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Localization of the Gene for Sclerosteosis to the van Buchem Disease–Gene Region on Chromosome 17q12–q21

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Summary

Sclerosteosis is an uncommon, autosomal recessive, progressive, sclerosing, bone dysplasia characterized by generalized osteosclerosis and hyperostosis of the skeleton, affecting mainly the skull and mandible. In most patients this causes facial paralysis and hearing loss. Other features are gigantism and hand abnormalities. In the present study, linkage analysis in two consanguineous families with sclerosteosis resulted in the assignment of the sclerosteosis gene to chromosome 17q12-q21. This region was analyzed because of the recent assignment to this chromosomal region of the gene causing van Buchem disease, a rare autosomal recessive condition with a hyperostosis similar to sclerosteosis. Because of the clinical similarities between sclerosteosis and van Buchem disease, it has previously been suggested that both conditions might be caused by mutations in the same gene. Our study now provides genetic evidence for this hypothesis.

Introduction

Sclerosteosis (MIM 269500) is a rare autosomal recessive disorder that is classified, according to Beighton (1988), among the craniotubular hyperostoses. The disorder was first thought to be a variant of osteopetrosis, until Hansen introduced the term "sclerosteosis" in 1967 (Hansen 1967). Sclerosteosis is characterized by bony overgrowth of the skull, the mandible, and the tubular bones, resulting in a very thick calvarium with macrocephaly and an enlarged mandible. The cortices of the long bones are thickened, and vertebral pedicles, ribs, and pelvis are dense. Skeletal deformities do not occur at birth but become noticeable at ~5 years of age and progress steadily thereafter (Nager et al. 1983). Fractures have never been described in patients with sclerosteosis. Recurrent facial-nerve palsy, deafness, and optic atrophy because of narrowing of the cranial foramina are frequent complications. Severe headaches can occur as a result of raised intracranial pressure, which may also lead to sudden death (Beighton et al. 1976; Nager et al. 1983). Additional features of sclerosteosis are excessive height—sometimes even gigantism (Beighton et al. 1984)—and hand abnormalities, including syndactyly of the digits, radial deviation of the terminal phalanges, and dysplastic or absent nails. These hand abnormalities are congenital and make an early diagnosis possible; moreover, they help to differentiate sclerosteosis from other dysplasias in the group of craniotubular hyperostoses.

Stein et al. (1983) performed a pathophysiological analysis and showed a significantly increased bone-formation rate but no osteoclast-related abnormalities. Therefore, they postulated that sclerosteosis is primarily a disorder of osteoblast hyperactivity.

Most patients with sclerosteosis are found in the Afrikaner community in South Africa, with >40 patients described (Beighton et al. 1984). Other cases of sclerosteosis are a kindred in New York (Higinbotham and Alexander 1941), a kindred of mixed ancestry in Maryland (Kelly and Lawlah 1946; Witkop 1961, 1965; Stein et al. 1983), a consanguineous family from Brazil (Paes-Alves et al. 1982), and single patients from Switzerland (Pietruscka 1958), Japan (Sugiura and Yasuhara 1975), Spain (Bueno et al. 1994), and Senegal (Tacconi et al. 1998).

The clinical picture of patients suffering from sclerosteosis closely resembles that of van Buchem disease

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(MIM 239100). Patients with the latter disorder have a generalized increased cortical thickness and an enlarged jaw. The increased thickness of the skull causes facial-nerve palsy and neurological complications because of cranial-nerve entrapment (van Buchem et al. 1976). The radiological findings in patients with van Buchem disease are very similar to those seen in patients with sclerosteosis. The major differences between the two conditions are the gigantism and the hand abnormalities, which are seen in most patients with sclerosteosis but never in patients with van Buchem disease. Beighton et al. (1984) postulated that van Buchem disease and sclerosteosis are allelic conditions, caused by mutations in the same gene. The prevalence of van Buchem disease worldwide is also low, with 15 patients of Dutch origin (Van Buchem et al. 1976; Van Hul et al. 1998), one family with four affected siblings (Dixon et al. 1982), and a few isolated cases (Lopez et al. 1985; Miguez et al. 1986; Fryns and Van der Berghe 1988; Cook et al. 1989; Bettini et al. 1991). In the literature, a diagnosis of van Buchem disease has been made in pedigrees with a mild or asymptomatic autosomal dominant hyperostosis (Maroteaux et al. 1971; Dyson 1972; Lapresle et al. 1976; Owen 1976; Vayssairat et al. 1976; Gelman 1977; Gorlin and Glass 1977; Ruckert et al. 1985; Perez-Vicente et al. 1987; Schendel 1988; Rodriguez et al. 1995), a condition first described by Worth and Wollin (1966).

Recently, we localized the gene responsible for van Buchem disease to chromosome 17q12–q21, through a genomewide search with highly polymorphic microsatellite markers (Van Hul et al. 1998). All 11 patients included in the present study live in a small ethnic isolate in the Netherlands and share a common ancestor from the 18th century. The van Buchem gene was subsequently mapped in an interval of 0.7 cM between genetic markers D17S1787 (proximal) and D17S934 (distal). The localization of the van Buchem gene to chromosome 17 allowed us to test whether sclerosteosis and van Buchem disease are linked to the same chromosomal region, which would suggest that the conditions are allelic, or whether they are caused by mutations in different genes.

Families and Methods

Families

We ascertained members of two previously described families with sclerosteosis, one from Brazil (Paes-Alves et al. 1982) and one from Maryland (Kelly and Lawlah 1946; Witkop 1961, 1965; Stein et al. 1983). Venous blood samples were acquired for DNA isolation after informed consent was obtained (National Institutes of Health protocol 77-CH-0070).

Paes-Alves et al. (1982) reported a family from Tucano in the State of Bahia, Brazil, with six cases of sclerosteosis, two of which were studied. We reanalyzed data from this family (fig. 1*a*) and studied two previously undescribed patients, IV-1 and V-7. Both cases from the study by Paes-Alves et al. (1982) are deceased (fig. 1*a*, cases A and B). Four other family members, two of whom are dead, were reported to be affected, bringing the total number of affected individuals in this pedigree to eight. The genealogy of the family showed a highly inbred pedigree (fig. 1*a*) with a common ancestor pair for seven of the eight patients. So far, evidence that the father of patient V-7 has the same ancestor is still missing. The family members were examined clinically and radiologically, to ensure a reliable diagnosis. Patient V-7, a 30-year-old woman, presented with a square face with little expression, midfacial hypoplasia with a hypoplastic nasal bridge, high forehead, hypertelorism, proptosis, prognatism, and a large mandible (fig. 2*a* and *b*). Her hands showed cutaneous syndactyly of left digits 2 and 3, radial deviation of the terminal phalanx and a hypoplastic nail on right digit 2, and diffuse thickening of the phalanges bilaterally (fig. 2*c*). Radiographs of the skull indicated thickening of the calvarium and facial bones, with obliteration of the paranasal sinuses and mastoid cells. A radiograph of the hands showed diffuse thickening of the cortex of phalanges and metacarpals with stenosis of the medullary canal. Patient IV-1, a 69-year-old man, presented with similar facial changes, although these were less prominent (fig. 2*d*). He is deaf and blind and suffers from intense headaches. He has bilateral partial cutaneous syndactyly on digits 2–4, a dysplastic nail on left digit 2, clinodactyly with radial deviation of the terminal phalanx of right digits 2 and 3, and bilateral camptodactyly of digit 5.

The American family has previously been studied by Stein et al. (1983), who reported seven cases of sclerosteosis in a triracial (white, American Indian, and black) isolate in southern Maryland. Five individuals—two patients and three nonaffected individuals—are included in this study. All individuals have a common ancestor, with patient V-2 being an uncle of patient VI-1 (fig. 1*b*). Patient V-2 (fig. 3*a* and *b*), a 64-year-old man, noted bilateral hearing loss and bilateral facial paralysis and suffered from headaches. He is quite debilitated, with poor fine-motor functions. The patient has nail dysplasia but no finger syndactyly. Exophthalmos, mild strabismus (extropia), diplopia, and gigantism are present. Radiographs indicated sclerosis of the skull and lateral widening of the mandible, with cortical thickening and abnormal diaphyseal modeling in the tubular bones. A computed tomography (CT) scan of the posterior fossa (fig. 3*c*) indicated marked thickening of the skull base, with obliteration of the diploic space. Patient VI-1, a 21-year-old man, was examined at age 5 years by Stein et al. (1983), but at that time he was too young to present

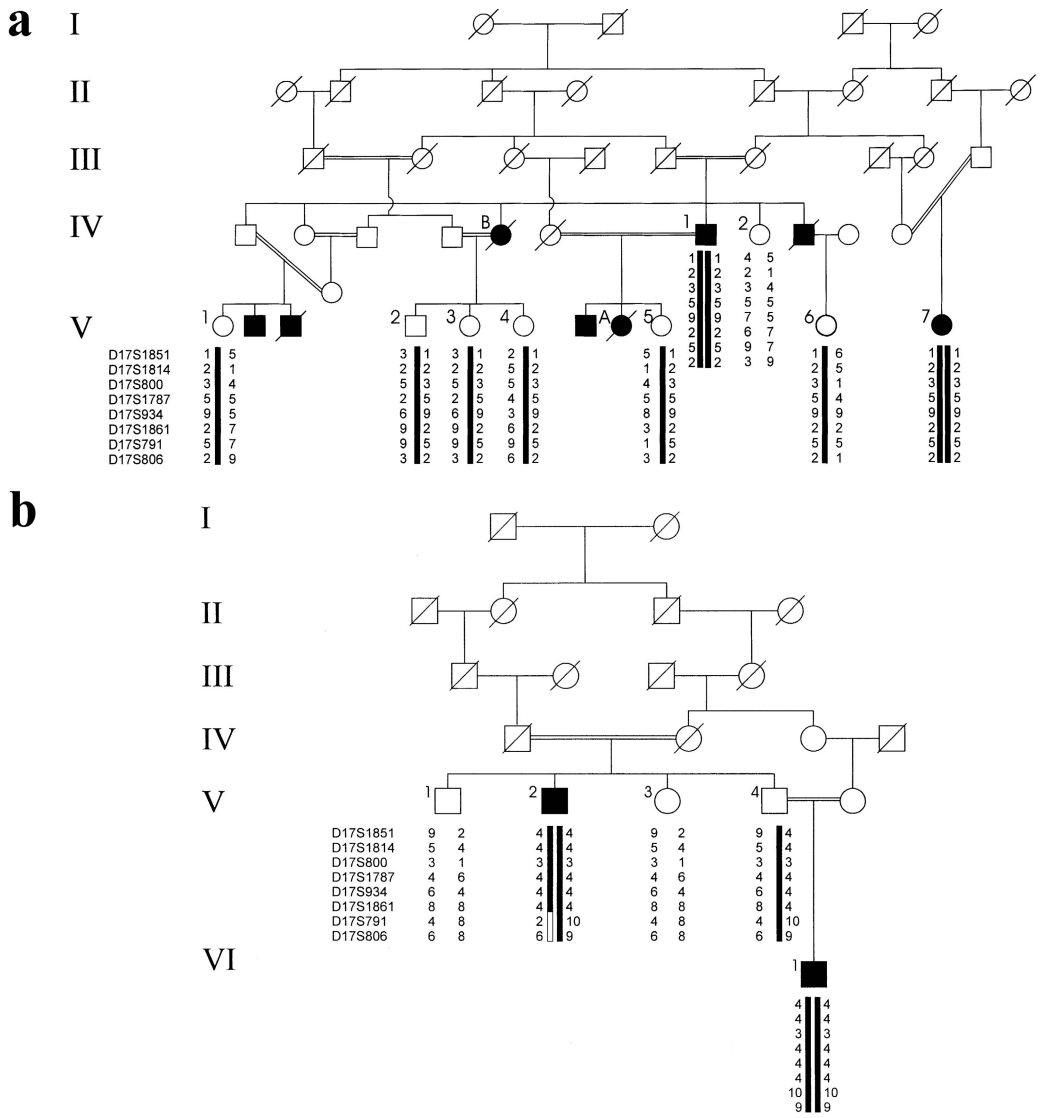

Figure 1 Pedigrees of families studied. Males are represented by squares, females by circles. Blackened symbols represent affected individuals. For the studied individuals, the haplotypes are given for the markers shown on the left. The haplotype segregating with the disease is indicated by a blackened bar. *a,* Pedigree of Brazilian family with sclerosteosis. Patients A and B were studied by Paes-Alves et al. (1982). *b,* Pedigree of American family.

the full picture of sclerosteosis. He now has bilateral facial paralysis, hearing and vision loss on the left side, exophthalmos, and an increased head circumference. There is no syndactyly, but some nails are dysplastic. The patient is of normal size.

Genotyping and Linkage Analysis

Sixteen polymorphic microsatellite markers from Généthon (Dib et al. 1996) were analyzed with eight proximal markers—D17S1850, D17S1872, D17S927, D17S1867, D17S1851, D17S1814, D17S800, and D17S1787—and eight distal markers—D17S934, D17S1861, D17S791, D17S806, D17S1795, D17S1820, D17S809, and D17S787—with regard to the van Buchem candidate interval between D17S1787 and D17S934. The markers are dispersed over a region of >20 cM. Radioactive PCRs (Hughes 1993) were done with 80 ng of genomic template and 4 pmol of each primer, in a total volume of 20 μl, with the following conditions: 26 cycles consisting of a 1-min denaturation step at 94°C, a 1-min annealing step at 55°C, and a 1-min extension step at 72°C. PCR products were separated on a 6% polyacrylamide gel and were analyzed after autoradiography.

Two-point LOD scores between the microsatellite markers and the disease were calculated by the LINK-

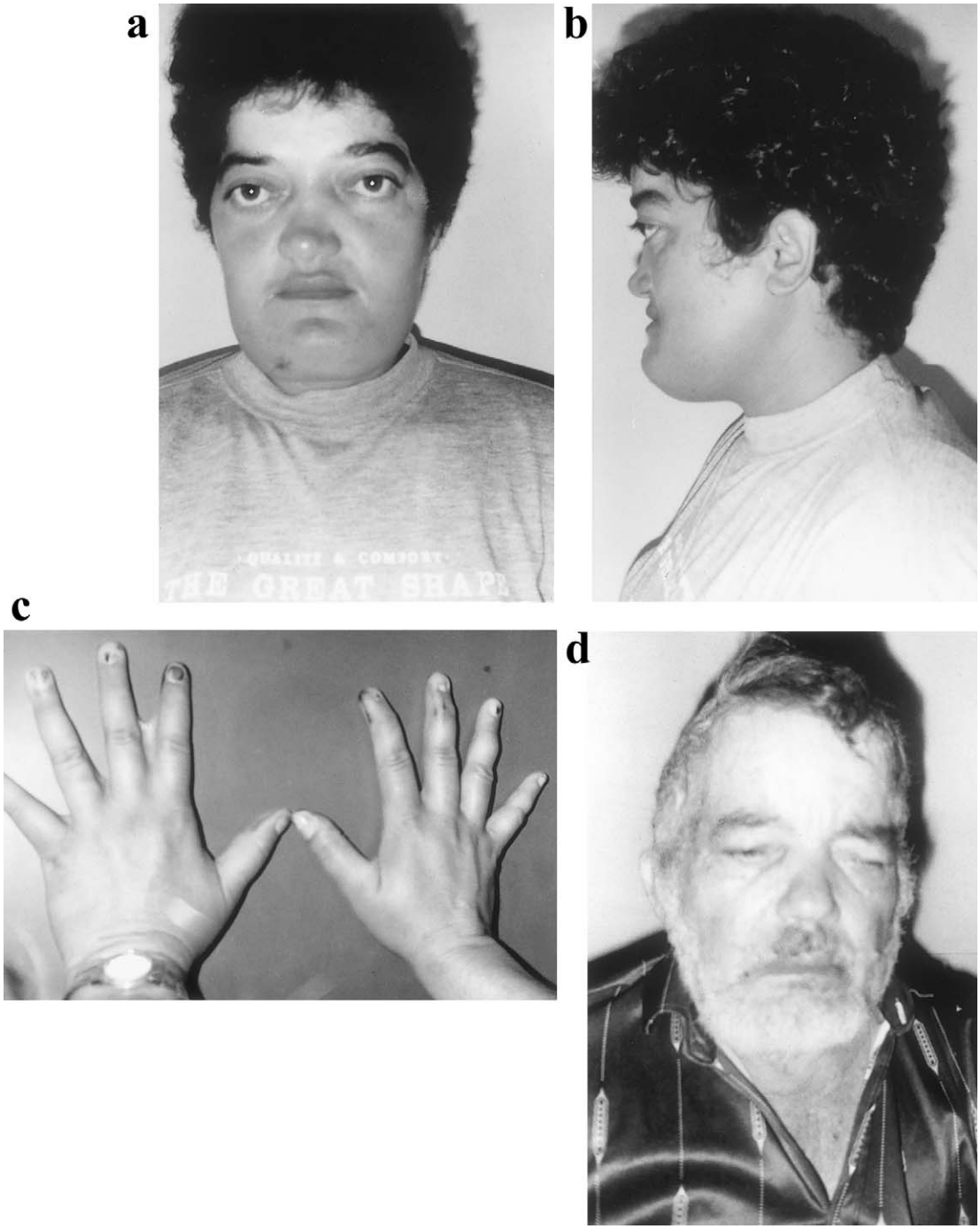

Figure 2 Clinical pictures of Brazilian patients with sclerosteosis. *a–c,* Frontal (*a*) and lateral *b* facial views and hands *c* of patient V-7. *d,* Frontal view of patient IV-1. Both patients show facial characteristics of sclerosteosis, with a high forehead, a protruding large chin, and facial-nerve paralysis; the hands of patients V-7 show syndactyly and nail dysplasia.

AGE software package, version 5.1 (Lathrop and Lalouel 1984). MLINK two-point linkage analysis was performed with parameters set for an autosomal recessive disease with a disease frequency of 1/1,000,000 and allele frequencies of 1/*N,* where *N* is the published number of alleles for each marker.

Results

Linkage Analysis

Initially, eight microsatellite markers localized either centromerically (D17S1851, D17S1814, D17S800, and

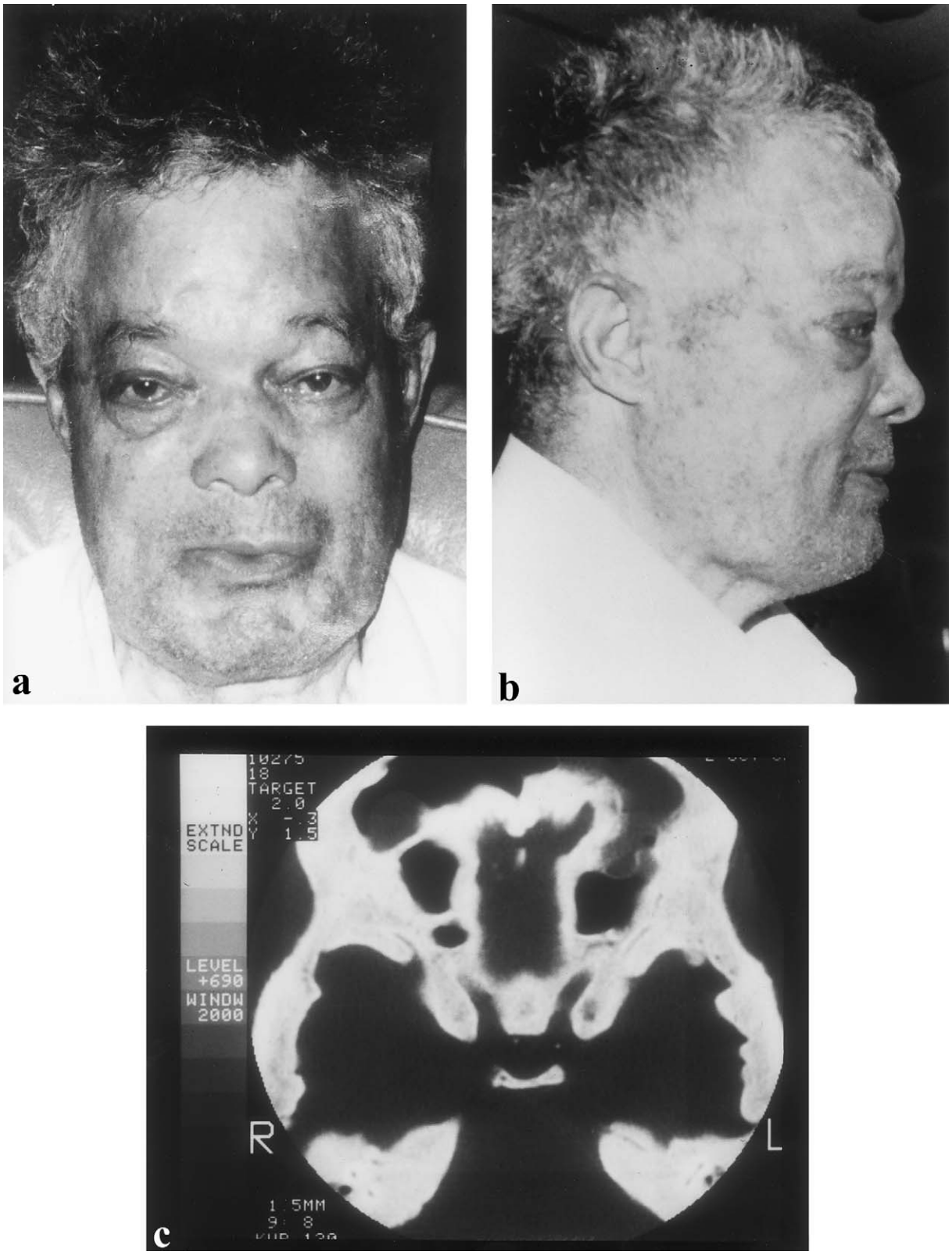

Figure 3 Clinical pictures and CT scan of an American patient V-2 showing characteristics of sclerosteosis. *a–b*, Frontal *a* and lateral *b* facial views. *c*, CT scan of posterior fossa, indicating extensive sclerosis and marked thickening of skull base, with obliteration of the diploic space. The frontal sinuses are well developed.

D17S1787) and telomerically (D17S934, D17S1861, D17S791, and D17S806) from the 0.7-cM van Buchem linkage interval were used for two-point LOD-score calculations and haplotype construction. These markers are spread over a 7.2-cM region. Linkage analysis was performed, and two-point LOD scores are listed in table 1.

For the Brazilian family, positive LOD scores were obtained for all markers except D17S1787. A maximum LOD score of 1.19 at 0 recombination was calculated for D17S1861. In the American family, six of eight microsatellite markers (D17S1851, D17S1814, D17S800, D17S1787, D17S934, and D17S1861) gave positive LOD scores at 0 recombination, with a maximum LOD score of 2.62 for D17S1851.

Summed LOD scores for the two families were >3 for three of the markers—D17S1851, D17S934, and D17S1861—with a maximum of 3.19, 3.29, and 3.69, respectively. Except for D17S791 and D17S806, all markers have a summed maximum LOD score at 0 recombination.

Delineation of the Candidate Region

The haplotypes from the Brazilian and American families with sclerosteosis are presented in figure 1. Both patients from the Brazilian family are homozygous for the same haplotype (fig. 1*a*). The obligate carriers (individuals V-2–V-6) and individual V-1 are heterozygous for the disease-associated haplotype. Individual IV-2 carries two normal haplotypes. In the American kindred (fig. 1*b*), patient VI-1 shows homozygosity for all eight markers analyzed. In patient V-2, homozygosity for the same allele was found for all markers except D17S791 and D17S806. This confirms the presence of a recombination between D17S1861 and D17S791 and localizes the sclerosteosis gene centromerically from D17S791.

For the further delineation of the sclerosteosis candidate-gene interval, we analyzed eight additional microsatellites—four on the centromeric side (D17S1850, D17S1872, D17S927, and D17S1867) and four on the telomeric side (D17S1795, D17S1820, D17S809, and D17S787)—from the panel of markers already analyzed. The haplotypes for all 16 markers are given in table 2. Two new recombinants were observed. The recombination between D17S809 and D17S787 in Brazilian patient V-7 does not result in a further refinement of the candidate region. The recombination in American patient V-2 indicates that marker D17S791 flanks the candidate region on the distal side. A crossover between D17S927 and D17S1867 in American patient VI-1 identified D17S927 as the closest flanking marker on the proximal side. Therefore, our study delineates the candidate region for the sclerosteosis gene, to the 6.8-cM region flanked by D17S927 and D17S791. This region spans the 0.7-cM linkage interval between D17S1787 and D17S934, delineated for the van Buchem disease gene (Van Hul et al. 1998).

Table 1

Two-Point LOD Scores between Sclerosteosis and Markers on Chromosome 17q12–q21

Marker and Population	LOD Score at θ= 0	.01	.05	.10	.20	.30	.40
D17S1851:							
Brazilian	.57	.57	.52	.44	.26	.10	.01
American	2.62	2.56	2.33	2.02	1.38	.76	.26
Total	3.19	3.13	2.85	2.46	1.64	.86	.27
D17S1814:							
Brazilian	.53	.52	.44	.35	.17	.06	.01
American	2.12	2.06	1.82	1.52	.95	.47	.15
Total	2.65	2.58	2.26	1.87	1.12	.53	.16
D17S800:							
Brazilian	.72	.69	.57	.43	.21	.07	.01
American	1.28	1.25	1.12	.96	.62	.33	.12
Total	2.00	1.94	1.69	1.39	.83	.40	.13
D17S1787:							
Brazilian	−.14	−.11	−.04	0	−.01	−.02	−.03
American	1.35	1.32	1.20	1.04	.68	.37	.14
Total	1.21	1.21	1.16	1.04	.67	.35	.11
D17S934:							
Brazilian	.97	.94	.85	.72	.47	.26	.09
American	2.32	2.26	2.01	1.69	1.09	.56	.19
Total	3.29	3.20	2.86	2.41	1.56	.82	.28
D17S1861:							
Brazilian	1.19	1.16	1.04	.89	.59	.31	.11
American	2.50	2.44	2.21	1.90	1.27	.67	.21
Total	3.69	3.60	3.25	2.79	1.86	.98	.32
D17S791:							
Brazilian	1.06	1.04	.96	.84	.57	.31	.11
American	−3.33	−.33	.22	.34	.27	.12	.01
Total	−2.27	.71	1.18	1.18	.84	.43	.12
D17S806:							
Brazilian	.81	.79	.68	.54	.30	.12	.01
American	−4.16	−.77	−.16	.02	.07	.03	0
Total	−3.35	.02	.52	.56	.37	.15	.01

Discussion

There are numerous examples of molecular geneticists having split clinical entities on the basis of proved genetic heterogeneity; the reverse is also true. Clinically diverse conditions have been united by the identification of a shared disease-causing gene (Fransen et al. 1997). It has been well recognized that sclerosteosis and van Buchem disease share such principal features as increased cortical thickness of the bones, enlarged jaw, and neurological complications due to cranial-nerve entrapment. Differential diagnosis is mainly based on the additional components, in sclerosteosis, of gigantism and syndactyly. Beighton et al. (1984) suggested that both conditions could be caused by mutations in the same gene, whereby either different mutations or epistatic influences of additional modifying genes cause the phenotypic differ-

Table 2

Haplotypes for 16 Chromosome 17 Markers Spanning 21.3 cM around the Linkage Interval

		Haplotype[b]					
		Sclerosteosis					
		Brazilian Family		American Family		van Buchem Disease, Dutch Family	
Marker	Genetic Distance[a] (cM)	Patient IV-1	Patient V-7	Patient V-2	Patient VI-1	R1	R2
D17S1850	3.3	2-2	2-2	1-1	1-1	1-1	1-1
D17S1872	.5	5-5	5-5	1-1	1-2	3-2	3-3
D17S927	1.1	3-3	3-3	3-3	3-4	3-3	3-3
D17S1867	1.1	4-4	4-4	4-4	4-4	5-3	5-5
D17S1851	1.9	1-1	1-1	4-4	4-4	1-2	1-1
D17S1814	.1	2-2	2-2	4-4	4-4	2-1	2-2
D17S800	.7	3-3	3-3	3-3	3-3	1-3	1-1
D17S1787	.7	5-5	5-5	4-4	4-4	4-2	4-4
D17S934	.5	9-9	9-9	4-4	4-4	3-3	3-6
D17S1861	.7	2-2	2-2	4-4	4-4	2-2	2-8
D17S791	2.6	5-5	5-5	10-2	10-10	9-9	9-8
D17S806	1.8	2-2	2-2	9-6	9-9	1-1	1-1
D17S1795	3.3	2-2	2-2	1-5	1-1	3-3	3-6
D17S1820	1.8	7-7	7-7	2-2	2-2	4-4	5-6
D17S809	1.2	3-3	3-3	4-5	4-4	2-2	4-4
D17S787		6-6	6-3	2-9	2-5	5-5	2-6

[a] Between genetic marker and that in the row below (Dib et al. 1996).

[b] Haplotypes are those that show recombinations previously used to delineate the candidate region for the van Buchem disease gene (Van Hul et al. 1998). Underlining denotes that the allele is different than that in the shared haplotype.

ences. The recent localization of the van Buchem gene between genetic markers D17S1787 and D17S934 on chromosome 17q12–q21 (Van Hul et al. 1998) offers the possibility for investigation of this hypothesis. The results of our linkage study in two multiplex families with sclerosteosis now confirm linkage of sclerosteosis to the van Buchem locus. LOD scores >3 were obtained with several markers on chromosome 17q, with a maximum of 3.69 for marker D17S1861 at 0 recombination. A candidate region of 6.8 cM was delineated that encompasses the previously identified candidate region for the van Buchem disease gene. Although the possibility that sclerosteosis is caused by another gene localized within the 6.8-cM candidate region cannot be excluded, it is much more likely that our data support the hypothesis of an allelic status for van Buchem disease and sclerosteosis. Final proof, however, can be obtained only by identification of a shared disease-causing gene.

Despite this evidence for an allelic status of the two conditions, our study confirms the previous clinical distinction between van Buchem disease and sclerosteosis. In both conditions, increased bone density of the skull leads to facial paralysis and hearing loss; however, hand abnormalities (nail dysplasia and syndactyly) are very frequent in sclerosteosis but never are seen in patients with van Buchem. Overall, the majority of patients with sclerosteosis are extremely large, but, remarkably, this is not the case in any of the Brazilian patients, one of whom attained a height of only 1.52 m (Paes-Alves et al. 1982). Besides these differences, sclerosteosis presents as a more severe condition, with increased intracranial pressure that sometimes resulted in a sudden death, especially among the American and South African patients.

The majority of patients with sclerosteosis are found among the white population in South Africa. This community is of Dutch ancestry, and a Dutch ancestry cannot be excluded for the Brazilian family. The Brazilian family lives in Tucano, a small city in the state of Bahia, ~250 km from Salvador. Progenitors of the Brazilian community left the Netherlands during the 17th century and settled in the bordering state of Pernambuco at the same time that they occupied South Africa. Therefore, the possibility of a genetic link with an ancestral mutation shared with the Dutch patients with van Buchem disease has been suggested (Paes-Alves et al. 1982; Beighton et al. 1984). This hypothesis would be supported by the identification of a shared haplotype for markers close to the disease gene. All patients with van Buchem who have been investigated by Van Hul et al. (1998) live in a small ethnic isolate in the Netherlands and have a common ancestor from the 18th century. No data are currently available for the South African patients, but comparison between the Brazilian and Dutch haplotypes indicates that the putative shared region must be smaller than the 0.7 cM between D17S1787 and D17S934 (table 2). If

it is assumed that the putative common ancestor lived during the period of the Dutch invasion of Brazil, then the probability that one will end up with such a small shared region is only 7% (te Meerman et al. 1995). This makes the hypothesis of a shared ancestor very unlikely, but either analysis of additional microsatellite markers or identification of the underlying mutations will eventually provide final evidence.

The major feature in both van Buchem disease and sclerosteosis is increased cortical-bone density. The underlying biochemical mechanism for this is unknown, but increased bone formation has been suggested (van Buchem et al. 1976; Stein et al. 1983). Interestingly, the process seems to be ongoing throughout life, and the bone tissue that is formed is of normal structure; in fact, no bone fracture has been reported in any patient with either van Buchem disease or sclerosteosis. All these arguments support the theoretical use of the disease-causing gene or gene product as a therapeutic tool for either the prevention of osteoporosis or the healing of bone fractures.

In conclusion, the colocalization of the van Buchem disease gene and the sclerosteosis gene to the same linkage interval on chromosome 17 supports the hypothesis that the two conditions are allelic. Unraveling of the underlying molecular mechanisms might explain the clinical differences between these conditions. Moreover, the identification of the disease gene will lead to a better understanding of the processes involved in bone homeostasis and could lead to new therapeutic tools to influence this system.

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Electronic-Database Information

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for sclerosteosis [MIM 269500] and van Buchem disease [MIM 239100])

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