both the entire Argentinean kindred (family A) and subfamily A.1 of the Argentinean kindred are depicted. Intermarker distances were obtained from public databases. We used VITESSE to generate the multipoint LOD scores (location scores expressed as LOD scores) by means of a six-point window (five markers and the disease locus) across an interval defined by the indicated markers.

that may result from a variety of metabolic, traumatic, and genetic abnormalities (Moskowitz 1993), we considered these members to be potential phenocopies. In an attempt to define the nature of the phenocopy in these members, we first excluded several metabolic disorders or trauma as the cause of the observed phenotype. Lacking any resolution with this strategy, we next analyzed the family of the spouse of member II-3, from whom the haplotype of these two anomalous members was inherited, to investigate whether we could be dealing with a family segregating two different disease haplotypes. Interestingly, among 28 members of this extended family who were examined, 6 were affected with chondrocalcinosis or pyrophosphate arthropathy (a radiologically distinct and phenotypically severe arthropathy that is often associated with advanced-stage CPPDD; see Dieppe et al. 1982). However, linkage analysis of this extended family, under the assumption of an autosomal dominant mode of inheritance, excluded linkage to the 5p locus (data not shown). The above-mentioned observations, however, led us to reanalyze the Argentinean family by eliminating the branch of the kindred that produced the anomalous members. Therefore, the branch of the Argentinean kindred that underwent two-point linkage analysis, labeled "A.1" in figure 1*A*, included genotype data from all living members depicted, with the exception of members IV-9 and IV-10 (table 1, family A.1). Confidence in the chromosome 5p locus was supported by linkage analysis of an unrelated French family displaying the same chondrocalcinosis phenotype. The two-point LOD scores for the French family (family B) are also shown in table 1; we performed linkage analysis by means of genotype data provided by all living relatives shown in figure 1*B*. Table 1 also includes the combined LOD score for both families (family A.1 and family B) and demonstrates a maximum two-point LOD score of 11.90 at the marker D5S1963 ($\theta = .05$). We performed the tabulated analyses by means of the model specifications described in Subjects, Material, and Methods. An affecteds-only analysis with reduced penetrance (.9) was also performed for both families, with similar results (not shown).

Recombination Analyses and Multipoint Linkage Analyses

Recombination events in the haplotype analysis of the pertinent nuclear family of the Argentinean kindred are shown in figure 3*A*. Three affected members showed recombination at the CPPDD locus; the disease haplotype observed in members IV-1 and V-1 places the CPPDD disease gene telomeric to marker D5S2114, and recombination in the disease haplotype of member V-7 indicates that the CPPDD gene is just centromeric to the D5S416 marker. In the French kindred, only one individual with recombination in the disease haplotype has been observed; as seen in figure 3*B*, member VII-19 carries the disease locus just centromeric to the marker D5S1991. Since the recombination analyses of the Argentinean kindred were the most informative with respect to specifying the disease interval, multipoint linkage analysis was undertaken to further specify the CPPDD locus. Results of the multipoint analysis of the entire Argentinean family (family A), as well as of subfamily A.1, show a peak between markers D5S416 and D5S2114, in a 1-cM interval, as can be seen in figure 4. An ideogram of the short arm of chromosome 5, depicting the most likely location of the CPPDD locus in the Argentinean and French kindreds, is shown in figure 5.

Discussion

This report identifies two more unrelated CPPDD families with phenotypes that show linkage to chromosome 5p. Analysis of recombinations in three affected members of the Argentinean kindred narrows the region of search for the candidate gene to the interval between the markers D5S416 and D5S2114, a distance interval of <1 cM. There are no other microsatellite markers in this interval (C. J. Williams and J. Overhauser, unpublished data). No candidate genes have been mapped to this interval; however, one expressed sequence tag (EST) has been identified (dbEST accession no. 182111; GenBank accession no. R11532) and may be considered a candidate for the CPPDD gene.

The clinical pattern of the disease in the two families

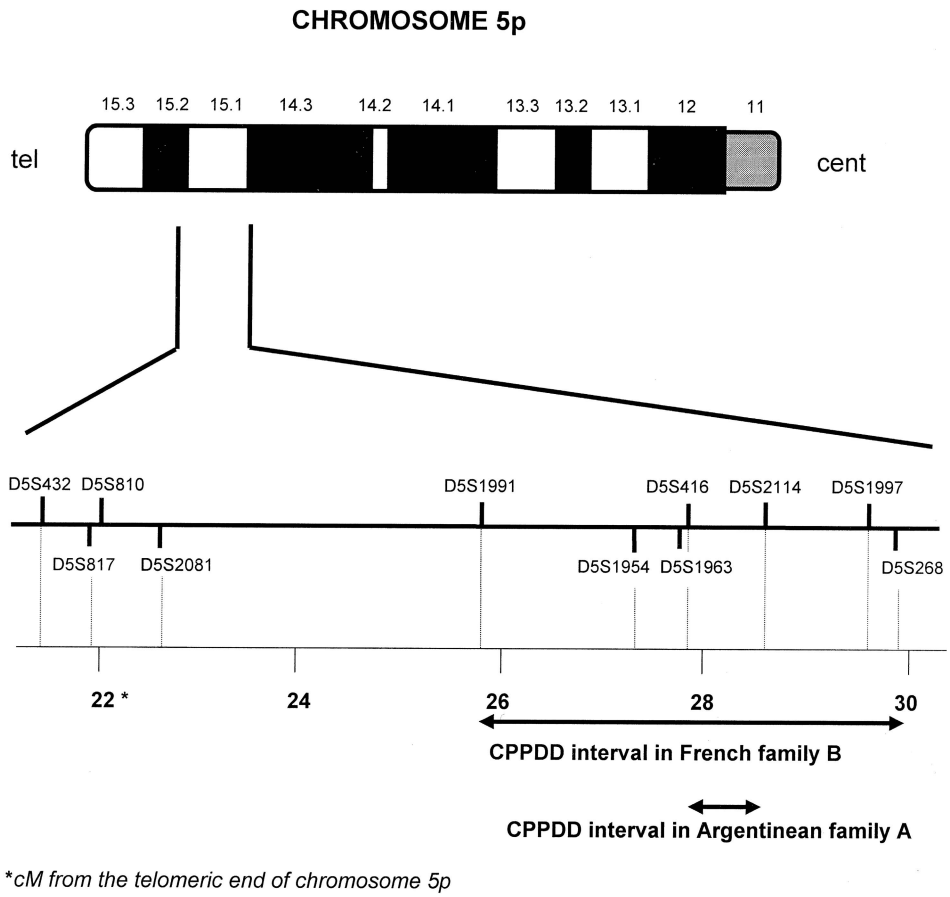

Figure 5 Ideogram of the short arm of chromosome 5, showing the CPPDD interval for the Argentinean and French families. Sex-averaged distances between markers are shown in centromeres.

reported here is somewhat different from that reported for other CPPDD families for which linkage analysis has been performed. In a large New England family in which linkage to chromosome 8q was noted, it was unclear whether CPPD deposition that progressed to degenerative joint disease was the primary event causing the disease or whether the degenerative changes in cartilage resulting from osteoarthritis enhanced the deposition of calcium-containing crystals (Baldwin et al. 1995). In a British kindred with chondrocalcinosis linked to chromosome 5p, the most likely candidate interval maps just distal to that specified by our families. Once again, however, the disease phenotype in this family is different from that displayed by our two families in that all affected individuals in the British kindred also experienced recurrent childhood seizures (Hughes et al. 1995). No such seizures were reported for any members of the two families that we studied. There still remain several families in the clinical literature whose phenotypes are very similar to those observed in the French and Argentinean families that we describe. In particular, a large kindred from Tunisia has been studied in which the clinical pattern of disease somewhat resembles that found in our families (Hamza et al. 1992). The phenotype in this family is also inherited as an autosomal dominant trait with somewhat reduced penetrance; however, no linkage analysis has yet been undertaken. The study of this family and other families with evidence of crystal deposition that precedes degenerative joint changes would make valuable additions to the study of the genetics of familial CPPDD.

The frequency of CPPDD in the general population is estimated to be ~10% (Felson et al. 1989; Sanmarti et al. 1993); however, this figure includes all types of chondrocalcinosis, including the type that occurs subsequent to late-stage osteoarthritis. The frequency of CPPDD in this context may be >50% among patients aged >80 years. Although the candidate gene that causes familial CPPDD as described here may not be wholly responsible for calcium deposition in the sporadic and more common forms of CPPDD, a knowledge of the biochemistry of crystal deposition in heritable CPPDD

may lead to a better understanding of mechanisms of calcium deposition in advanced osteoarthritis and other metabolic disorders.

Notes added in proof: Subsequent to the submission of this manuscript, additional members of the French family underwent genotype analysis. These members included one affected sibling of members VII-1 and VII-2 of family B. A recombination between the markers D5S416 and D5S2114 was revealed in this new member, such that his disease haplotype encompassed the region telomeric to marker D5S2114. Furthermore, the EST database has been updated and additional ESTs have been mapped to the candidate interval described in this report.

Acknowledgments

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

dbEST, http://www.ncbi.nlm.nih.gov/dbEST (for EST in the chondrocalcinosis candidate interval and for markers)

GenBank, http://www.ncbi.nlm.nih.gov/Web/Genbank/ (for polymorphic marker information)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/omim (for CPPDD phenotypes with linkage to the 5p15 region on the short arm of chromosome 5 [MIM 118600] and with linkage to a locus on the long arm of chromosome 8 [MIM 600668])

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