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Report

Mapping of Autosomal Dominant Osteopetrosis Type II (Albers-Schönberg Disease) to Chromosome 16p13.3

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The osteopetroses are a heterogeneous group of conditions characterized by a bone-density increase due to impaired bone resorption. As well as the two or more autosomal recessive types, two autosomal dominant forms of osteopetrosis, differentiated by clinical and radiological signs, are described. Autosomal dominant osteopetrosis (ADO) type II, also known as "Albers-Schönberg disease," is characterized by sclerosis, predominantly involving the spine (vertebral end-plate thickening, or Rugger-Jersey spine), the pelvis ("bone-within-bone" structures), and the skull base. An increased fracture rate can be observed in these patients. By linkage analysis, the presence, on chromosome 1p21, of a gene causing ADO type II was previously suggested. However, analysis of further families with ADO type II indicated genetic heterogeneity within ADO type II, with the chromosome 1p21 locus being only a minor locus. We now perform a genomewide linkage scan of a French extended family with ADO type II, which allows us to localize an ADO type II gene on chromosome 16p13.3. Analysis of microsatellite markers in five further families with ADO type II could not exclude this chromosomal region. A summed maximum LOD score of 12.70 was generated with marker D16S3027, at a recombination fraction (θ) of 0. On the basis of the key recombinants in the families, a candidate region of 8.4 cM could be delineated, flanked by marker D16S521, on distal side, and marker D16S423, on the proximal side. Surprisingly, one of the families analyzed is the Danish family previously suggested to have linkage to chromosome 1p21. Linkage to chromosome 16p13.3 clearly cannot be excluded in this family, since a maximum LOD score of 4.21 at $\theta = 0$ is generated with marker D16S3027. Because at present no other family with ADO type II has proved to have linkage to chromosome 1p21, we consider the most likely localization of the disease-causing gene in this family to be to chromosome 16p13.3. This thus reopens the possibility that ADO type II is genetically homogeneous because of a single gene on chromosome 16p13.3.

Bone turnover is a highly regulated phenomenon that involves bone resorption by osteoclasts and bone formation by osteoblasts. Sclerosing bone disorders thus result from either an excess of bone formation or a defect of bone resorption or, in some conditions, a combination of both. The osteopetrosis group encompasses >20 forms of mammalian diseases, including ⩾4 human forms (Shapiro 1993; Felix et al. 1996). Some genes underlying different types of human osteopetrosis have been identified. Recessive osteopetrosis with renal tubular acidosis (MIM 259730) results from a mutation in the gene encoding carbonic anhydrase type II (Sly et al. 1983), and malignant recessive osteopetrosis can be due to mutations either in the *TCIRG1* gene (MIM 604592)—encoding the α3 subunit of the vacuolar proton pump (Frattini et al. 2000; Kornak et al. 2000)—or in the *CLCN7* gene (MIM 602727)—encoding an osteoclast-specific chloride channel (Kornak et al. 2001).

The autosomal dominant form generally presents with a milder phenotype and is therefore also known as the "benign" type. On the basis of radiological and clinical differences, two subtypes have been recognized (Andersen and Bollerslev 1987; Bollerslev and Andersen 1988). Autosomal dominant osteopetrosis (ADO) type II (MIM 166600) was the first type of osteopetrosis recognized, as described—as early as 1904—by Albers-Schönberg

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(1904). In other types of osteopetrosis, the phenotype is an inherited sclerosing bone disorder that involves a bone-resorption defect (Bollerslev 1989). Clinical manifestations of ADO type II are dominated by long-bone fractures, which occur, with or without trauma, in ⩽75% of the patients (Bénichou et al. 2000*b*). Other classic manifestations of ADO type II include hip osteoarthritis, facial nerve palsy, and mandibular osteomyelitis. Many patients undergo several orthopedic procedures that are often complicated owing to the hardness and the brittleness of their skeletons. However, 20%–40% of the patients remain asymptomatic (Bollerslev 1989; Bénichou et al. 2000*b*). The estimated prevalence of ADO type II is from 0.2/100,000, in Brazil, to 5.5/100,000, in Denmark (Salzano 1961; Bollerslev 1987). Skeletal alterations of patients with ADO type II are often so dramatic that the diagnosis is usually easy to ascertain by standard radiographs. These demonstrate a sclerosis that predominates in several sites, including the spine (vertebral end-plate thickening, or Rugger-Jersey spine), the pelvis ("bone-within-bone" structures), and the skull base (fig. 1). However, the radiological penetrance is only 60%–90% (Bollerslev 1987; Bénichou et al. 2000*a*).

The genes involved in the dominant types of osteopetrosis are not yet known, but the gene underlying ADO type I has been assigned to chromosome 11q12-13 (Van Hul et al. 2000), precisely in the region where a high-bone-mass syndrome has been localized (Johnson et al. 1997). For ADO type II, we previously reported a gene localization to chromosome 1p21 (Van Hul et al. 1997), after genotyping a Danish extended family by use of markers surrounding the macrophage-specific colony-stimulating factor (MCSF) gene (MIM 120420). However, the gene encoding MCSF was excluded by mapping the gene outside the candidate region. It has since been reported, however, that ADO type II was not linked to 1p21 in five other families with ADO type II (White et al. 1999; Bénichou et al. 2000*a*, and in press). In two remaining families, linkage with this chromosomal region could not be excluded, but these families were too small for conclusive results to be obtained (Bénichou et al. 2000*a*). These results already had suggested that 1p21 is only a minor locus in ADO type II.

To search for other loci involved in ADO type II, we undertook a linkage study of five French families (A–E) and one Danish family (F). These families have all been described elsewhere: family A by Bénichou et al. (in press), families B–E by Bénichou et al. (2000*a*), and family F by Bollerslev (1987). The diagnosis of ADO type II was ascertained by standard radiographs of the spine and of the pelvis. In some individuals, bone-mineral densitometry also was used to define the osteopetrotic phenotype (Bénichou et al., in press). If there were indica-

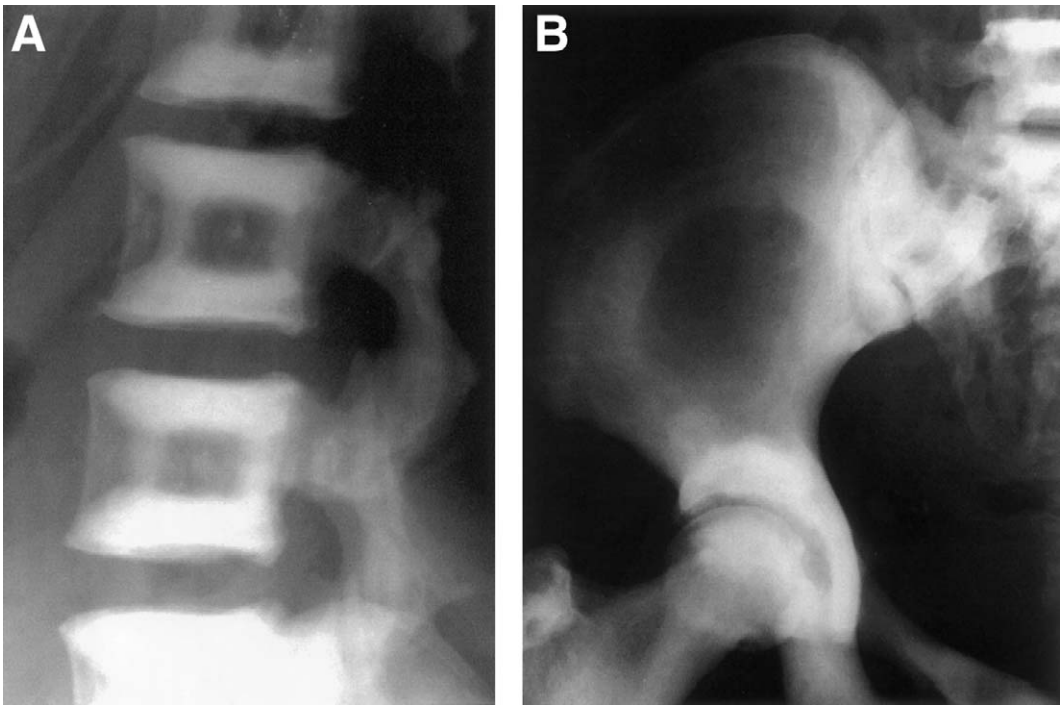


Figure 1 Radiological features of female patient CII-2 at age 45 years. *A*, Lumbar-spine standard radiograph showing thickened and sclerotic vertebral end plates. This feature, usually named "Rugger-Jersey spine," is characteristic of ADO type II. *B*, Pelvic-front standard radiograph with bone-within-bone sign—usually consisting of concentric bands of sclerosis in round and flat bones, especially in the iliac wings.

tions of ADO type II in any of these three analyses, the individual was considered to be affected.

In the six pedigrees, 114 family members, including 40 affected subjects, were willing to participate in the study, after written, informed consent was obtained. Blood samples were collected from all of the participants, for DNA extraction. The study was conducted in accordance with the precepts of the Declaration of Helsinki, after agreement by a local medical-ethics committee.

Genomic DNA was isolated from fresh leukocytes, by standard techniques. The Co-operative Human Linkage Centre Human Screening Set (Weber version 6) was used in a genomewide linkage study of family A. This set contains 391 fluorescently labeled, highly polymorphic markers, with an average spacing of 10 cM, covering the entire human genome. The markers were analyzed by an automated sequencing apparatus (model 377; Applied Biosystems). Extra markers for regions of interest were chosen from the Généthon linkage map (Dib et al. 1996). These were analyzed by either radioactive-isotope labeling or 5′–infra red dye (IRD) labeling. In the first approach, radioactive end-labeling of one oligonucleotide was performed, with T7 polynucleotide kinase, prior to PCR. Amplification products were separated, according to size, on a 6% polyacrylamide gel and were analyzed after autoradiography. In the second approach, one of the primers is synthesized with an M13 forward or reverse sequence on the 5′ end. An IRD-labeled (800 nm) M13 primer is included in the PCR reaction and is incorporated from the second cycle, thus labeling the PCR product. Gel electrophoresis and pattern visualization were performed by a LI-COR model 4200 DNA analyzer Gene Readir (Westburg).

Two-point LOD scores were calculated by MLINK version 5.1 (Lathrop and Lalouel 1984). The disease frequency was set at 1/100,000. An autosomal dominant mode of inheritance was assumed, with a disease penetrance of 70%. Allele frequencies were set at $1/n$, where n is the number of observed alleles.

The pedigrees are shown in figure 2. All affected subjects from families B–F displayed typical clinical and radiological manifestations of ADO type II (Bollerslev 1987; Bénichou et al. 2000*a*). In family A, manifestations were milder, as described elsewhere (Bénichou et al., in press). Clinical manifestations were less frequent in this family than in the other families, although the proband had already sustained three fractures at age <15 years (Bénichou et al., in press). In four of nine affected subjects in family A, the classic radiological sign described as vertebral end-plate thickening was absent or doubtful. In these subjects, the diagnosis was made on the basis of either the presence of bone-within-bone sign, especially in iliac wings or femoral heads, or a very high spinal and femoral bone-mineral density dual X-ray absorptiometry (DXA; z score >4 SD).

In family A, linkage analysis throughout the whole genome excluded >50% of the human genome. D16S423 was the marker most suggestive for linkage, with a maximum LOD score of 3.73 at a recombination fraction (θ) of 0 (table 1). To confirm these data, extra markers from this region were analyzed. The maximum LOD score of 4.05 at $\theta = 0$ was obtained with markers D16S3082 and D16S3027 (table 1), confirming the linkage between ADO type II and this chromosomal region, in family A. Analysis of four other French families (families B–E) illustrated cosegregation between a chromosome 16p13.3 haplotype and ADO type II in each of these families (fig. 2). The LOD scores obtained in family B are conclusive—that is, >3—for two markers (table 1). The restricted size of families C–E, however, makes impossible conclusive assignment in these families. Finally, we analyzed the Danish family (family F), which previously had been shown to have linkage to chromosome 1p21. Unexpectedly, a chromosome 16p13.3 haplotype cosegregating with ADO type II was found also in this family, generating significant positive LOD scores for several markers (table 1). In family F, the maximum LOD score of 4.21 was obtained with marker D16S3027, at $\theta = 0$. These results are comparable with those obtained with chromosome 1 markers, with a maximum two-point LOD score of 3.65, for marker D1S495, increasing to 4.09 in multipoint analysis (Van Hul et al. 1997). There are two ways in which these results can be explained. First, cosegregation between a disease and, simultaneously, two chromosomal regions can occur under a digenic model. In our case, this explanation is very unlikely, since—aside from the fact that the majority of the other families with ADO type II do not have linkage to chromosome 1p21—the reoccurrence rate in family F is ~50%, whereas under a digenic model only 25% is expected. Therefore, the second and more likely explanation is that one of the two suggestions for linkage is due only to incidental cosegregation. Several at-risk individuals (FII-6, FIII-8, FIII-29, and FIII-36) without any clinical or radiological signs of the disease, inherited the affected haplotype for only one of the two chromosomal regions. However, owing to the reduced penetrance, this does not provide a clear indication as to which of the two assignments might be spurious. Given that, thus far, conclusive evidence for genetic linkage to chromosome 1p21 could be obtained only in family F—whereas, in this study, cosegregation between ADO type II and chromosome 16p13.3 was observed in all families—we clearly favor the hypothesis that 16p13.3 is the gene locus in family F also.

The delineation of the candidate region for the ADO type II gene is based on recombination events that occur in the families. Because of the reduced penetrance of ADO type II, only those recombinants that occurred in affected individuals can be taken into account. Since, at

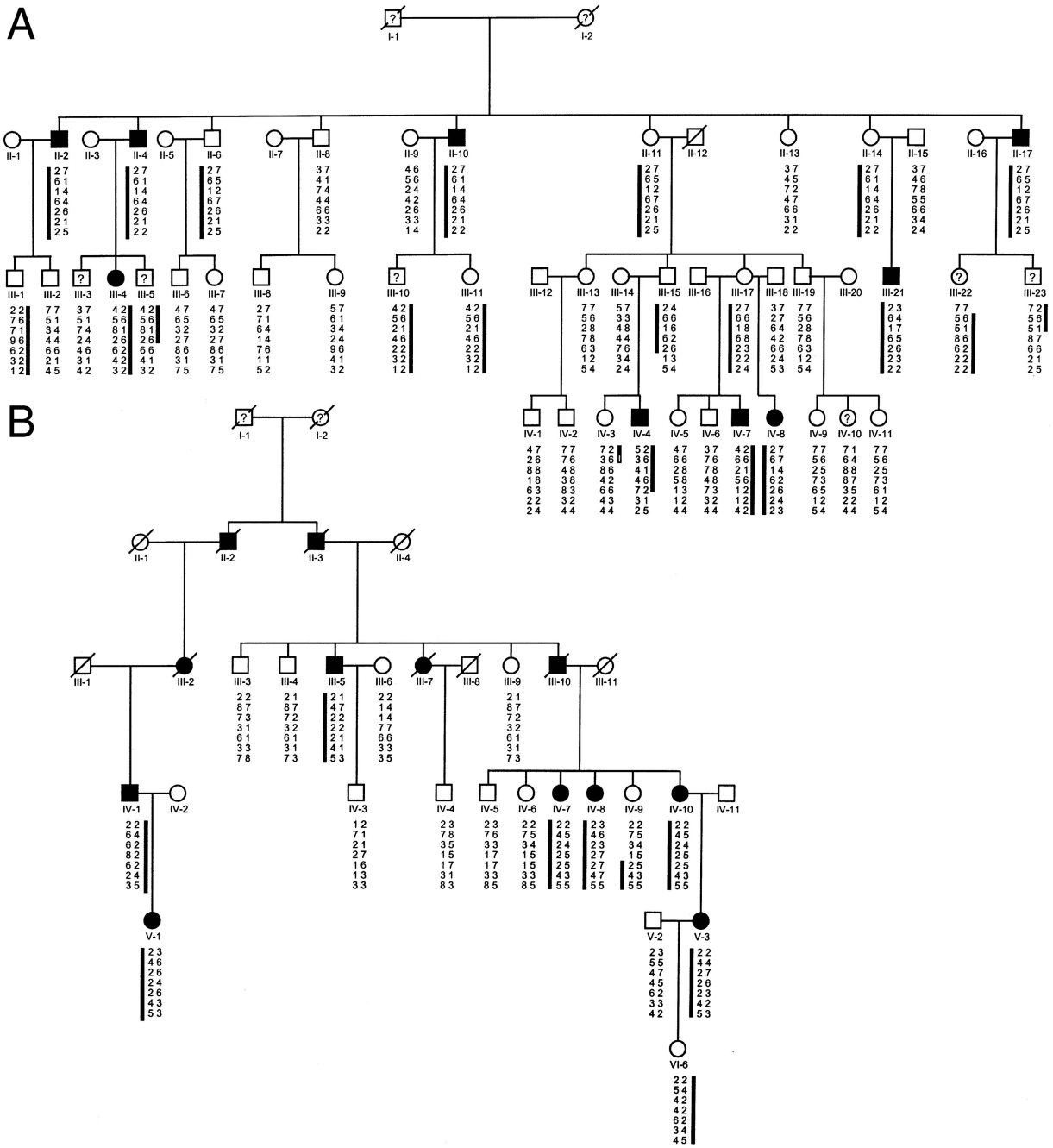
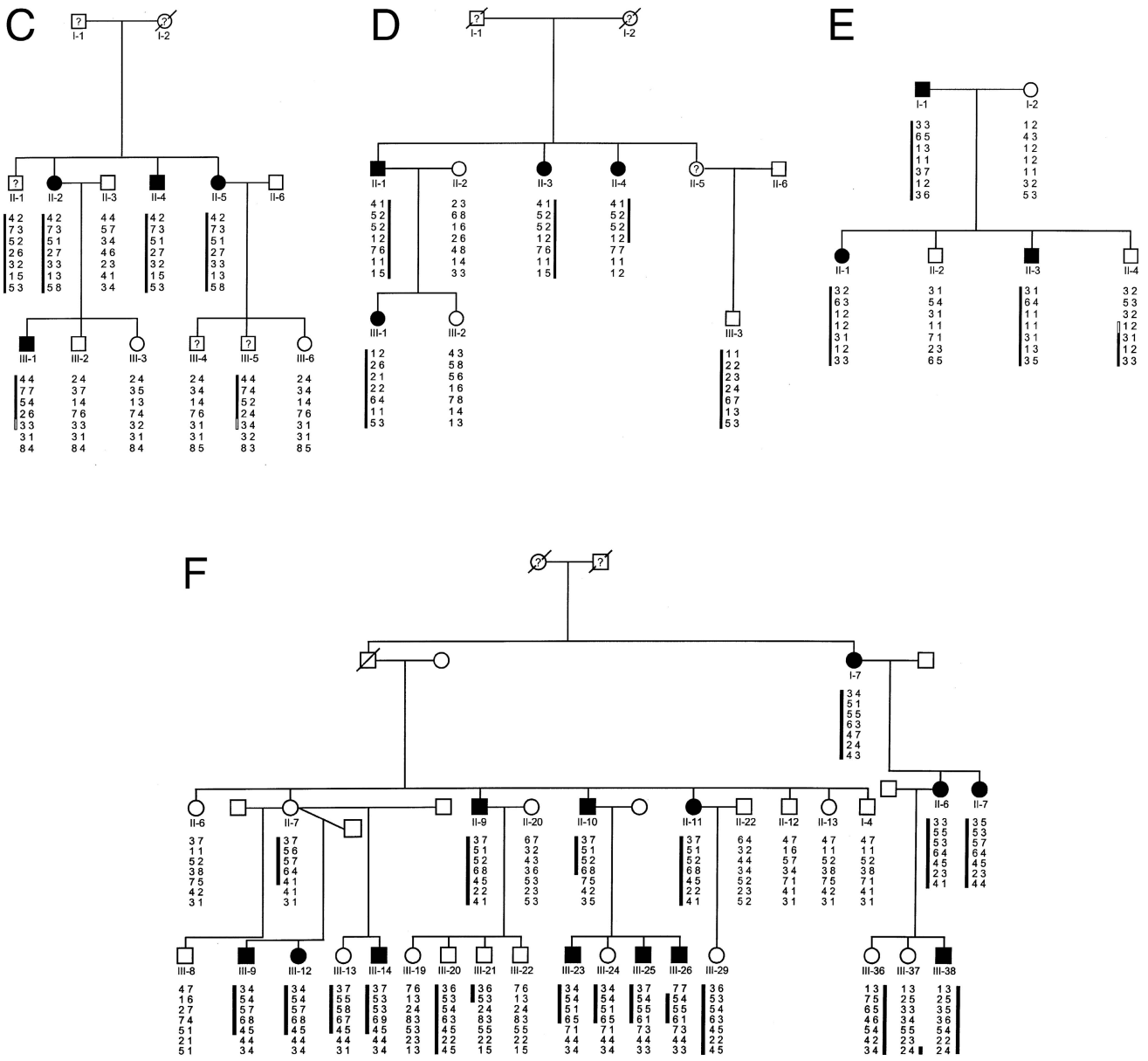


Figure 2 *A–F,* Pedigrees of families A–F, respectively. Squares represent males, and circles represent females. Blackened symbols indicate affected individuals, and unblackened symbols indicate individuals without clinical or radiological signs. The haplotypes from the chromosome 16p13.3 markers are shown below the symbols. The order of the seven markers analyzed is, from telomere (*top*) to centromere (*bottom*), D16S521, D16S3024, D16S3082, D16S3027, D16S423, D16S3030, and D16S3128. Blackened bars indicate the haplotype that cosegregates with the disease.

this point, genetic heterogeneity for ADO type II cannot be excluded, the most conservative approach is to include only those families who have been proved to be linked (i.e., families A and B). On the telomeric side, no recombinant is present, whereas, on the proximal side, marker D16S3030 is recombining in individuals AIII-15 and AIV-4, an obligate carrier and his affected son, respectively (fig. 3). This delineates a candidate region of 10.6 cM, starting from 16pter. As discussed above, we favor the possibility that the linkage results obtained in family F, with markers from chromosome 16p13.3, reflect the real gene assignment. On the basis of this as-



sumption, recombinations in individual FIII-26 enable us to narrow the candidate region to 8.4 cM between markers D16S423 and D16S521 (fig. 3). A recombination event in the candidate region seen in family B (individual BIV-9), cannot, at this point, contribute to the delineation of the candidate region, since this individual is unaffected; however, this might be due to nonpenetrance. To further narrow the candidate region, we looked for (partial) haplotypes shared among the affected individuals from different families, assuming that some of them might be related, although we were not able to find any evidence of this (data not shown).

Since the candidate region delineated for ADO type II still is of respectable size, it includes a large number of genes. Of the genes currently assigned to this chromosomal region, two in particular are definitely to be considered as candidate genes for ADO type II. The first is the *CLCN7* gene, which encodes a chloride-channel protein that is highly expressed in osteoclasts and in which mutations recently have been found in a child with malignant recessive osteopetrosis (Kornak et al. 2001). The function of this protein is to provide chloride conductance, which is obligatory for efficient proton pumping to generate the acidic extracellular environment necessary

Table 1

Pairwise LOD Scores between ADO Type II and Seven Chromosome 16p13.3 Markers

Marker and Family	LOD Score At θ = 0	.01	.05	.10	.20	.30	.40	For Affecteds Only (θ=0)
D16S521:								
A	3.53	3.48	3.29	3.01	2.36	1.57	.65	
B	.35	.35	.31	.27	.19	.12	.06	
C	.94	.92	.82	.70	.46	.23	.06	
D	.29	.29	.28	.26	.19	.10	.03	
E	.00	.00	.00	.00	.00	.00	.00	
F	−2.04	.44	1.09	1.29	1.25	.93	.44	
Total	3.07	5.48	5.79	5.53	4.45	2.95	1.24	
D16S3024:								
A	2.34	2.31	2.20	2.03	1.59	1.02	.36	1.78
B	3.19	3.13	2.87	2.54	1.86	1.15	.46	1.54
C	.98	.96	.86	.73	.48	.25	.07	.48
D	.29	.29	.28	.26	.19	.10	.03	.48
E	.68	.66	.60	.52	.36	.19	.06	.30
F	3.17	3.13	2.99	2.77	2.23	1.53	.71	3.05
Total	10.65	10.48	9.80	8.85	6.71	4.24	1.69	7.63
D16S3082:								
A	4.05	3.99	3.75	3.41	2.66	1.76	.75	2.28
B	2.76	2.71	2.50	2.21	1.61	.96	.32	1.23
C	1.00	.98	.88	.75	.50	.26	.08	.48
D	.38	.37	.35	.31	.21	.11	.03	.48
E	.68	.66	.60	.52	.36	.19	.06	.30
F	1.29	1.28	1.26	1.20	1.01	.73	.40	1.93
Total	10.16	9.99	9.34	8.40	6.35	4.01	1.64	6.70
D16S3027:								
A	4.05	3.99	3.74	3.41	2.65	1.75	.74	2.69
B	3.06	3.01	2.77	2.45	1.78	1.07	.37	1.53
C	1.00	.98	.88	.75	.50	.26	.08	.48
D	.38	.37	.35	.31	.21	.11	.03	.48
E	.00	.00	.00	.00	.00	.00	.00	.00
F	4.21	4.16	3.93	3.62	2.87	1.99	.95	3.56
Total	12.70	12.51	11.67	10.54	8.01	5.18	2.17	8.74
D16S423:								
A	3.73	3.67	3.41	3.07	2.30	1.44	.54	
B	2.41	2.37	2.21	1.98	1.49	.95	.40	
C	.14	.13	.11	.09	.05	.03	.01	
D	−3.19	−1.15	−.50	−.25	−.06	.00	.01	
E	.15	.15	.14	.13	.09	.04	.01	
F	−2.73	1.84	2.37	2.41	2.09	1.51	.74	
Total	.51	7.01	7.74	7.43	5.96	3.97	1.71	
D16S3030:								
A	−1.11	.85	1.40	1.48	1.28	.86	.33	
B	2.67	2.62	2.43	2.17	1.60	.98	.38	
C	−3.90	−1.18	−.53	−.29	−.11	−.04	−.01	
D	.41	.40	.36	.31	.21	.11	.03	
E	.15	.15	.14	.13	.09	.04	.01	
F	−2.63	−.09	1.12	1.45	1.45	1.08	.55	
Total	−4.41	2.75	4.92	5.25	4.52	3.03	1.29	
D16S3128:								
A	−1.85	.13	.71	.86	.81	.60	.34	
B	2.09	2.06	1.90	1.69	1.21	.69	.20	
C	−3.90	−1.18	−.53	−.29	−.11	−.04	−.01	
D	−3.35	−1.13	−.63	−.34	−.10	−.01	.01	
E	.15	.15	.14	.13	.09	.04	.01	
F	−2.93	−.34	.91	1.31	1.38	1.0	.57	
Total	−9.79	−.31	2.50	3.36	3.28	2.35	1.12	

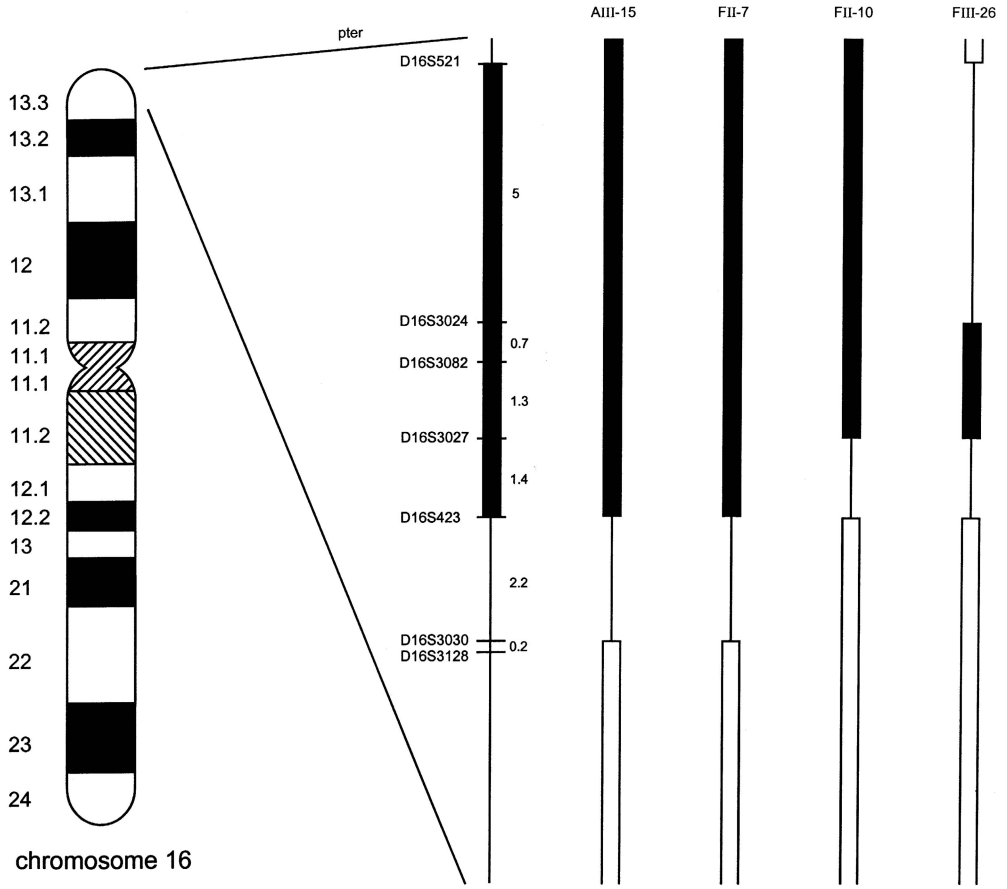


Figure 3 Ideogram of chromosome 16 and genetic map of markers used to delineate candidate region. The candidate region is shown as a blackened bar on the first vertical line, and the intermarker distances (in cM) are given. On the other vertical lines, blackened bars indicate those regions that cosegregate, and unblackened bars indicate regions that recombine and that therefore cannot contain the disease gene. The lines between rectangles indicate uninformative regions.

for the degradation of bone tissue. This proton pumping is performed by a vacuolar H^+-ATPase protein complex comprising 13 subunits. The gene encoding the $\alpha 3$ subunit of this protein complex has been shown to be mutated in a subset of patients with recessive osteopetrosis (Frattini et al. 2000; Kornak et al. 2000). Since the gene encoding another subunit (ATP6L [MIM 108745]) of the vacuolar H^+-ATPase protein complex is located in the region, on chromosome 16p13.3, delineated for ADO type II (Gillespie et al. 1991), this gene needs to be considered as a candidate disease gene also.

In conclusion, we have provided evidence that a major gene for ADO type II is on chromosome 16p13.3. Moreover, analysis of what is thus far the only family with ADO type II assigned to chromosome 1p21 indicates that this previous assignment might be due only to incidental cosegregation and that ADO type II might still be genetically homogeneous because of a single, still-unidentified gene on chromosome 16p13.3. Identification of this gene will definitely provide further insight into the processes of bone metabolism—more specifically, that of bone resorption.

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Electronic-Database Information

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

Généthon, http://www.genethon.fr/ (for extra markers for regions of interest)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for ADO type II [MIM 166600], ATP6L [MIM 108745], *CLCN7* [MIM 602727], osteopetrosis with renal tubular acidosis [MIM 257920], MCSF [MIM 120420], and *TCIRG1* [MIM 604592])

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