Am. J. Hum. Genet. 75:310–317, 2004

Report

Autosomal Dominant Avascular Necrosis of Femoral Head in Two Taiwanese Pedigrees and Linkage to Chromosome 12q13

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Avascular necrosis of the femoral head (ANFH) is a debilitating disease that commonly leads to destruction of the hip joint in adults. The etiology of ANFH is unknown, but previous studies have indicated that heritable thrombophilia (increased tendency to form thrombi) and hypofibrinolysis (reduced ability to lyse thrombi), alcohol intake, and steroid use are risk factors for ANFH. We recently identified two families with ANFH showing autosomal dominant inheritance. By applying linkage analysis to a four-generation pedigree, we excluded linkage between the family and three genes related to thrombophilia and hypofibrinolysis: protein C, protein S, and plasminogen activator inhibitor. Furthermore, by a genomewide scan, a significant two-point LOD score of 3.45 (recombination fraction [θ] = 0) was obtained between the family with ANFH and marker D12S85 on chromosome 12. High-resolution mapping was conducted in a second family with ANFH and replicated the linkage to D12S368 (pedigree I: LOD score 2.47, $\theta = 0.05$; pedigree II: LOD score 2.81, $\theta = 0.10$). When an age-dependent–penetrance model was applied, the combined multipoint LOD score was 6.43 between D12S1663 and D12S85. Thus, we mapped the candidate gene for autosomal dominant ANFH to a 15-cM region between D12S1663 and D12S1632 on chromosome 12q13.

Avascular necrosis of the femoral head (ANFH) is a debilitating disease that usually leads to destruction of the hip joint in the 3rd to 5th decade of life (average age 36 years) (Mont and Hungerford 1995). As a clinical entity, the disease is characterized by progressive pain in the groin, mechanical failure of the subcondral bone, and degeneration of the hip joint. ANFH represents a specific form of the broader disease category of osteonecrosis. Although ANFH shares with osteonecrosis the same histopathological features and possibly the same etiology, the affected tissue is restricted to the hip joints in ANFH (see the work of Assouline-Dayan et al. [2002] for a review of osteonecrosis). The disease prevalence is unknown, but it has been estimated that 10,000–20,000 new cases are diagnosed in the United States each year (Mankin 1992; Mont and Hungerford 1995). Nearly half of the patients eventually require hip replacement before 40 years of age.

It has been suggested that a common pathogenesis pathway of ANFH involves the interruption of blood circulation to the anterior-superior-lateral part of the femoral head, leading to ischemic insult and bone collapse (Atsumi and Kuroki 1992). The disease is aggravated by mechanical disruption (e.g., hip fracture [Bachiller et al. 2002]), external pressure on or damage to a vessel wall (e.g., vasculitis [Wang et al. 1988], radiation therapy [Massin and Duparc 1995], and systemic lupus erythematosus [Abu-Shakra et al. 2003]), arterial thrombosis or embolism (e.g., sickle-cell disease [Milner et al. 1991], corticosteroid use [Fisher 1978], and alcohol abuse

Received March 26, 2004; accepted for publication May 11, 2004; electronically published June 3, 2004.

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0002-9297/2004/7502-0016$15.00

[Wang et al. 2003]), and venous or blood outflow occlusion (e.g., infection [Benjamin and Khan 1994]). In addition, other pathophysiological mechanisms and etiological factors are postulated to be associated with ANFH. Legg-Calve-Perthes disease (LCP [MIM 150600]) is characterized by loss of circulation to the femoral head, resulting in avascular necrosis in a growing child. Clinical pictures of the disease vary, depending on the phase of disease progression through ischemia, revascularization, fracture and collapse, and repair and remodeling of the bone. The disease occurs more frequently in boys, and most patients tend to be shorter than their peers. Both familial and isolated cases of LCP have been reported.

Although a major proportion of individuals with ANFH have underlying risk factors and are classified as having secondary ANFH, 15%–30% of patients showing no apparent risk factors are classified as having primary or idiopathic ANFH (Assouline-Dayan et al. 2002). It has been proposed that many cases of ANFH previously considered idiopathic actually are associated with heritable thrombophilia (an increased tendency for intravascular thrombosis) or hypofibrinolysis (a reduced ability to lyse thrombi) (Glueck et al. 1997, 2001; Jones et al. 2003). Deficiency of antithrombotic protein C or protein S, resulting in thrombophilia, has been reported to be associated with osteonecrosis of the hip (Glueck et al. 1997) and of the jaws (Glueck et al. 1996*b*) in adults and with LCP in children (Glueck et al. 1994*b*). On the other hand, hypofibrinolysis, mediated by high levels of plasminogen activator inhibitor (PAI), has been cited as a major cause of idiopathic osteonecrosis (Glueck et al. 1994*a*). Familial protein C and protein S deficiencies and high levels of PAI are transmitted as autosomal dominant traits (Glueck et al. 1993, 1994*c*, 1996*a*; Pierre-Jacques et al. 1997). The three genes have been mapped on chromosome 2q13-q14 (protein C gene) (Patracchini et al. 1989), chromosome 3q11.1-q11.2 (protein S gene) (Watkins et al. 1988), and chromosome 7q21.3-q22 (PAI gene) (Klinger et al. 1987).

Although most cases of idiopathic ANFH are sporadic, we recently identified two multiplex families with ANFH that showed an autosomal dominant mode of inheritance. Both families were from Taiwan. Affected individuals were identified by clinical and radiological examination. The radiographic stage of osteonecrosis of the femoral head was graded according to the Ficat classification system (Ficat 1985). Initially, clinical and genetic analyses of familial ANFH were focused on pedigree I. Of 75 subjects in the family, 5 males and 11 females were affected with idiopathic ANFH, including 2 twin sisters (fig. 1*A*). In this pedigree, the mode of inheritance was apparently autosomal dominant. Of the 12 patients whose clinical data and DNA were available for this study, the average age at onset was 26 years (range 15–48 years). Index patients and affected relatives from the family presented with symptoms of pain in the groin, and physical examination revealed that they had average height and normal appearance in the musculoskeletal system; there was no sign of chondrodysplasia in the patients. The twins showed no evidence of systemic lupus erythematosus, sickle-cell disease, or Gaucher disease. Furthermore, except for individual II-9, the patients were not alcohol users. With the use of the Ficat index, seven patients were graded as stage IV and five as stage II. Subsequently, another family affected with ANFH also was identified, and the two pedigrees were not related to each other. As shown in figure 1*B*, the second family with ANFH (designated "pedigree II") included 77 members in four generations. Among them, 16 (8 males and 8 females) were affected with ANFH, with an age at onset of 12–37 years.

Three genes associated with thrombophilia and hypofibrinolysis were investigated by linkage analysis to identify the pathoetiologic association of heritable coagulation disorders with idiopathic ANFH in pedigree I. Markers D2S410, D2S347, D2S1328, D2S368, and D2S1334, spanning 19.9 cM, were selected for the protein C gene region. Markers D3S4529, D3S1271, and D3S2459 covered a 6.6-cM distance for the protein S gene. The PAI gene, residing on chromosome 7q21.3-q22, was investigated by use of the markers D7S657, D7S821, D7S515, and D7S1799, spanning 9.1 cM.

Two-point LOD scores were calculated for markers near the protein C, protein S, and PAI genes, at a variety of recombination fractions. LOD scores <-2.0 were observed at small recombination fractions ($\theta \leqslant 0.01$) for all the markers and were still negative, even at higher recombination fractions ($\theta = 0.40$), for most markers (data not shown). Furthermore, multipoint linkage results, yielded by the LINKMAP program (Lathrop et al. 1985), also showed negative LOD scores ranging from -1.21 to -21.99 for the protein C gene, -5.65 to -14.81 for the protein S gene, and -2.26 to -11.14 for the PAI gene (data not shown). By use of the criterion of a LOD score <-2, the results from the two-point and multipoint linkage analyses provided evidence for the exclusion of these genes as candidates for idiopathic ANFH in this family.

We then conducted a genomewide scan for linkage analysis in pedigree I. A significant two-point LOD score of 3.45 was found for the marker D12S85, and nearby markers also showed positive LOD scores (data not shown). Furthermore, multipoint linkage analysis revealed significant LOD scores (LOD >3) in an interval of 33 cM spanning the markers D12S345 and D12S326 (data not shown). A peak multipoint LOD score of 4.11 was obtained between the markers D12S83 and D12S326 on chromosome 12q13. No other suggestive or significant LOD scores were observed for markers on the other 21 autosomes.

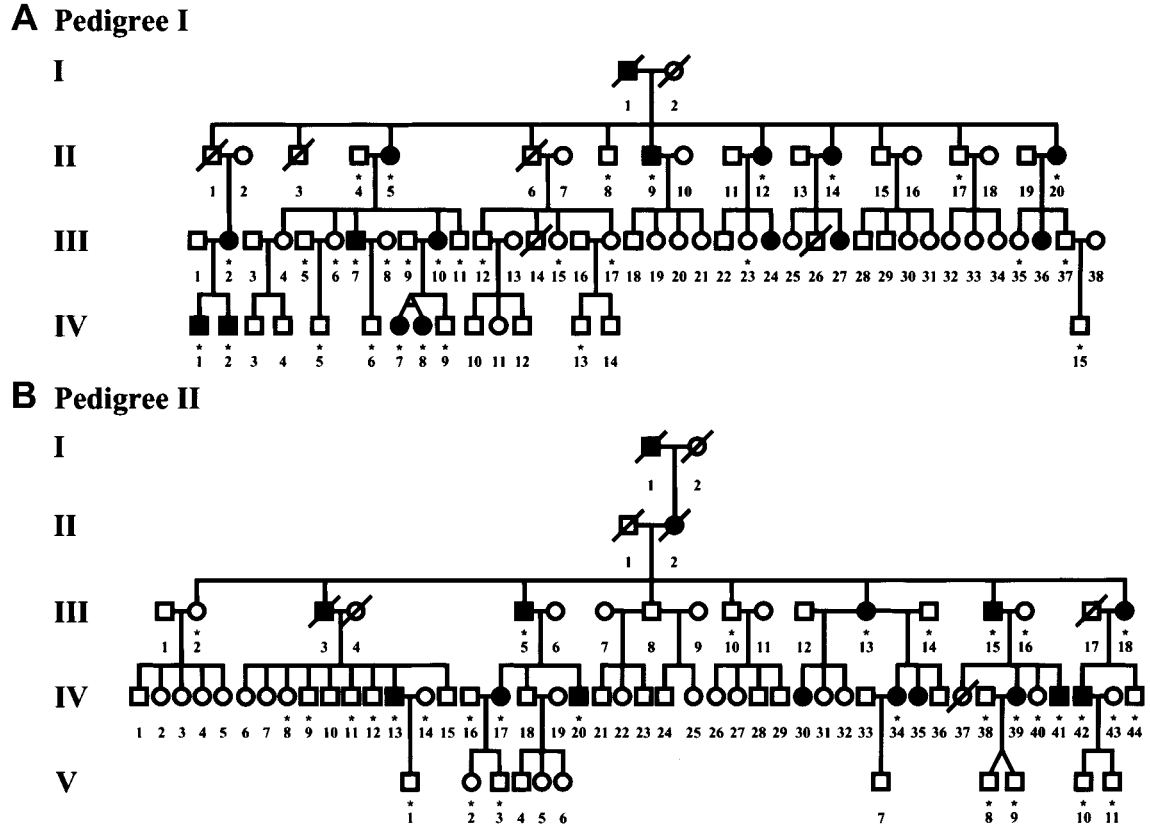

Figure 1 Pedigree structure of the two families with idiopathic ANFH. Individuals whose DNA was available for linkage analysis are indicated by an asterisk (*).

On the basis of the genomewide scan, the chromosome 12q13 region was fine mapped with 29 additional microsatellite markers in pedigree I. Furthermore, we conducted a replication study on pedigree II with 39 chromosome 12 markers. Linkage analysis was performed under two genetic models. Model 1 was a dominant genetic model with a disease-gene frequency of 0.0001 and a constant penetrance of 0.99 for both homozygous and heterozygous individuals. Model 2 was an age-dependent–penetrance dominant model with a disease-gene frequency of 0.0001 and various age-dependent penetrances. The penetrance values were specified as 0, 0.20, 0.80, 0.99, respectively, for the following four age groups (a = age): $a \leq 10$ years, $10 < a \leq 20$ years, $20 < a \leq 30$ years, and $a > 30$ years. Allele frequency for each marker was calculated from 24 unrelated individuals, including founders and married-in individuals in the pedigrees.

Table 1 summarizes the two-point LOD scores under model 1 conditions. We recalculated two-point LOD scores on the basis of the combined allele frequency of the two families, and several markers revealed significant LOD scores (LOD >3) for pedigree I. In the second family with ANFH (pedigree II), a maximum two-point LOD score of 2.81 ($\theta = 0.10$) was found for the marker D12S368, which was located in the same region of significant linkage as in pedigree I. When we combined the results of these two families, these two pedigrees generated a maximum two-point LOD score of 5.22 for the marker D12S368 ($\theta = 0.10$).

By use of the same data set, we conducted multipoint linkage analysis with the chromosome 12 markers. With the two pedigrees combined, a maximum multipoint LOD score of 2.54 was obtained for the interval of D12S368–D12S803 under constant penetrance (model 1) (fig. 2). Considering the age at onset for individuals with this disease, we then performed multipoint linkage analysis under the conditions of age-dependent penetrance (model 2). With this model, a plateau of multipoint LOD scores was observed between markers D12S1663 and D12S1632. A peak LOD score of 6.43 occurred between markers D12S1663 and D12S85. Taking together the results from the two-point and multipoint linkage analyses, we defined the interval between D12S1663 and D12S1632 as the candidate region for ANFH.

Table 1

Two-Point LOD Scores for Chromosome 12 Markers in Two Pedigrees with ANFH

Marker	Position (cM)[a]	Results for Pedigree I		Results for Pedigree II		Total	
		Peak LOD	θ	Peak LOD	θ	Peak LOD	θ
D12S336[b]	19.68	.24	.30	−.27	.40	−.16	.40
D12S310[b]	36.06	.10	.30	−.09	.40	−.02	.40
D12S1617[b]	44.03	1.52	.05	.00	.40	.77	.30
D12S345[b,c]	53.09	.13	.30	NA	...	NA	...
D12S1692	53.28	.80	.20	.44	.20	1.24	.20
D12S1668	55.29	2.36	.00	.14	.30	1.77	.10
D12S1653	56.38	.57	.30	1.53	.20	2.05	.20
D12S1301[d]	56.25	1.37	.10	.09	.30	1.20	.20
D12S1663	56.38	2.09	.00	.13	.20	1.53	.10
D12S85[b]	61.34	2.97	.05	1.01	.20	3.42	.20
D12S1701	62.54	3.00	.05	1.50	.20	4.20	.10
D12S2196	63.89	1.19	.10	−.21	.40	.19	.30
D12S339	64.43	1.81	.10	1.05	.20	2.81	.20
D12S1635	64.96	2.35	.10	1.32	.20	3.36	.20
D12S1677	65.49	1.40	.20	.45	.20	1.85	.20
D12S368[b]	66.03	2.47	.05	2.81	.10	5.22	.10
D12S803	67.63	1.40	.00	1.16	.20	2.02	.20
D12S398	68.16	.00	.10	1.12	.20	1.12	.20
D12S1618	68.16	2.57	.10	−.08	.30	1.89	.20
D12S1586	69.23	2.28	.10	1.48	.20	3.44	.10
D12S1724	69.82	.59	.20	1.33	.20	1.92	.20
D12S1707	69.82	.00	.20	2.62	.00	2.62	.00
D12S1632	71.61	1.86	.00	.17	.30	1.04	.20
D12S1644[d]	72.20	.88	.10	.77	.20	1.41	.20
D12S90	71.61	3.28	.05	.01	.40	2.95	.10
D12S305	74.58	1.21	.10	1.20	.20	2.27	.20
D12S1700[d]	75.76	.01	.40	−.05	.40	−.05	.40
D12S1056	75.17	1.29	.10	.02	.40	.85	.20
D12S1072	75.17	1.79	.10	.19	.30	1.48	.20
D12S83[b,c]	75.17	3.46	.05	NA	...	NA	...
D12S298[d]	74.58	4.45	.00	−.09	.40	2.01	.20
D12S329[d]	74.58	.60	.10	−.21	.40	−.10	.40
D12S1585[d]	74.76	2.72	.05	−.10	.40	1.42	.20
D12S75	76.36	2.23	.05	.00	.30	1.24	.20
D12S313	79.93	1.00	.00	−.16	.40	.12	.30
D12S1680	80.52	3.69	.05	−.39	.40	.94	.20
D12S326[b]	86.40	1.61	.00	−.13	.40	.33	.30
D12S346[b]	104.65	−.05	.40	−.21	.40	−.26	.40
D12S324[b]	147.17	−.27	.40	.05	.40	−.23	.40
D12S1659[b]	155.94	−.05	.40	−.10	.40	−.15	.40
D12S1723[b]	164.63	−.05	.40	.13	.40	.07	.40

[a] Marker position on the Marshfield genetic map (Marshfield Center for Medical Genetics Web site).

[b] Markers used for whole-genome scan.

[c] Markers not analyzed in pedigree II.

[d] Marker ordered according to the NCBI physical map.

In this study, we report two Taiwanese families with idiopathic ANFH that showed an autosomal dominant mode of inheritance. To our knowledge, this is the first study in the literature of multiple pedigrees with idiopathic ANFH. Although genetic factors, such as heritable coagulation disorders, hemoglobinopathies, and lipid-storage diseases (Jones 1997), have been proposed to be associated with osteonecrosis, only one case in which an MZ twin developed an idiopathic ANFH has been described (Nobillot et al. 1994). In fact, nearly all cases of ANFH are sporadic. The availability of these rare pedigrees provides an opportunity to investigate the genetic basis for the development of idiopathic ANFH. Furthermore, the identification of two autosomal dominant families with ANFH from Taiwan—but so far nowhere else—suggests that genetic heterogeneity in ANFH might exist in different populations.

Step-by-step linkage analysis was conducted in the

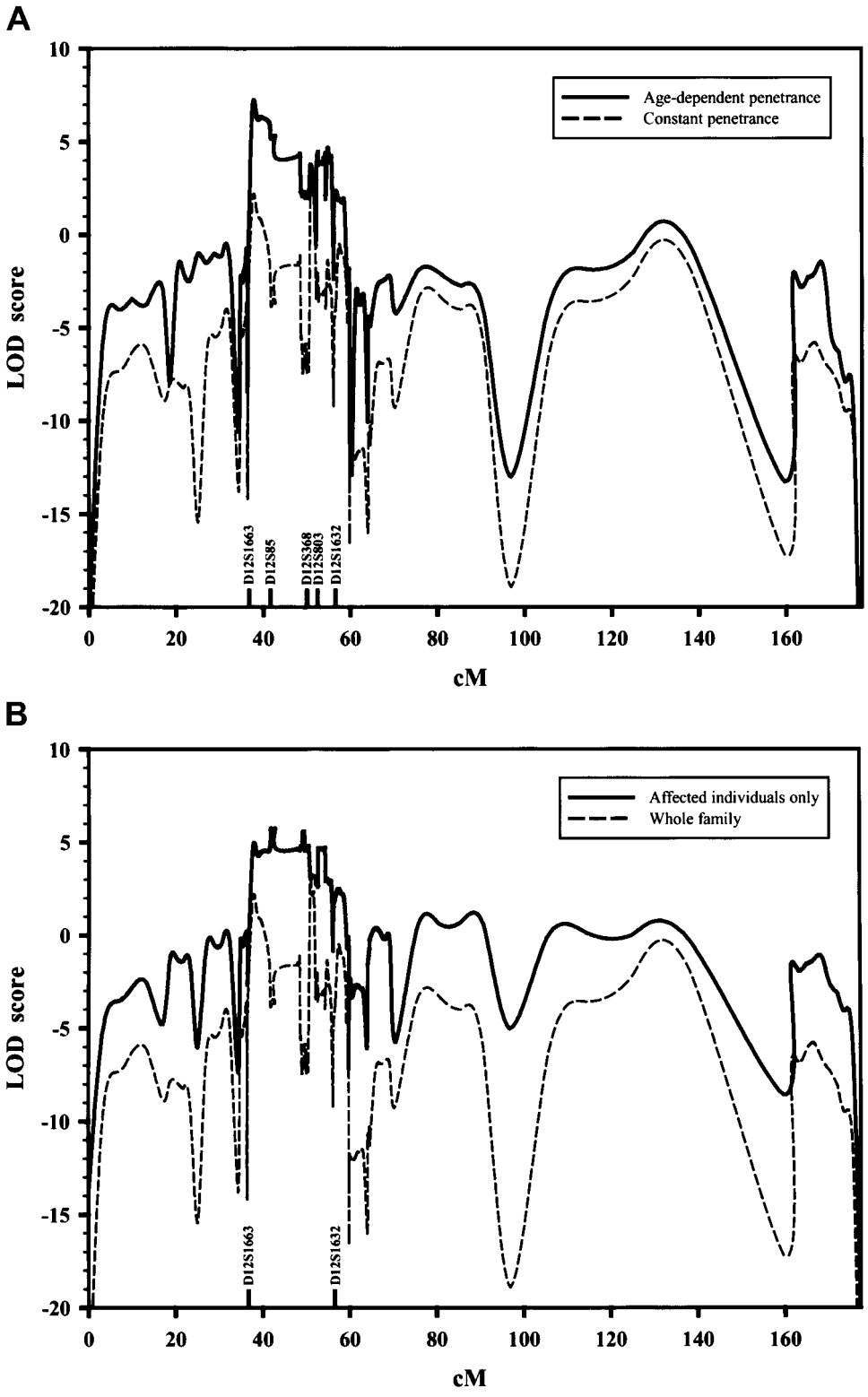

Figure 2 Multipoint linkage analysis of chromosome 12 markers of the pedigrees with ANFH. *A*, Multipoint analysis was applied to the two pedigrees with ANFH under the age-dependent model (*solid line*) and under the constant-penetrance model (*dashed line*). *B*, Multipoint analysis was applied to the two pedigrees with ANFH under the constant-penetrance model, with all family members (*dashed line*) and with affected individuals only (*solid line*). The candidate-gene region for ANFH, between D12S1663 and D12S1632, is indicated.

families with ANFH, to map the chromosomal position of the disease gene. A simulation study showed a probability of 79% to detect a LOD score >3 in pedigree I. Even with this level of power, substantially negative LOD scores were observed for the majority of flanking markers for the protein C, protein S, and PAI genes. This indicates that the exclusion of linkage between these three genes and ANFH is likely genuine. Indeed, a genomewide scan using medium-density STR markers subsequently revealed a significant LOD score of 3.45 ($\theta = 0$) at D12S85 by two-point analysis in one of the families (pedigree I). On this basis, high-resolution mapping was conducted for the candidate region on chromosome 12, and the two-point and multipoint analyses provided evidence that, in the two pedigrees, genetic markers between D12S1663 and D121632 are linked to the disease phenotype.

We observed that, in the families with ANFH, affected individuals typically developed symptoms after age 15 years. Thus, age at onset could critically affect the results of linkage analysis. We took into consideration that the two pedigrees with ANFH include subjects who were <10 years old; therefore, the LOD score was calculated under two different conditions. As shown in figure 2*A*, the LOD score increased significantly on the assumption that the penetrance of familial ANFH is dependent on age. The effect is particularly prominent for the genetic interval that shows significant linkage. In contrast, the enhancement of the LOD score calculated under the age-dependent–penetrance condition is less striking for other chromosomal regions outside the candidate region for ANFH. Although, in some regions, LOD scores became elevated under the age-dependent model, the LOD scores were still below zero.

Considering the possibility that some asymptomatic individuals in the pedigrees with ANFH might bear the mutant allele and that the inclusion of ANFH carriers in calculating the LOD score might obscure the linkage, we conducted a multipoint analysis with the affected individuals only. As shown in figure 2*B*, higher multipoint LOD scores were obtained for nearly all the chromosome 12 markers, but significant linkage was observed only in the interval between D12S1663 and D12S1632. Thus, we conclude that age-dependent linkage reflects a true association of the chromosome 12 region with autosomal dominant ANFH.

With the successful mapping of the ANFH locus to chromosome 12q13, we next considered what genes in the region could be candidate genes. Avascular necrosis has been reported to be associated with a variety of conditions. In trauma, there is a clear association between avascular necrosis and the disruption of the vessels supplying the femoral head. For nontraumatic avascular necrosis, on the other hand, many theories have been proposed to explain the pathogenesis. These include vascular occlusion, altered fat metabolism and fat emboli, intravascular coagulation, the healing process, elevated intracortical pressure, inhibition of angiogenesis, intramedullary hemorrhage, mechanical stress, and primary bone cell death (Assouline-Dayan et al. 2002). In the candidate region for ANFH identified by genetic mapping, there are 248 annotated genes and 150 known genes between D12S1663 and D12S1632 (National Center for Biotechnology Information [NCBI] build 34, version 2). Among them, two closely linked genes, *COL2A1* (MIM 120140) and *VDR* (MIM 601769), deserve scrutiny. The *COL2A1* gene encodes the α1 chain of type II collagen. Mutations of the *COL2A1* gene are associated with a wide spectrum of disorders that are attributed to anomalous expression of the gene in cartilage or in the vitreous humor of the eye (Ahmad et al. 1991; Bonaventure et al. 1995). To our knowledge, there has been no previous report of a *COL2A1* mutation causing ANFH. The *VDR* gene encodes the vitamin D3 receptor that binds $1,25(OH)_2D_3$ and mediates its transcription regulation function through interaction with nuclear targets. Mutations of the *VDR* gene have been reported to cause vitamin D–resistant rickets (Hughes et al. 1988). It is of interest to note that the association of *VDR* gene polymorphisms and bone density has been a subject of intensive study and debate (Hustmyer et al. 1994; Morrison et al. 1994). Furthermore, the *VDR* gene and the *COL2A1* gene appear to be in linkage disequilibrium (Pedeutour et al. 1994). Given the physiological relevance of the genes, they should be considered as possible candidates for ANFH.

In conclusion, our linkage results indicated that a 15-cM region between D12S1663 and D12S1632 might harbor a gene for ANFH. Currently, gene-based mutation detection is under way to identify an ANFH disease gene from the region. We envision that, by isolating the disease gene, it will be possible to further our understanding of the molecular mechanism of ANFH pathogenesis, eventually leading to better management of patients and/or a novel therapeutic regimen for individuals with this degenerative disease.

Acknowledgments

The authors express their gratitude to K. D. Wuu for enthusiastic support of the collaborative research on ANFH and to Richard Yang for critical reading of the manuscript. This project was funded by grants from the National Research Program for Genomic Medicine of the National Science Council (91-3112-B-075-003 to W.-M.C. and 91-3112-P-010-002-Y to K.-J.H.) and intramural grants from the National Health Reasearch Institutes (to S.-F.T.) and Taipei Veterans General Hospital (to W.-M.C.).

Electronic-Database Information

The URLs for data presented herein are as follows:

Entrez Genome, http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi (for map view build 34 and identification of genes in the interval of interest)
Marshfield Center for Medical Genetics, http://research.marshfieldclinic.org/genetics/ (for genetic distance between markers)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for LCP, *COL2A1,* and *VDR*)
UniSTS, http://www.ncbi.nlm.nih.gov/genome/sts/ (for marker sequences and positions)

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