Am. J. Hum. Genet. 59:146–151, 1996

Osteoporosis-Pseudoglioma Syndrome, a Disorder Affecting Skeletal Strength and Vision, Is Assigned to Chromosome Region 11q12-13

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Summary

Osteoporosis-pseudoglioma syndrome (OPS) is an autosomal recessive disorder characterized by severe juvenile-onset osteoporosis and congenital or juvenile-onset blindness. The pathogenic mechanism is not known. Clinical, biochemical, and microscopic analyses suggest that OPS may be a disorder of matrix homeostasis rather than a disorder of matrix structure. Consequently, identification of the OPS gene and its protein product could provide insights regarding common osteoporotic conditions, such as postmenopausal and senile osteoporosis. As a first step toward determining the cause of OPS, we utilized a combination of traditional linkage analysis and homozygosity mapping to assign the OPS locus to chromosome region 11q12-13. Mapping was accomplished by analyzing 16 DNA samples (seven affected individuals) from three different consanguineous kindreds. Studies in 10 additional families narrowed the candidate region, supported locus homogeneity, and did not detect founder effects. The OPS locus maps to a 13-cM interval between D11S1298 and D11S971 and most likely lies in a 3-cM region between GSTP1 and D11S1296. At present, no strong candidate genes colocalize with OPS.

Received January 5, 1996; accepted for publication April 25, 1996.

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0002-9297/96/5901-0021$02.00

Introduction

Osteoporosis is a common medical problem with major morbidity and societal cost (Melton 1993). Diminished bone strength, a consequence of low bone mineral content, is the significant complication of the disease (Smith and Smith 1976). Heritable factors have been identified as major contributors to bone mineral content, accounting for most of the observed variance in bone density (Peacock 1995). Although biological analyses indicate the complexity of this process (Manolagas and Jilka 1995), the precise genetic factors involved are not known (Morrison et al. 1994; Peacock 1995). Osteoporosis-pseudoglioma syndrome (OPS) (259770, OMIM 1995) provides an opportunity to study genetic factors involved in skeletal homeostasis. This autosomal recessive disorder is characterized by severe juvenile-onset osteoporosis and congenital or juvenile-onset blindness (Frontali et al. 1985). Collagen I biosynthesis, osteoid, osteoblasts, osteocytes, and osteoclasts appear normal in patients with OPS (Brude and Stoss 1986; Somer et al. 1988; Swoboda and Grill 1988), and visual loss in patients has been associated with aberrant vitreo-retinal vascular growth (Saraux et al. 1969; Sauvegrain et al. 1981). These observations suggest a regulatory role, rather than a structural role, for the OPS gene product. We report the assignment of the OPS locus to chromosome region 11q12-13, using a combination of traditional linkage analysis and homozygosity mapping (Lander and Botstein 1987).

Subjects and Methods

Patient Ascertainment

All families in this study were diagnosed with OPS on the basis of a constellation of clinical, ophthalmologic,

and radiographic findings (Frontali et al. 1985). After informed consent was obtained, blood was obtained for DNA extraction. Descriptions of several families participating in this study have been previously published (Beighton et al. 1985; Frontali et al. 1985; Superti-Furga et al. 1986; Somer et al. 1988; Swoboda and Grill 1988; De Paepe et al. 1993).

Genotyping

DNA extraction and linkage analysis were performed as described by Boon et al. (1994). Primers flanking simple-sequence repeat polymorphisms (SSRPs) were used to PCR amplify genomic DNA in 10-μl volumes containing 37.5 ng of DNA and 2 pmol of each primer. Alleles were detected by end-labeling the forward primer. Primer sequences were obtained from published databases, and primers were purchased from Research Genetics.

Typical conditions for PCR included an initial denaturation at 95°C for 4 min, followed by 30 cycles of 94°C for 40 s, 55°C for 50 s, and 72°C for 50 s, with a final extension of 72°C for 7 min. PCR products were denatured in the presence of 40% formamide. Then, 1.5-μl aliquots were separated on denaturing polyacrylamide gels and alleles were detected by autoradiography.

Linkage Analysis

Two-point lod scores were calculated using the program MLINK (Lathrop et al. 1985) with consanguinity loops, where known, as indicated in figure 1. Linkage calculations assumed autosomal recessive inheritance with complete penetrance of the mutant phenotype, a phenocopy frequency of 10^{-5}, and a mutant gene frequency of 10^{-3}. Linkage calculations initially assumed a 4-allele system with equal allele frequencies. Following the identification of linkage, >20 ethnically/geographically matched controls for families 1–6 and 9 were used to determine specific allele frequencies for each kindred.

SSC Analysis and Cycle Sequence Analysis to Exclude PPP1CA, ROM1, FKBP13, and CNTF

Previously published primer pairs or sequences (Hendrickson et al. 1993; Mochinzuki and Prochaza 1994; Nichols et al. 1994; Takahashi et al. 1994) were used to amplify portions of the above genes for evaluation by either SSC (Orita et al. 1989) or cycle sequence (Murray 1989) analysis.

Results

Sixteen DNA samples from three different consanguineous kindreds (from Finland, South Africa, and Italy) were used in the initial mapping (fig. 1). If OPS exhibited locus heterogeneity, only family 2 would have provided significant statistical strength to achieve a lod score >3. Conversely, if there were locus homogeneity, homozygosity for a tightly linked informative marker would have yielded a combined lod score >5. Since there were no a priori candidate genes, we initiated a genome-wide scan using SSRPs spaced at 20-cM intervals. For the preliminary scan, regions having lod scores <−1 were not evaluated further, while intervals with combined lod scores >1 in all three families, or >0 in family 2 alone, were tested with additional nearby SSRPs.

One-hundred sixty SSRPs distributed across 20 autosomes were tested before marker D11S905 yielded a combined lod score of 1.6 at $\theta = .1$. Testing additional nearby markers suggested identity by descent in affected patients (fig. 1). D11S987 yielded the highest combined lod score (5.99 at $\theta = 0$), when ethnically/geographically matched control haplotype frequencies were used for each kindred.

On the assumption of homozygosity by descent for the OPS mutation in each consanguineous kindred, the OPS locus can be placed within a 13-cM genetic interval bounded by D11S1298 and D11S971 on chromosome region 11q12-13 (Leppert et al. 1994). However, results in family 2 indicate that the homozygous markers within this 13-cM region comprise two noncontiguous, although physically close, intervals (fig. 1) (Leppert et al. 1994; van Heyningen and Little 1995). One interval is bounded by D11S1298 and D11S1368, the other by PYGM and FGF3. The occurrence of heterozygosity between these two intervals in family 2 may reflect either a double recombinant event occurring in an intermediate ancestor, or reintroduction of ancestral markers through additional consanguineous unions (Beighton et al. 1985). An alternative, less likely, explanation is that affected individuals in family 2 are compound heterozygotes for allelic OPS mutations and that markers are homozygous by chance rather than by descent.

Ten additional kindreds with OPS, including two consanguineous kindreds, were studied to refine the candidate region and to test for locus homogeneity and founder effects. Data from families 4 and 9–13 were consistent with a single OPS locus on chromosome 11q but did not exclude either interval (fig. 2). However, results in family 10 potentially narrow both intervals (fig. 2). Families 5–8 were too small to provide linkage data but could be used to look for shared haplotypes. Analysis of markers compatible with identity by descent did not suggest a common founder mutation, even among families of similar geographic background (table 1). However, shared founder haplotypes may emerge as the OPS locus is further refined.

Discussion

We have mapped the OPS locus to chromosome 11q12-13 by initially analyzing 16 DNA samples (seven

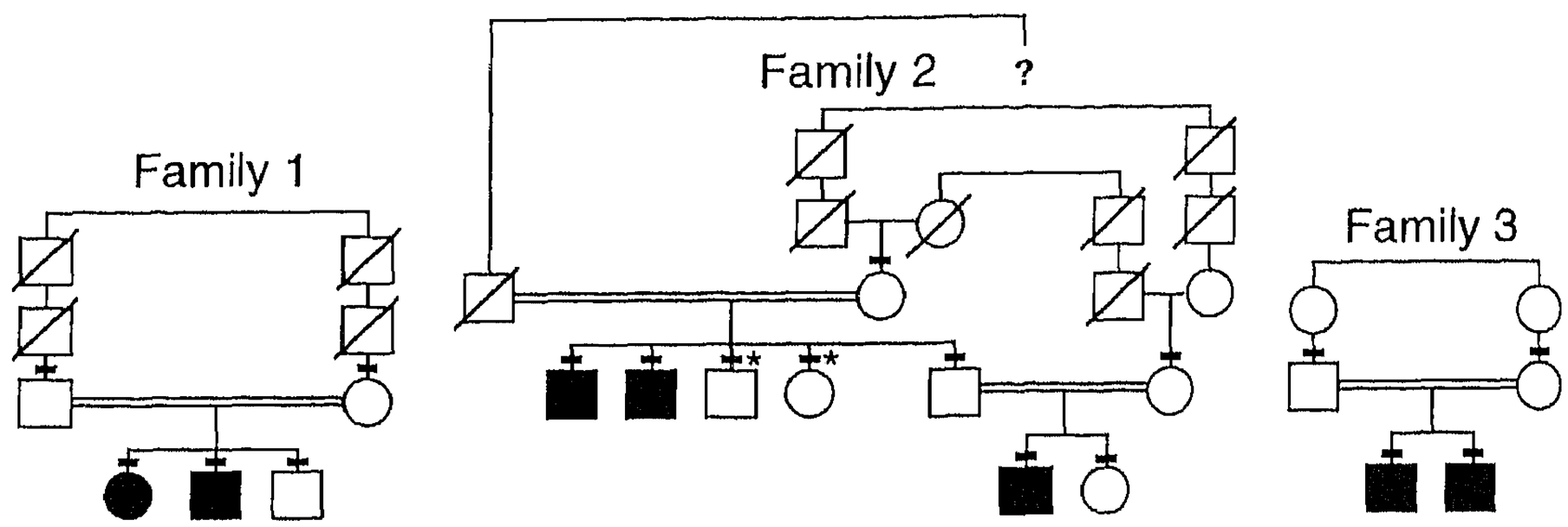

Figure 1 Pedigree structures of the first three kindreds studied with genotypes of SSRP and SSCP markers within and flanking the OPS region. Sex-averaged genetic distances between several markers are indicated. Consanguinity is denoted by double lines between parents. Bars indicate DNA samples available for analysis. Two unaffected siblings in family 2, who were not included among the original 16 samples studied, are indicated with an asterisk (*). Paternally derived alleles are on the left of each offspring's genotype. Fully informative genotypes within the family are in bold, uninformative genotypes are denoted by hyphens (-), incomplete genotypes are left blank. Boxed areas indicate markers for which homozygosity by descent cannot be excluded. Markers within the dashed region in family 2 are consistent with identity by descent, but not homozygosity by descent. A deduced genotype for the deceased father in family 2 is in italics. SSRP marker D11S987 (in bold) is fully informative in each kindred.

affected individuals) from three different consanguineous kindreds. Studies in 10 additional families confirmed the assignment, supported locus homogeneity, and did not detect founder effects. On the assumption of homozygosity by descent in all affected patients from consanguineous unions, the most likely site of the OPS locus is between GSTP1 and D11S1296. This interval has a genetic distance of 3 cM and a physical distance of >3 Mb (van Heyningen and Little 1995). Within the interval, a highly polymorphic SSRP, D11S987, was fully informative in every kindred. In contrast, the other homozygous interval, between D11S1298 and D11S1335, contained SSRPs that were not fully informative. Consequently, in some families, homozygosity by chance, rather than homozygosity by descent, may have occurred. The low heterozygosity content of several other markers (e.g., D11S913, D11S970, D11S1917) also probably results in homozygosity by chance for these loci in several patients (table 1). On the assumption of homozygosity by descent, family 10 requires at least two recombinant events closely flanking the OPS locus to have occurred in only six meioses. Locus heterogeneity or compound heterozygosity are alternative explanations for this family's results; additional DNA samples from intermediate relatives, and additional highly polymorphic markers within the candidate region, may resolve this issue.

At present, no likely candidate genes have been mapped within either OPS candidate interval. On the assumption of homozygosity by descent for mutations at the OPS locus in all consanguineous kindreds, several genes (CNTF, FKBP13, ROM1, PYGM, PPP1CA, GSTP1, and FGF3) can be excluded as candidates on the basis of the finding of heterozygosity for intragenic SSRPs or sequence polymorphisms in one or more affected individuals (data not shown). Ophthalmologic disorders have been previously assigned to chromosome 11q12-13, including neovascular inflammatory vitreore-

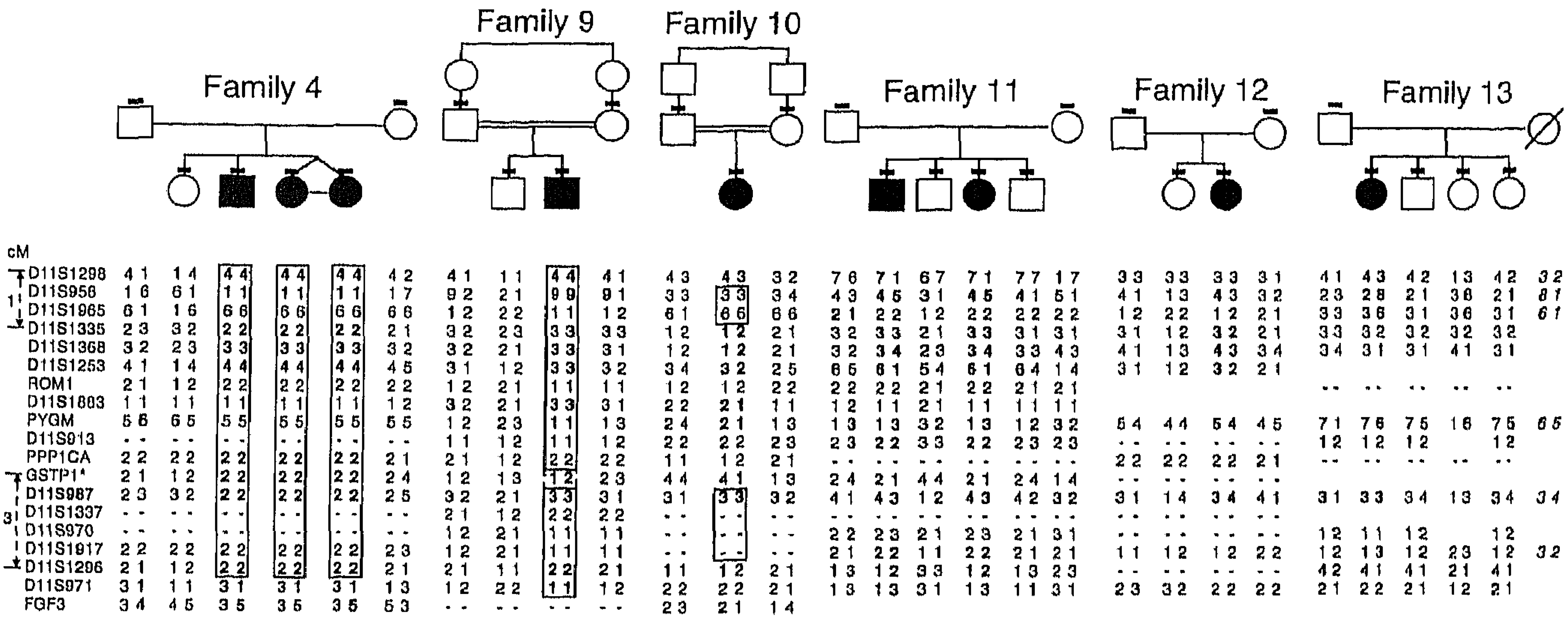

Figure 2 Pedigree structure and genotypes in six additional families. Four nonconsanguinous, single-offspring families are not shown. Sex-averaged genetic distances spanning the two candidate intervals (on the assumption of homozygosity by descent in family 10) are indicated. Notations are the same as for figure 1. Affected individuals in family 4 are homozygous for most markers in the region, which is consistent with unsuspected consanguinity. Marker GSTP1 (asterisk [*]), appears recombinant in family 9. This is more likely to represent a de novo SSRP mutation than a double-recombinant event. A deduced genotype for the deceased mother in family 13 is in italics.

tinopathy (VRNI) and exudative vitreoretinopathy-1 (EVR1) (Li et al. 1992; Stone et al. 1992; Leppert et al. 1994; Nichols et al. 1994); however, none colocalize with OPS. It has been suggested that the abundance of nonallelic eye disorders on chromosome 11q may be due to a clustered gene family or a family of interacting proteins, having roles in ocular development (Nichols et al. 1994). This is particularly intriguing, since OPS shares several features with both VRNI and EVR1, and genes for interacting retinal proteins have previously been colocalized to 11q13 (Benovic et al. 1991; Calabrese et al. 1994). Autosomal recessive forms of isolated osteoporosis, as well as isolated congenital retinal detachment, have also been described (e.g., 259750 and 221900, OMIM 1995). This may reflect locus heterogeneity for these traits. However, certain of these patients may have had unrecognized OPS, since ocular and skeletal manifestations may not have been manifest at the time patients were evaluated. One may also speculate that OPS, which is quite rare, is the consequence of

Table 1

OPS-Linked Marker Alleles in Affected Patients

Family	Origin	D11S956	D11S1965	D11S1335	D11S1253	D11S913	GSTP1	D11S987	D11S970	D11S1917
1[a]	Finnish	5	4	1	5	2	4	5	2	2
8	German	6,7	2,7	2,4	. . .	1,2	4,5	5	3	2,3
11	Austrian	4,5	2	3	1,6	2	1,2	3,4	2,3	2
13	Dutch	2,8	3,6	2,3	. . .	1,2	4	3	1	1,3
5	Belgian	4,8	5,6	3	3	1,2	2,5	4	2	1
6	Belgian	2,6	1,5	2,3	1,5	1	3,4	3,4	3	2,3
2[a]	Indian (South African)	5	6	3	2,5	2	4	3	2	3
10[a]	Moroccan	3	6	1,2	2,3	2	1,4	3	2	1
3[a]	Italian	4	1	3	7	1	2	5	2	3
4	Italian	1	6	2	4	1	2	2	2	2
9[a]	Italian	9	1	3	3	1	1,2	3	1	1
7	Puerto Rican	3,9	4,6	3	. . .	1,2	3,4	2,3	2,3	2
12	Guatemalan	3,4	1,2	2,3	2,3	2	1	3,4	2	1,2

NOTE.—Several homozygous marker alleles (e.g., D11S913, D11S970, D11S1917) also have high homozygosity rates in ethnically/geographically matched controls (control frequencies were available for families 1–6 and 9).

[a] Family with known consanguinity.

homozygosity for mutations at two tightly linked loci, one responsible for skeletal manifestations, the other for ocular features.

Murine homologues of OPS have not been reported. Two autosomal recessive murine skeletal disorders, *osteosclerosis* (*oc*) (Marks et al. 1985) and *osteochondrodystrophy* (*ocd*) (Sweet and Bronson 1991) map to murine chromosome 19, in the region homologous to human 11q12-13. However, neither is an obvious phenocopy or allelic variant for OPS. *Osteosclerosis* is characterized by hypercalcuria and metaphyseal rickets with concurrent osteopetrosis, not osteoporosis. *Osteochondrodystrophy* is characterized by abnormal growth plate morphology and stunted growth. Although growth plate morphology has not been specifically evaluated in patients with OPS, disproportionate growth is not a feature of the disease. A second region of homology exists between human 11q13 and murine chromosome 7. Murine skeletal or ocular phenotypes have not been assigned to this region.

Until the precise pathophysiological processes accounting for the skeletal and ocular manifestations of OPS are known, it remains difficult to predict specific roles for the OPS gene and its protein product. It is intriguing that osteoporosis is not progressive in every affected individual and that several obligate heterozygotes for the OPS mutation have developed adult-onset osteoporosis (Superti-Furga et al. 1986; authors' unpublished observations); whether the osteoporosis observed in heterozygotes is coincidental, or truly associated with the OPS mutation, is not known. We speculate that the OPS gene serves a regulatory function, which is itself modulated by other factors. Even in the absence of cloning the OPS gene, the locus can now be tested as a genetic determinant for other osteoporotic conditions (Spotila et al. 1993; OMIM 1995). These conditions may include common forms of osteoporosis, such as senile and postmenopausal osteoporosis, which can be tested using approaches similar to those applied to the vitamin D–receptor locus (Morrison et al. 1994; Peacock 1995). OPS is a rare disorder; consequently, heterozygosity for the OPS mutation will not be a common risk factor for developing osteoporosis. However, other mutations or polymorphisms within this gene could be associated with significant risk.

For rare autosomal recessive disorders, such as OPS, the occurrence of consanguinity within affected kindreds is increased, and homozygosity mapping is a powerful approach (Lander and Botstein 1987). However, the utility of this approach is dependent on the number of affected offspring, the coefficient of inbreeding, and the map density at which markers are tested. By coupling traditional linkage mapping with homozygosity mapping, we were able to use a less-dense marker screen to suggest initially the OPS region and then saturate this region with additional markers to reveal homozygosity, which is presumed to be by descent. This coupled approach can facilitate the mapping of any rare autosomal recessive disorder in which consanguinity or a founder mutation is present, because it need not rely on a dense primary mapping screen or on the analysis of a large number of DNA samples.

Acknowledgments

Y.G. is a recipient of a World Health Organization fellowship. This work was supported by the Osteogenesis Imperfecta Foundation, Inc. (to M.L.W.), the National Institutes of Health (AR36819 and AR36820 to B.R.O.), the Medical Research Council of South Africa, the Harry Crossley Foundation, the Mauerberger Foundation, the University of Cape Town Staff Research Fund (to P.B.), and the Swiss National Foundation (32-45401.95 to A.S.-F. and 32-42198.94 to B.S.). The authors thank the families for participating in this study; Drs. J. Opitz, H. Willard, and A. Chakravarti for their critical review of this manuscript; and Drs. J. Seidman, S. Sunden, A. Stafford, A. Monaco, R. McInnes, M. Higgins, J. Lu, T. Shows, M. Prochazka, A. Beggs, D. Beier, P. Byers, and G. Wallis and the Japanese Cancer Research Resources Bank for sharing resources and unpublished data.

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