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Meta-analysis of genome-wide linkage studies for bone mineral density

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Abstract Genome-wide linkage studies have shown several chromosome loci that may harbor genes that regulate bone mineral density (BMD), but results have been inconsistent. A meta-analysis was performed to assess evidence for linkage of BMD across whole genome scan studies. Eleven whole-genome scans of BMD or osteoporosis containing 3,097 families with 12,685 individuals were included in this genome scan meta-analysis (GSMA). For each study, 120 genomic bins of ~30 cM were defined and ranked according to maximum evidence for linkage within each bin. Bin ranks were weighted and summed across all studies. The summed rank for each bin was assessed empirically for significance using permutation methods. A total of seven bins lie above the 95% confidence level ($P=0.05$) and one bin was above the 99% confidence level ($P=0.01$) in the GSMA of eleven linkage studies: bins 16.1 (16pter-16p12.3, *Psumrnk* <0.01), 3.3 (3p22.2-3p14.1), 1.1 (1pter-1p36.22), 18.2 (18p11.23-18q12.2), 6.3 (6p21.1-6q15), 20.1 (20pter-20p12.3), and 18.1 (18pter-18p11.23). GSMA was performed with seven studies with linkage scores of LOD > 1–1.85 for sensitivity test, confirming the linkage on chromosome 16p and 3p and revealing evidence of new linkage in bins 10.2 (10p14-10q11.21) and 22.2 (22q12.3-22pter). In conclusion, the meta-analysis of whole-genome linkage studies of BMD has shown chromosome 16pter-16p12.3 to have the greatest evidence of linkage as well as revealing evidence of linkage in chromosomes 1p, 3p, 6, 10, 18, 20p, and 22q across studies. This data may provide a basis with which to carry out targeted linkage and candidate gene studies particularly in these regions.

Keywords Osteoporosis · Bone mineral density · Linkage · Meta-analysis

Introduction

Osteoporosis is a skeletal condition characterized by decreased density (mass/volume) of normally mineralized bone (Glaser and Kaplan 1997). The World Health Organization has established diagnostic criteria for osteoporosis that are based on bone density measurements determined by dual-energy X-ray absorptiometry (DXA). A diagnosis of osteoporosis is made if a patient's bone density is 2.5 standard deviations or more below the mean for young normal people. Identification of specific loci or genes involved in determining bone mineral density (BMD) variation are important because low BMD is an important risk factor for osteoporosis-associated fractures (Cummings et al. 1985; Melton et al. 1989). Twin studies and family studies have shown that BMD has a high genetic determination, with heritability estimates ranging from 0.5 to 0.9 (Deng et al. 2000; Dequeker et al. 1987; Gueguen et al. 1995). Many whole genome scan studies have been performed to search for quantitative trait loci that regulate BMD or osteoporosis (Devoto et al. 1998; Kammerer et al. 2003; Karasik et al. 2002; Koller et al. 2000; Niu et al. 1999; Ralston et al. 2005; Shen et al. 2004; Stykarsdottir et al. 2003; Wilson et al. 2003). The genomic regions thus revealed are largely inconsistent and only few of these regions were replicated because the linkage studies were limited by small sample size, as well as clinical or genetic heterogeneity. Replication and confirmation of the findings are essential to enable conclusions to be drawn. Although literature reviews exist, no systematic statistical assessment of results has yet been carried out. Meta-analysis reduces the type I error rates resulting from independent tests of common hypotheses and provides greater statistical power. Therefore, meta-analysis may identify regions where the genetic effect is too small to be

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detected in an individual study. Combining the results of many studies through meta-analysis can aid the assessment of the consistency of evidence of linkage. Genome scan meta-analysis (GSMA) pools linkage results across studies by considering the genome to be made up of distinct bins of approximately equal length (Wise et al. 1999). GSMA was designed to deal with variation in study design, analytical methods and marker densities used in different genome scans (Levinson et al. 2003). The power of GSMA is known to be optimal in detecting effects observed across a large number of studies rather than effects in a few families or samples. The method is at its most useful when many weakly linked loci are seen across many studies. We performed GSMA of whole genome scans of BMD or osteoporosis using published data to assess evidence for linkage across studies.

Materials and methods

Selection of genome scans

The GSMA method assumes a uniform map in each scan, so we did not consider the second stages of genome scans where candidate regions were more densely mapped or samples were modified. Partial scans and candidate gene studies were excluded and genome scans with duplicated data also were not included. Whole genome scans for BMD or osteoporosis were identified via a PubMed search and via recent reviews of the literature. When there were duplicated data, we selected a study that had more information in terms of greater sample size such as included family numbers. Thus, there was no overlap of samples in this meta-analysis. Finally, nine genome-wide scans for BMD were included in this GSMA (Devoto et al. 1998; Kammerer et al. 2003; Karasik et al. 2002; Koller et al. 2000; Niu et al. 1999; Ralston et al. 2005; Shen et al. 2004; Stykarsdottir et al. 2003; Wilson et al. 2003). Two studies contained data on two different genome scans and we treated them independently (Kammerer et al. 2003; Wilson et al. 2003). Therefore, a total of 11 separate genome scans were considered in this meta-analysis. They included 3,097 families comprising 12,685 individuals. The main characteristics of the published genome scans are summarized in Table 1. Several studies did not show whole-genome linkage data (Devoto et al. 1998; Kammerer et al. 2003; Karasik et al. 2002; Koller et al. 2000; Niu et al. 1999; Ralston et al. 2005; Shen et al. 2004; Stykarsdottir et al. 2003; Wilson et al. 2003). Inclusion of a large number of studies increases the power to detect loci with small effects. Linkage scores were obtained from each study for the rank-ordering procedure. We used the maximum of linkage scores for any skeletal sites and proportion of linked families at each marker. Linkage scores were input in the bins and linkage scores with no data or zero were substituted as LOD scores of 0 and were considered ties. We performed the GSMA with all

available studies; we also conducted the GSMA with seven studies with linkage scores of $\text{LOD} > 1-1.85$ for sensitivity analysis (Devoto et al. 1998; Kammerer et al. 2003; Karasik et al. 2002; Koller et al. 2000; Niu et al. 1999; Ralston et al. 2005; Shen et al. 2004; Stykarsdottir et al. 2003; Wilson et al. 2003).

Genome scan meta-analysis

The GSMA was performed as described (Wise et al. 1999; Levinson et al. 2003). In brief, the autosomes were divided into 120 30-cM bins defined by Genethon markers (CEPH-Genethon Integrated Map Web site <http://www.cephb.fr/ceph-genethon-map.html>). On the Marshfield map, the average bin width was 29.1 cM. Each marker was placed within one of these bins, on the basis of its location on the Genethon or Marshfield map (available at <http://www.marshfieldclinic.org/research/genetics>). For each study, each bin was assigned a within-study rank (R_{study}) based on maximum linkage score within the bin. Bins were ranked in descending order (120 is the most significant result). A weighted GSMA was carried out to allow results to reflect the relative contribution of each study. For the weighted analysis, each R_{study} value was multiplied by its study's weight (square root of individual numbers), divided by the mean of this value over all studies. The rank of each bin was summed across the studies. A bin with high summed rank indicates evidence for linkage across several studies. Two pointwise P -values were determined, P_{sumrnk} and P_{ord} , as described and determined by 10,000 permutations of the weighted dataset. P_{sumrnk} is the probability of observing a bin's summed rank by chance, and P_{ord} is the probability of observing the j th place bin's summed rank in j th place bins in randomly permuted data. P_{sumrnk} is the most important as this measures whether the summed rank in a specific bin is significantly higher than expected.

The GSMA results were tested for heterogeneity between studies, using the Q statistic proposed by Zintzaras and Ioannidis (2005). Both tails of the distribution of Q were used for testing: high values indicate heterogeneity of linkage evidence between studies; low values indicate consistent linkage evidence across studies. High summed ranks have high study ranks and less potential to show genetic heterogeneity. The P -value for Q in each bin, P_{het} , was assessed from the subset of 10,000 simulations with summed rank closest to the observed summed rank for that bin.

Results

Individual genome scans

A variety of study designs have been used, including analysis of families with a history of osteoporosis (Devoto et al. 1998; Kammerer et al. 2003; Karasik et al.

Table 1 Characteristics of genome-wide scans for bone mineral density (BMD) or osteoporosis included in the meta-analysis

Genome scan (year)	Devoto et al. (1998)	Niu et al. (1999)	Koller et al. (2000)	Karasik et al. (2002)	Styrkarsdottir et al. (2003)	Kammerer et al. (2003)	Kammerer et al. (2003)	Wilson et al. (2003)	Wilson et al. (2003)	Shen et al. (2004)	Ralston et al. (2005)
Country or ethnicity (%)	United States	Asian	Caucasian African-American	United States	Caucasian	Mexican-American	Mexican-American	United Kingdom	United Kingdom	Caucasian	European
Study design	History of osteoporosis	Healthy sib-pairs	Healthy sib-pairs	Normal population	History of osteoporosis	Normal population	Normal population	Dizygotic twins	History of osteoporosis	Normal population	History of osteoporosis
No. of families	7	96	286	330	207	14	15	1,094	254	79	715
No. of individuals	149	218	636	1,557	1,323	259	261	2,188	587	1,816	3,691
BMD measurement sites	Spine, hip	Forearm	Spine, hip	Spine, hip	Spine, hip, whole body	Forearm, hip	Hip	Spine, hip, whole body	Spine, hip, whole body	Spine, hip, wrist	Spine, hip
Weighting factor	0.13	0.19	0.55	1.35	1.15	0.23	0.23	1.9	0.51	1.58	3.18
No. of autosomal markers	330	387	270	401	1,000	416	416	737	737	451	360
Test statistic	LOD	LOD	LOD	LOD	LOD	LOD	LOD	NPL	NPL	MLS	LOD
Major findings	1p36.22 (LOD = 3.51) 4q34.1 (LOD = 2.95)	2p21-2p24 (LOD = 2.15) 13q21-13q34 (LOD + 1.67)	1q21-23 (LOD = 3.11) 22q12-13 (LOD = 2.13)	21qter (LOD = 3.14) 6p21.2 (LOD = 2.93)	20p13-20p12.3 (LOD = 4.93) 18p11.31 (LOD = 2.12)	2p12 (LOD = 3.98) 13q13.1 (LOD = 3.46)	20p13 (LOD = 2.18) 7p14.1 (LOD = 1.83)	3p14.3 (NPL = 3.54) 16q12.2 (NPL = 3.12)	3p21.31 (NPL = 3.23) 4q25 (NPL = 2.81)	11q23 (ML S = 3.13) 7p15 (MLS = 2.64)	10q21 (LOD = 4.42) 20q13 (LOD = 3.20)

2002; Koller et al. 2000; Niu et al. 1999; Ralston et al. 2005; Shen et al. 2004; Stykarsdottir et al. 2003; Wilson et al. 2003), families drawn from the normal population (Devoto et al. 1998; Kammerer et al. 2003; Karasik et al. 2002; Koller et al. 2000; Niu et al. 1999; Ralston et al. 2005; Shen et al. 2004; Stykarsdottir et al. 2003; Wilson et al. 2003), healthy sib-pairs (Niu et al. 1999; Koller et al. 2000) and dizygotic twins (Wilson et al. 2003). The number of individuals included in the genome scans ranged from 149 to 3,691 and individual weighting factors were from 0.13 to 3.18. The number of autosomal markers used for the genome scans ranged from 330 to 1,000. Table 1 shows characteristics of the whole genome scans included in this GSMA. The strongest linkage findings were different across the genome scans. The strongest linkage loci in each individual study were 1p36.22, 2p21-2p24, 1q21-23, 21qter, 20p13-20p12.3, 2p12, 20p13, 3p13, 3p14.3, 3p21.31, 11q23, and 10q21, respectively. Among them, there were no replicated locus except for chromosome 20p13.

Meta-analysis of genome-wide scans for BMD

Figure 1 shows the summed ranks for each bin giving *Psumrnk* and the distribution of the weighted summed ranks across the genome. A total of seven bins lie above the 95% confidence level ($P=0.05$) and one bin is above the 99% confidence level ($P=0.01$) in osteoporosis GSMA: bins 16.1 (16pter-16p12.3, *Psumrnk* = 0.0022),

3.3 (3p22.2-3p14.1, *Psumrnk* = 0.012), 1.1 (1pter-1p36.22, *Psumrnk* = 0.028), 18.2 (18p11.23-18q12.2, *Psumrnk* = 0.029), 6.3 (6p21.1-6q15, *Psumrnk* = 0.03), 20.1 (20pter-20p12.3), and 18.1 (18pter-18p11.23). Table 2 summarizes the highest 10% of bins when ordered by summed rank. Chromosome 16 was the most significant, with a summed value of 919 (16pter-16p12.3, *Psumrnk* = 0.0022).

Heterogeneity *P*-values for the high-ranking bins are shown in Table 2. Low *P*-values indicate consistent evidence for linkage in all studies; high *P*-values indicate genetic heterogeneity with different evidence for linkage attained across studies. No bins showed significant evidence for genetic heterogeneity between studies.

Sensitivity analysis

For consistency within this meta-analysis, we conducted the GSMA with seven studies having linkage scores of LOD > 1–1.85 (Devoto et al. 1998; Kammerer et al. 2003; Karasik et al. 2002; Koller et al. 2000; Niu et al. 1999; Ralston et al. 2005; Shen et al. 2004; Stykarsdottir et al. 2003; Wilson et al. 2003). The GSMA showed four bins of *Psumrnk* < 0.05; bins 16.1 (*Psumrnk* = 0.0204), 3.3 (*Psumrnk* = 0.0269), 10.2 (*Psumrnk* = 0.0277), and 22.2 (*Psumrnk* = 0.0397). The most significant results in this GSMA were also shown in 11 studies with all available data (bin 16.1 and 3.3). The GSMA for sensitivity analysis confirmed the linkage on chromosome

Fig. 1 Meta-analysis results for genome-wide linkage scans of bone mineral density (BMD) or osteoporosis. Individual chromosomes were sub-divided into ~30 cM bins (represented by a dot), and bins

were ranked by the significance after summing weighted data across the studies. Significance levels corresponding to 99% (*Psumrnk* < 0.01) and 95% (*Psumrnk* < 0.05) are indicated by horizontal lines

Table 2 Meta-analysis results showing chromosomal bins with a summed rank within the highest 10% of observed summed rank values in weighted analysis

Bin	Marshfield location (cM)		Cytogenetic location	Weighted analyses			<i>Phet</i>
	Begin	End		Rank	<i>Psumrnk</i>	<i>Pord</i>	
16.1	0	32.07	16pter-16p12.3	985	0.00222	0.23728	0.36415
3.3	63.12	88.6	3p22.2-3p14.1	919	0.01210	0.43806	0.51095
1.1	0	20.61	1pter-1p36.22	885	0.02802	0.69813	0.44810
18.2	24.08	38.76	18p11.23-18q12.2	882	0.02947	0.48595	0.39070
6.3	65.14	99.01	6p21.1-6q15	882	0.02965	0.25787	0.14345
20.1	0	21.15	20pter-20p12.3	853	0.04736	0.52425	0.09170
18.1	0	24.08	18pter-18p11.23	853	0.04754	0.33247	0.08190
16.4	100.39	134.12	16q23.1-qter	847	0.05140	0.24408	0.06925
4.5	78.97	109.02	4q13.3-4q24	836	0.05928	0.25028	0.39320
4.6	134.74	159.3	4q28.3-4q32.1	833	0.06175	0.16088	0.45195
20.4	72.27	101.22	20q13.13-qter	826	0.06962	0.15668	0.09420
7.2	29.28	59.93	7p21.1-7p14.1	821	0.07763	0.15698	0.01700
14.2	40.11	74.96	14q13.1-14q24.1	818	0.08253	0.11559	0.00210
1.6	142.24	170.84	1p13.3-1q23.3	816	0.08422	0.06059	0.13025
10.3	62.23	91.13	10p11.21-10q22.1	814	0.09054	0.04400	0.90505
3.2	32.36	63.12	3p25.3-3p22.2	810	0.09794	0.03870	0.02390

3p and 16p and revealed new linkage in bins 10.2 (10p14-10q11.21) and 22.2 (22q12.3-22pter). We also performed the meta-analysis of the two study groups using large pedigrees (>100 families) and small pedigrees (≤ 100), respectively. The GSMA with large pedigrees showed two significant bins 16.1 (*Psumrnk* = 0.0134) and 1.1 (*Psumrnk* = 0.0150), but the GSMA of small pedigrees did not reveal any significant bin among the significant bins found by the GSMA with all families (data not shown).

Discussion

Whole-genome linkage studies of BMD or osteoporosis have revealed several chromosomal regions that are likely to harbor susceptibility genes predisposing to osteoporosis or BMD. However, the results of linkage studies have been inconsistent across the studies and only a few loci have been replicated. This may have been due to small sample size and heterogeneity in the nature of the genetic component between different skeletal sites, between the two sexes, and between different ethnic groups (Duncan et al. 2003; Naganathan et al. 2002). In addition, many of these loci may have a small locus-specific effect on susceptibility, thus it may be hard to find consistency without using very large number of families or meta-analysis (Altmuller et al. 2001).

Here we have conducted a meta-analysis of genome wide scans of BMD from 3,097 families with 12,685 individuals taking part in 11 studies in an attempt to increase statistical power and to enhance evidence of linkage in BMD regulation. Our meta-analysis showed summarized linkage loci for BMD across whole-genome linkage studies. The meta-analysis revealed seven interesting linkage loci, including bin 16.1 with the highest summed rank (chromosome 1p, 3p, 6, 16p, 18p, 18q, and 20p). There were no bins that showed significant evidence for genetic heterogeneity between studies.

GSMA with seven studies having linkage scores of LOD > 1–1.85 confirmed linkage on chromosome 3p and 16p and revealed new linkage in bins 10.2 and 22.2 (chromosome 10 and 22q). It is important to note that 3 out of 11 studies have shown suggestive linkage evidence in chromosome 16pter-16p12.3 (bin 16.1) (LOD scores 1.75, 2.26, and 2.526, respectively) (Karasik et al. 2002; Wilson et al. 2003; Ralston et al. 2005). The GSMA method is based on several studies of genetically diverse populations and is powerful for genes contributing to all populations. GSMA is useful when there are weakly linked loci seen across many studies. Consistency of the linkage evidence across different studies may be more indicative of true linkage than the actual magnitude of any one finding. Therefore, it is likely that some of the regions identified by the present GSMA contain genes that regulate BMD or predispose to osteoporosis.

There were limitations to this meta-analysis. First, we could not exclude an effect of different ethnic groups on the results in this meta-analysis because of limited information. Ethnic differences in linkage for osteoporosis need to be investigated further. Second, we examined published genome scans. Our analysis was a little different from the original GSMA (Wise et al. 1999). We used published linkage scores instead of whole genome data. Our study might have lower statistical power or more bias than the GSMA method using whole genome linkage data. Had the GSMA method with whole genome data been used, it is possible that other chromosomal regions may show evidence for linkage. Although there might be a possible bias in our analysis, we believe that our meta-analysis using published data is not invalid to assess evidence for linkage of RA across genome scan studies. For example, a previous meta-analysis using published data instead of whole genome data has shown that the analysis is more powerful than one of several genome scans in detecting significant linkage without increasing false positives, and is also robust to a considerable amount of heterogeneity

(Badner and Gershon 2002). Third, although the meta-analysis significantly increases the sample size, it also may introduce heterogeneity, arising from phenotypic differences between different populations, ethnic and geographic differences. There is a need for the judicious application of phenotypic stratification as a means of reducing heterogeneity in gene mapping studies.

Choosing candidate genes for association studies is an uncertain process in a complex disease such as osteoporosis. The major susceptibility genes are likely to remain unknown as yet. However, this meta-analysis supports the hypothesis that there may be important gene(s) on several loci identified by the GSMA. Possible candidate genes in linkage regions on chromosomes contain bone morphogenetic protein-6 (BMP-6) at chromosome 6pter-6p21 (Feldman et al. 1995), and BMP2 on chromosome 20 (Fujii et al. 1999), methylenetetrahydrofolate reductase (MTHFR), Rb-interacting zinc finger (RIZ1), tumor necrosis factor receptor (TNFRF) superfamily members 2, 9, and 18, and lysyl hydroxylase (PLOD1) on 1pter-1p36 (Spotila et al. 2003). The MTHFR 677TT genotype is associated with low BMD and increased fracture incidence in early postmenopausal women in Japanese and European populations (Abrahamsen et al. 2003). Future efforts to identify genes regulating BMD may need to investigate the chromosomes highlighted by the GSMA. Many candidate genes in other chromosome regions have been reported to be associated with BMD, such as vitamin D receptor, collagen type 1 alpha 1 (COL1A1), estrogen receptor, transforming growth factor beta-1, lipoprotein receptor-related protein-5, sclerostin, and TCF12. This might reflect the limited power of linkage studies compared with association analyses.

In conclusion, this meta-analysis of genome-wide linkage studies of BMD has shown chromosome 16pter-16p12.3 to have the greatest linkage evidence, and revealed evidence of linkage in chromosome 1p, 3p, 6, 10, 18, 20p, and 22q across studies. We believe that this data may provide a basis from which to carry out targeted linkage and candidate gene studies in these regions.

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