Association Between Serum Insulin Growth Factor-I (IGF-I) and a Simple Sequence Repeat in IGF-I Gene: Implications for Genetic Studies of Bone Mineral Density


The Jackson Laboratory (C.J.R., D.V.), Bar Harbor, Maine 04605; Department of Medicine (E.S.K., J.P.B.) and Department of Pharmacology (J.P.B.), College of Physicians and Surgeons, Columbia University, New York, New York 10032; Medical College of Virginia and McGuire Veterans Administration Hospital (R.A.A.), Richmond, Virginia 23249; Beth Israel Medical Center (P.J.R.), New York, New York 10003; Foundation for Blood Research (W.Y.C.), Scarborough, Maine 04070; and Southwest Foundation for Biomedical Research (S.W., J.R.), San Antonio, Texas 78228

ABSTRACT

We recently demonstrated that insulin growth factor-I (IGF-I) cosegregates with bone mineral density (BMD) in progenitor crosses of two inbred strains of mice. Additionally, we reported that men with idiopathic osteoporosis (IOM) have low serum IGF-I levels, which can be related to BMD and bone turnover. In this study, we considered the possibility that serum IGF-I levels are influenced by molecular genetic variation in the IGF-I structural gene, and that a polymorphic microsatellite (CA repeat) in this locus can be used as a genetic marker for such comparisons. We studied 171 men and women, classified according to the trial in which they were participating. First, in 25 Caucasian men with IOM we noted a very high frequency (64%) of homozygosity for the most common allele (192 bp) in a dinucleotide microsatellite (CA repeat) in this locus can be used as a genetic marker for such comparisons. We studied 171 men and women, classified according to the trial in which they were participating. First, in 25 Caucasian men with IOM we noted a very high frequency (64%) of homozygosity for the most common allele (192 bp) in a dinucleotide repeat 1 kb upstream from the transcription start site of the IGF-I gene. This compared with a frequency of only 32% in healthy populations (both men and women) (P < 0.004). Next, we determined that for 116 healthy Caucasian men and women the 192/192 genotype was associated with lower serum IGF-I levels than all other genotypes (192/192: 129±7 ng/mL, vs. others: 154±7 ng/mL, P = 0.03). We also noted that subjects possessing one 194-bp allele exhibited serum IGF-I levels 25% higher than those homozygous for 192 bp (192/192), (P < 0.005) even after correction for age and sex. Similarly, for men with the 192/192 genotype, serum IGF-I concentrations were lower than any other genotype (145±10 ng/mL vs. 183±9 ng/mL, P < 0.02). In conclusion, low serum IGF-I levels found in men with IOM are associated with homozygosity for a specific allele of the IGF-I microsatellite (192/192), and individual variation in serum IGF-I levels is influenced by genetic factors and may be specifically influenced by variation at the IGF-I structural locus. Further family and pedigree studies are needed to characterize the relationship of bone mass acquisition to the IGF-I genotype. (J Clin Endocrinol Metab 83:2286–2290, 1998)

INSULIN-like growth factor-I (IGF-I) is a ubiquitous polypeptide that is important for cell growth and differentiation (1). IGF-I stimulates linear growth in all mammals, and its circulating concentration during growth is directly related to the pulsatile release of GH. In the skeleton, IGF-I and its binding proteins (IGFBPs), are synthesized by osteoblasts and regulated by GH as well as several endocrine and autocrine factors (1, 2). IGF-I is important for bone cell proliferation, differentiation, and collagen synthesis (1–4). During active bone resorption, IGF-I is released from the bone matrix to recruit new osteoblasts to the remodeling surface. It is likely that skeletal IGF-I is one of several coupling factors in the bone remodeling process.

IGF-I is vital for the growth and maintenance of other tissues. IGF-I is also present in relatively large concentrations in the circulation of normal postpubertal individuals, although its precise function is not known. It appears likely that the primary source of circulating IGF-I is the liver, although the skeleton also contributes to total serum levels (5).

Received January 26, 1998. Revision received March 2, 1998. Accepted April 10, 1998.

Address all correspondence and requests for reprints to: Clifford J. Rosen, Maine Center for Osteoporosis Research and Education, St. Joseph Hospital, 360 Broadway, Bangor, Maine 04401. E-mail: crosen@maine.maine.edu.
highly polymorphic microsatellite composed of variable cytosine-adenosine (CA) repeats 1 kb upstream from the transcription start site of IGF-I.

Methods

Subjects

A total of 171 Caucasian men and women were studied over the course of 2 yr. The groups were categorized by cohort according to location. The subjects reported in this manuscript belong to one of four distinct study groups. Each study was approved by the individual institutional review board (Columbia Presbyterian Medical Center, St. Joseph Hospital, McGuire Veterans Administration Hospital), and all subjects provided informed consent for the studies.

Subject categorization (Table 1)

Group 1. Twenty-five men (mean age, 50.2 ± 1.9 yr) from New York City recruited with IOM for a 2-yr randomized trial of human PTH were the initial group investigated for polymorphisms in the IGF-I gene. Characteristics of this cohort have been described in previous publications (9, 10).

Group 2. Thirty healthy men (HM) (mean age, 48 ± 1.1 yr) of approximately the same age as group 1, from Richmond, VA, were recruited for a longitudinal observational study of hormonal determinants of BMD.

Group 3. Thirty-seven healthy ambulatory postmenopausal women (mean age, 72.3 ± 2.1 yr) from rural Maine involved in a calcium intervention (CAI) trial comprised the third group.

Group 4. The final cohort comprised 79 consecutive men and women (AP) (mean age, 58.6 ± 1.4 yr) referred to a cardiology practice for evaluation of chronic chest pain, some of whom had coronary artery disease but were otherwise healthy and were followed longitudinally for 6 months.

None of the subjects had medical diseases known to affect serum IGF-I or bone density. None were taking medications such as glucocorticoids, estrogen replacement, anticonvulsants, antiresorptive agents, fluoride, androgens, or GH. In addition, all subjects were ambulatory and had serum creatinine levels less than 1.5 mg/dL. None of the individuals had type 1 or type II diabetes mellitus or pituitary disease.

None of the subjects was hospitalized within 3 months before obtaining blood samples. Dietary records were obtained and no subjects were noted to have low protein or calorie intake.

Serum IGF-I

Serum was obtained on 171 subjects in the fasting state and stored at −70°C. The RIA was performed using a double-antibody assay (supplied by Nichols Institute, San Juan Capistrano, CA) following acid-ethanol cryoprecipitation extraction to remove IGFBPs as reported previously (12). This method removes nearly all IGFBPs and correlates very closely with serum IGF-I measurements made after acid-gel chromatography separation (9, 12). All the samples were measured in duplicate by one technician at the laboratory of the Maine Center for Osteoporosis Research and Education. Assays were performed over a 2-yr period on freshly thawed samples, none of which had been stored for longer than 12 months at the time of defrosting. Based on our earlier studies in which we demonstrated that the RIA for IGF-I is not affected by sample age (i.e., ≤24 months and no previous thaw cycles), accuracy of the assay was not compromised by sample storage (12). Sample assays were run as batches for each cohort. However, to minimize interassay variation, samples from each cohort were measured in the ensuing assay. In addition, samples from the IOM cohort have been assayed twice yearly in follow-up and found to have an intraassay variation of less than 10%. The detection limit of the IGF-I assay is 12 ng/mL. The inter- and intraassay coefficients of variation for IGF-I in our laboratory were 8.8% and 2.7%, respectively. There is less than 1% cross-reactivity with IGF-II or insulin in this assay. In the longitudinal studies from three cohorts (IOM, CAI, and AP), replicate serum IGF-I measurements changed less than 10% over 24 months. This is consistent with other recent studies showing minimal variation in serum IGF-I over time in the same individual (12, 14). The present study analyzes data from baseline samples only for subjects involved in longitudinal trials.

IGF-I genotyping

PCR was performed using oligonucleotide primers designed to amplify the polymorphic cytosine-adenosine (CA), repeat upstream of the transcription start site of the IGF-I gene (14, 15). The PCR primers were: 5′ GCTAGCCACCTTGTTTATT; 3′ ACCACCTCTGGGAGAAAGGT.

The primers were obtained from Research Genetics (Huntsville, AL). The location of the nucleotide position is 947–984 in the original human IGF-I DNA sequence (Genbank accession number M12659, M77496).

Using standard proteinase K digestion and phenol/chloroform extraction, genomic DNA was obtained from the buffy coats of whole blood samples. Genotyping of the simple sequence (microsatellite) repeat in the IGF-I locus used a slight modification of the published protocol by Weber and May (16). One hundred nanograms template DNA, 0.25 μM each primer, 200 μM each deoxynucleotide triphosphate, 1.5 mM MgCl₂, 2% dimethyl sulfoxide, 1 U Taq polymerase (Promega, Madison, WI), and manufacturer’s recommended buffers were combined in 25-μl reactions. One primer was radiolabeled with 32P using T4 polynucleotide kinase (Pharmacia, Piscataway, NJ). For PCR amplification, 35 cycles were performed. The initial temperature cycle for amplification was 94°C denaturation for 45 sec, 70°C annealing for 30 sec, and 72°C extension for 30 sec. The next 9 cycles each reduced the annealing temperature 1°C per cycle. This was followed by 25 additional cycles of 94°C for 35 sec, 61°C for 30 sec, and 72°C for 30 sec. The reaction was ended with a final extension at 72°C for 5 min. Radiolabeled PCR products were screened for length variation through electrophoresis in standard denaturing polyacrylamide gels. Autoradiographs were exposed for 4–12 h in cassettes without intensifying screens. All genotypes were scored by two independent investigators. The term 192 was used to signify the 19 CA repeats (192 bp) as reported by Weber and May (16) and labeled Z in their initial report. Other PCR product sizes ranging

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>Location</th>
<th>M/F</th>
<th>Age (yr) range</th>
<th>IGF-I (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOM</td>
<td>25</td>
<td>New York</td>
<td>25/0</td>
<td>50.2 ± 1.9</td>
<td>158.0 ± 7.6*</td>
</tr>
<tr>
<td></td>
<td>35–60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HM</td>
<td>30</td>
<td>Virginia</td>
<td>30/0</td>
<td>48.1 ± 1.2</td>
<td>196.8 ± 13.8</td>
</tr>
<tr>
<td>CAI</td>
<td>37</td>
<td>Maine</td>
<td>0/37</td>
<td>72.3 ± 2.1</td>
<td>128.7 ± 15.0</td>
</tr>
<tr>
<td>AP</td>
<td>79</td>
<td>Maine</td>
<td>59/20</td>
<td>58.6 ± 1.4</td>
<td>170.7 ± 20.5</td>
</tr>
</tbody>
</table>

* P < 0.04 between IOM and HM.

![Fig. 1. A representative gel delineating different alleles noted for this microsatellite in IGF-I gene. PCR was performed using oligonucleotide primers designed to amplify the polymorphic transcribed CA repeat upstream of the transcription start site of IGF-I gene as reported in Ref. 16. Lanes are numbered from left to right and are from a single gel performed on DNA from Virginia HM cohort. Lanes 1, 3, 8, and 10 are genotypes 192/194; lanes 4, 5, 6, and 7 are homozygous 192/192; lane 6 is 192/196; lane 2 is 192/188; and lane 9 is 192/190.](image-url)
from 188–198 were given a number designated by the size of the CA repeat (188–198; Fig. 1). Genotyping was performed on 171 subjects.

**BMD**

BMD of the spine (L2-L4) and hip are reported for the two male studies (IOM and HM) and were performed using dual energy X-ray absorptiometry with the Hologic QDR-1000 DXA machine (Hologic Inc., Waltham, MA). Both are located at centers (College of Physicians and Surgeons, Columbia University and Medical College of Virginia) performing clinical trials that require daily phantom scanning and quality assurance. Precision errors for the various sites were as follows: lumbar spine 0.68%, femoral neck 1.3%, and distal radius 0.70%. T scores were reported as units of standard deviation from young male normals accounting for the reference data supplied by the manufacturer. The total hip was utilized for the femur studies to assure continuity in databases.

**Statistical analysis**

The Fisher’s exact test was employed to compare the difference in frequency of the 192/192 genotype in the IOM to the rest of the population under investigation. Ninety-five percent confidence intervals (CIs) are reported, and \( P < 0.05 \) was considered significant. An unpaired two-tailed Student's \( t \) test was used to compare serum IGF-I levels between subjects possessing or not possessing the 192/192 genotype in the microsatellite CA repeat. Age and sex adjustments were performed on IGF-I values using linear regression analysis. A statistical analysis utilized for the femur studies to assure continuity in databases.

**Results**

**Serum IGF-I**

The mean serum IGF-I concentration in each cohort is noted in Table 1. The age range for subjects in these studies was 35–88 yr. The range of serum IGF-I was 35–379 ng/mL. Serum IGF-I was negatively associated with age in each cohort and for the combined population of 146 men and women (\( r = -0.75; P < 0.001 \)). In the largest trial of consecutively recruited men and women (AP), there was an age-associated decline in serum IGF-I (\( n = 79; r = -0.55 P < 0.001 \); males: \( n = 59; r = -0.39, P = 0.002 \); females: \( n = 20, r = -0.64, P = 0.003 \)). In this cohort, women had significantly lower serum IGF-I levels than men (176 ± 5 ng/mL vs. 112 ± 8 ng/mL \( P = 0.0002 \)).

As reported previously, subjects with IOM have lower serum IGF-I levels compared with normative values from our laboratory for men of this age group (10, 12). Mean IGF-I levels in IOM also differed significantly from the HM cohort in this study despite nearly identical ages (10, 12) (Table 1).

**Allele frequencies in a dinucleotide repeat of IGF-I gene**

To investigate the mechanism underlying the difference between IOM and HM, as well as the normal variation in IGF-I serum levels within human populations, we examined a polymorphic CA dinucleotide repeat 1 kb upstream of the IGF-I transcription start site (15, 16). The most frequent allele in our population samples is 192 bp in length, which corresponds to the observations of Weber and May (16) in 1989. Among 146 subjects (cohorts HM, CAI, and AP) for 292 chromosomes, the allele frequencies for the 192 bp and 194 bp were 59% and 24%, respectively. Thirty-two were homozygous for the 192-bp allele (here designated 192/192) and 28% were heterozygous for the 192/194 alleles. Five percent were homozygous for the 194 allele.

In men with IOM, 16 of 25 (64%) were homozygous for the 192 allele. Thus, the frequency for the 192/192 genotype in IOM was twice that of other populations \( [\text{frequency} = 0.64 \text{ (IOM)} vs. 0.32 \text{ (others)}; P < 0.004] \). A similar relationship was noted when the frequency of the 192/192 genotype from the IOM cohort was compared with the frequency of 192/192 in only male subjects \( (P < 0.02) \).

**Genotypes and serum IGF-I**

Next we asked whether a single polymorphism within this microsatellite of the IGF-I gene was associated with serum IGF-I levels. First, among 116 consecutively recruited (AP and CAI) men \( (n = 59) \) and women \( (n = 57) \), 30% \( (n = 37) \) possessed the 192/192 genotype. The mean serum IGF-I for those with the 192/192 genotype was significantly lower than subjects with any other genotype \( [192/194, 194/194, 194/196, 192/198, \text{ or } 192/190 \ (n = 79); 192/192, 129 ± 7 \text{ ng/mL} \text{ vs. others, } 154 ± 9 \text{ ng/mL}; P = 0.03] \). Similarly, in the AP cohort of consecutive men and women \( (n = 79) \), serum IGF-I differed significantly by genotype: 192/192, 128.4 ± 9.8 vs. others, 162 ± 9.3 ng/mL \( P = 0.02 \) (Table 2).

Because the IOM group was composed exclusively of males, we next examined whether gender affected genotype frequency or serum IGF-I levels. For non-IOM men \( (n = 89) \), the 192/192 genotype was associated with significantly lower serum IGF-I concentrations than any other genotype \( [192/192, 158.6 ± 9.0 \text{ vs. others, } 188.8 ± 8.6 \text{ ng/mL}; P = 0.02] \). This result was consistent between different cohorts, reaching statistical significance in the AP cohort \( (n = 59): 192/192, 145 ± 10 \text{ [95% CI, 124–166 ng/mL] vs. others, } 183 ± 10 \text{ [95% CI, 162–203 ng/mL]; P < 0.02 (Fig. 2), but not in the smaller HM cohort (median values: 192/192, 166.5 ng/mL [95% CI, 144–218 ng/mL] vs. others, 190 ng/mL [95% CI, 169–229 ng/mL]) \text{ (Table 2).} \)

In contrast to homozygous 192/192 individuals, the 192 heterozygotes did not have different serum IGF-I concentrations or BMDs compared with subjects with any other genotype. However, the presence of a single 194-bp allele (the second most common allele in this microsatellite) was found in 52/114 subjects (29 men and 23 women) from the

**TABLE 2. Differences in serum IGF-I by IGF-I genotype**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>Gender</th>
<th>Frequency of the 192/192 genotype</th>
<th>IGF-I 192/192 genotype (ng/mL)</th>
<th>IGF-I other genotypes (ng/mL)</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP + CAI</td>
<td>116</td>
<td>M+F</td>
<td>0.30</td>
<td>129 ± 7</td>
<td>154 ± 9</td>
<td>0.03</td>
</tr>
<tr>
<td>AP + HM</td>
<td>89</td>
<td>M</td>
<td>0.35</td>
<td>159 ± 9</td>
<td>188 ± 9</td>
<td>0.02</td>
</tr>
<tr>
<td>AP</td>
<td>59</td>
<td>M</td>
<td>0.30</td>
<td>145 ± 10</td>
<td>183 ± 10</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

\( ^a \) \text{ P value for unpaired } t \text{ test between serum levels of IGF-I in 192/192 homozygotes vs. serum levels from subjects with any other genotype.}
Fig. 2. Serum levels of IGF-I according to genotype in males recruited for an ongoing study of cardiovascular health and angina pectoris. Genotypes are labeled in following manner: 192/192 is homozygosity at most common allele in this microsatellite 1 kb upstream from transcription start site. All Others represent various combinations of alleles beside 192/192; mean ± SEM are noted as follows: 192/192, 145 ± 10 ng/mL vs. others, 183 ± 10 ng/mL, P < 0.02. Men (n = 19) possessing 192/194, the second most common genotype, had a mean serum IGF-I level of 183 ± 12 ng/mL, exactly same value as those men with all genotypes (n = 19) other than 192/192.

Maine cohorts (CAI and AP) and 7/30 from the HM group. Mean serum IGF-I levels in the AP cohort for those carrying a single 194-bp allele were 25% higher than those with the 192/192 genotype (165.1 ± 8.2 vs. 130 ± 8 ng/mL, P < 0.005).

The most frequent heterozygous allele combination in all cohorts was the 192/194, which was present in 39/146 individuals. Differences in serum IGF-I levels were even more dramatic in the AP cohort when comparing the two most frequently observed genotypes: 192/192, 130.6 ± 10 ng/mL vs. 192/194, 185 ± 10 ng/mL, P < 0.001. Similarly, in the HM group, although the number of subjects was smaller and therefore the difference was not statistically significant, the 192/192 genotype had consistently lower serum IGF-I levels than 192/194: 192/192, 182 ± 17 ng/mL vs. 192/194, 220 ± 32 ng/mL.

Because gender and age were variables that affected serum IGF-I, and there was a wide age range of subjects recruited in these cohorts, we compared IGF-I data between men and women with the two most common genotypes (192/192 vs. 192/194) after adjusting for sex and age. Those subjects with the 192/192 genotype still had serum IGF-I levels 20% lower than those with 192/194 (P = 0.02).

**IGF-I alleles and BMD**

As shown above, males with IOM have low serum IGF-I levels and a higher frequency of the 192/192 genotype. Therefore, we examined whether healthy males from the HM cohort in Virginia who were 192/192 had reduced spine or hip BMDs compared with those with any other genotype. Consistent with the 192/192 frequency observed for all non-IOM subjects, 12/30 males in this cohort were 192/192. These men (Table 3) had lower median BMD T scores at both the spine and hip than did the other 18 men with various genotypes, although the differences between the two did not quite achieve statistical significance (P = 0.15).

**Table 3.** Healthy males from Virginia (HM): IGF-I genotype and T scores of spine and hip

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Total hip (95% CI)</th>
<th>L-S spine (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>192/192</td>
<td>12</td>
<td>−1.035 (−1.4 to −0.18)</td>
<td>−0.58 (−1.53 to −0.03)</td>
</tr>
<tr>
<td>Others</td>
<td>18</td>
<td>−0.475 (−0.9 to −0.12)</td>
<td>−0.15 (−0.99 to +0.22)</td>
</tr>
</tbody>
</table>

**Discussion**

In this study we asked two questions: first, whether the variation noted in serum IGF-I levels among adult patients could be related to genetic determinants, and second, whether men with IOM were more likely to carry specific DNA sequences in a portion of the IGF-I gene. These questions arose because of our earlier findings that IOM was associated with low serum IGF-I levels, yet peak stimulated GH secretion was normal (10, 11). Those findings plus our recent studies in normal inbred strains of mice (8, 9) and work by Comuzie et al. (13) demonstrated that there are heritable determinants of serum IGF-I. Hence, we studied a number of distinct cohorts to assess association between a polymorphism in the IGF-I gene and serum levels.

Several lines of evidence from this study support our working hypothesis. First, we noted that men with IOM and low serum IGF-I concentrations were twice as likely to be homozygous for a 192-bp allele in the IGF-I gene. Moreover, in 30 HM, the 192/192 genotype was also associated with decreased BMD at both the spine and hip and lower serum IGF-I levels than men with any other genotype. These findings imply that there is a relationship between this polymorphism and the bone density phenotype.

Second, we noted that homozygosity for the 192 allele is associated with low serum levels of IGF-I for both men and women even after correction for age and gender. In fact, among all men in this study possessing the 192/192 genotype, the mean serum IGF-I level was almost identical to those who suffered from IOM. Yet that concentration of IGF-I is almost 1 sd below age-adjusted means for healthy men (9, 10, 12). This difference in serum IGF-I could have implications in determining acquisition of peak bone mass. For example, in our studies of inbred strains of mice, interstrain differences in serum IGF-I of 30% were strongly correlated with differences of 30% in femoral BMD (8, 9). Further studies will be required to assess whether there is a causative relationship between serum IGF-I and peak bone mass in man. These findings could have major implications in terms of screening men for osteoporosis and for understanding the pathogenesis of this devastating disease.

Although our data suggest an association between low levels of IGF-I and a polymorphism in the IGF-I gene, the cause of this association is, at present, not clear. This particular microsatellite is located only 1 kilobase upstream from the transcription start site, and is known to contain specific regulatory elements (17). Therefore, it is conceivable that allelic variation in this region could lead to changes in a promoter, thereby altering transcription of IGF-I (18). Alternatively, this polymorphism may be in linkage disequilibrium with another sequence in or near a promoter where message stability, or the half-life of circulating IGF-I could be affected (19). Both these possibilities require further investigation but lend credence to the hypothesis that there are
multiple non-GH regulators of IGF-I. For example, we have noted that GH secretion and nutritional determinants are normal in men with IOM (10, 11). These findings plus data generated from this study, could lead to identification of factors that control tissue-specific expression of IGF-I. Certainly, this has already been demonstrated for skeletal IGF-I, which is induced by PTH, and whose promoter region for cAMP is located very near the microsatellite reported in this study (17). Clearly, more studies will be needed to understand the genetic component of this relationship and its functional effects.

There are several limitations to this study. First, this is an association study and therefore a direct effect of IGF-I genotype on serum levels cannot be determined. Although the frequency distribution is suggestive, the number of subjects we studied, or less likely, some environmental factor unique to these 30 healthy men. Conclusions about a relationship between homozygosity in the 192 allele and BMD or IGF-I must await further studies in larger populations.

A second limitation is that we have so far studied only Caucasians who live on the east coast of the United States. Examination of other ethnic groups will be required to assess whether this relationship holds in other population groups. For example, African-American men have greater serum IGF-I levels and GH secretion than Caucasians (20). Also, there are measurable differences in body composition between Asians and Caucasians that could be related to expression of IGF-I. Therefore studies of this IGF-I polymorphism among different population groups may be particularly illuminating.

More rigorous proof of the relationship between genotype and the IGF-I phenotype can come through more definitive linkage studies, especially among extended families and pedigrees. Larger studies are planned in homogenous populations in which environmental factors have been at least partially controlled.

Finally, we do not know whether differences in serum IGF-I can be related to tissue expression of this peptide. Clearly, most circulating IGF-I is derived from the liver, and other investigators have shown that alternative splicing in exon 1 can occur in extrahepatic tissues such as bone (18). Because we have excluded GH deficiency (by provocative testing) in the IOM cohort, it is conceivable that nonhepatic sources of IGF-I could contribute to the serum levels of IGF-I observed in this study. Still, a more intensive investigation of tissue-specific IGF-I expression, as well as examination of several IGFBPs that regulate IGF bioactivity, will be required to determine the significance of these findings at a tissue level.

In summary, we report that serum IGF-I levels are related to a polymorphism in a microsatellite within the IGF-I gene. The consequence of such an association may include differences in acquisition of BMD. Further studies are needed to define the role of this polymorphism in the expression of serum and tissue IGF-I levels.

References