Symposium on ‘Genetic polymorphisms and disease risk’

Genetics of osteoporosis

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Osteoporosis is a common disease with a strong genetic component characterised by reduced bone mass and an increased risk of fragility fractures. Twin and family studies have shown that genetic factors contribute to osteoporosis by influencing bone mineral density (BMD), and other phenotypes that are associated with fracture risk, although the heritability of fracture itself is modest. Linkage studies have identified several quantitative trait loci that regulate BMD but most causal genes remain to be identified. In contrast, linkage studies in monogenic bone diseases have been successful in gene identification, and polymorphisms in many of these genes have been found to contribute to the regulation of bone mass in the normal population. Population-based studies have identified polymorphisms in several candidate genes that have been associated with bone mass or osteoporotic fracture, although individually these polymorphisms only account for a small amount of the genetic contribution to BMD regulation. Environmental factors such as diet and physical activity are also important determinants of BMD, and in some cases specific nutrients have been found to interact with genetic polymorphisms to regulate BMD. From a clinical standpoint, advances in knowledge about the genetic basis of osteoporosis are likely to be important in increasing the understanding of the pathophysiology of the disease; providing new genetic markers with which to assess fracture risk and in identifying genes and pathways that form molecular targets for the design of the next generation of drug treatments.

Osteoporosis: Fracture: Bone mineral density: Linkage, genetic and association studies

Genetic factors play an important role in the pathogenesis of osteoporosis. Twin- and family-based studies have indicated that 60–85% of the variance in bone mineral density (BMD) is genetically determined (Krall & Dawson-Hughes, 1993; Gueguen et al. 1995), and other risk factors for osteoporotic fractures, such as quantitative ultrasound properties of bone, femoral neck geometry and bone turnover markers range, have also been shown to have a strong heritable component (Arden et al. 1996; Garnero et al. 1996). Family history of fracture has been shown in several studies to be a risk factor for fractures independently of BMD (Cummings et al. 1995; Torgerson et al. 1996), and in keeping with this finding several investigators (Deng et al. 2000; Andrew et al. 2005) have reported that fracture may have a heritable component. In one study of post-menopausal women (Deng et al. 2000) heritability of wrist fracture was estimated as about 25%, whereas another study of twins (Andrew et al. 2005) has suggested that the heritability of wrist fracture may be as much as 54%. Interestingly, the heritability of wrist fracture in both these studies was shown to be largely independent of BMD, suggesting that predisposition may have been mediated through genetic influences on other factors such as bone turnover, bone geometry or even perhaps the risk of falling. However, another study (Kannus et al. 1999) has failed to detect any evidence for heritability of fractures in elderly twins. These divergent results are probably explained by the fact that the heritability of fracture decreases with age, as environmental factors become more important. This relationship has

Abbreviations: BMD, bone mineral density; LRP, lipoprotein receptor-related protein; QTL, quantitative trait loci; VDR, vitamin D receptor.
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been demonstrated in a large study of Swedish twins (Michaelsson et al. 2005), which has shown that the heritability of hip fracture is about 68% in those aged <65 years but drops off rapidly with age to reach a value of almost zero by the eighth decade. This finding illustrates that identifying genes that are related to risk factors for osteoporosis such as BMD does not necessarily mean that these genes will influence the risk of fracture.

### Human linkage studies

Several genome-wide linkage scans have been performed to try to identify loci that regulate BMD. The most important quantitative trait loci (QTL) for BMD identified by these studies are summarised in Table 1. Few of the genome-wide scans so far performed have identified QTL that meet the criteria for genome-wide significance, and only one gene that regulates susceptibility to osteoporosis has been identified by this approach; the *BMP2* gene that encodes bone morphogenic protein 2, an important regulator of osteoblast differentiation (Styrkarsdottir et al. 2003). Several important findings have emerged from these studies. First, it appears that the genes that regulate BMD probably do so in a site-specific and gender-specific manner (Peacock et al. 2005; Ralston et al. 2005). The lack of replication of linkage peaks between studies mirrors experience in other complex diseases and might reflect the fact that genes that regulate BMD differ in different populations or that genes that predispose to osteoporosis have modest effects that are difficult to detect by conventional linkage analysis. Technical advances such as the development of densely-spaced panels of single-nucleotide polymorphisms for genome-wide scans are likely to improve the chances of detecting genes of modest effect size in the future (Sawcer et al. 2004). There is also a prospect that meta-analysis of genome-wide scans may reveal significant QTL that have not been detected by individual studies (Fisher et al. 2003).

Interest has also focused on identifying QTL for the regulation of other phenotypes relevant to the pathogenesis of osteoporosis. For example, genome-wide linkage scans have identified several QTL that strongly influence hip geometry (Koller et al. 2001), while others have been performed that have identified QTL that regulate the quantitative ultrasound properties of bone (Wilson et al. 2004).

### Animal linkage studies

Linkage studies in mice (Klein et al. 1998; Beamer et al. 2001), rats (Koller et al. 2005) and primates (Mahaney 2002) have been performed that have identified QTL that regulate the quantitative ultrasound properties of bone (Wilson et al. 2004).

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**Table 1. Quantitative trait loci for bone mineral density detected by genome-wide linkage scan**

<table>
<thead>
<tr>
<th>Study</th>
<th>Chromosome</th>
<th>cM†</th>
<th>Nearest marker</th>
<th>LOD score</th>
<th>Site</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng et al. (2002)</td>
<td>4q31–32</td>
<td>152</td>
<td>D4S424</td>
<td>3.08</td>
<td>Spine</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>13q33–34</td>
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<td>D13S285</td>
<td>2.43</td>
<td>Spine</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>10q26</td>
<td>170</td>
<td>D10S1651</td>
<td>2.29</td>
<td>Fem neck</td>
<td>Both</td>
</tr>
<tr>
<td>Koller et al. (2000)</td>
<td>1q21–23</td>
<td>169</td>
<td>D1S484</td>
<td>3.11</td>
<td>Spine</td>
<td>Female</td>
</tr>
<tr>
<td>Wilson et al. (2003)</td>
<td>1p36</td>
<td>17</td>
<td>D1S214</td>
<td>2.38</td>
<td>Total hip</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>3p22</td>
<td>76</td>
<td>D3S1289</td>
<td>2.72</td>
<td>Spine</td>
<td>Female</td>
</tr>
<tr>
<td>Karasik et al. (2002)</td>
<td>21q22.2</td>
<td>40</td>
<td>D21S2055</td>
<td>2.39</td>
<td>Total hip</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>21qter</td>
<td>58</td>
<td>D21S1446</td>
<td>3.14</td>
<td>Total hip</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>9q22</td>
<td>120</td>
<td>D9S930</td>
<td>2.71</td>
<td>Fem neck</td>
<td>Both</td>
</tr>
<tr>
<td>Devoto et al. (1998)</td>
<td>1p36</td>
<td>36</td>
<td>D1S450</td>
<td>2.29</td>
<td>Fem neck</td>
<td>Both</td>
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<tr>
<td></td>
<td>2p23–24</td>
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<td>D2S149</td>
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<td>Both</td>
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<tr>
<td></td>
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<td>265</td>
<td>D4S1535</td>
<td>2.28</td>
<td>Spine</td>
<td>Both</td>
</tr>
<tr>
<td>Styrkarsdottir et al. (2003)</td>
<td>20p12</td>
<td>20</td>
<td>D2OS905</td>
<td>2.89</td>
<td>Spine</td>
<td>Both</td>
</tr>
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<td>D2OS905</td>
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<td>D9S930</td>
<td>2.71</td>
<td>Fem neck</td>
<td>Both</td>
</tr>
<tr>
<td>Kammerer et al. (2003)</td>
<td>6q27</td>
<td>190</td>
<td>D6S281</td>
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<td>Trochanter</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>2pter</td>
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<tr>
<td></td>
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<td>D13S788</td>
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<td>D13S788</td>
<td>2.51</td>
<td>Fem neck</td>
<td>Male</td>
</tr>
<tr>
<td>Ralston et al. (2005)</td>
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<td>D3S1279</td>
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<td>Fem neck</td>
<td>Male</td>
</tr>
<tr>
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<td>4q25</td>
<td>117</td>
<td>D4S1572</td>
<td>2.22</td>
<td>Fem neck</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>7p14</td>
<td>57</td>
<td>D7S516</td>
<td>2.28</td>
<td>Fem neck</td>
<td>Male</td>
</tr>
<tr>
<td></td>
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<td>80</td>
<td>D10S196</td>
<td>4.20</td>
<td>Fem neck</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>16p13</td>
<td>31</td>
<td>D16S3075</td>
<td>2.52</td>
<td>Fem neck</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>4q25</td>
<td>117</td>
<td>D4S1572</td>
<td>2.55</td>
<td>Fem neck</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>16q23</td>
<td>31</td>
<td>D16S3091</td>
<td>2.28</td>
<td>Spine</td>
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<td></td>
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<tr>
<td></td>
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<td>90</td>
<td>D20S196</td>
<td>3.20</td>
<td>Spine</td>
<td>Female</td>
</tr>
</tbody>
</table>

*The loci shown are those identified by genome-wide scan for which the LOD score exceeded +2.2. The LOD score is the logarithm of the odds that the disease gene and the marker being studied are linked. For complex diseases linkage is considered significant when the LOD score exceeds +3.6, whereas linkage is considered suggestive when the LOD score exceeds +2.2.*

†A measure of the physical distance between the locus identified and the telomere (tip) of the chromosome.
et al. 1997) have resulted in the identification of several QTL that regulate BMD. Linkage analysis has also been used to localise QTL for other osteoporosis-related phenotypes such as bone structure, bone shape and bone strength (Turner et al. 2003; Alam et al. 2005) and circulating levels of insulin-like growth factor-1 (Bouxsein et al. 2002). Loci for the regulation of BMD have now been identified on almost all mouse chromosomes, and several rat chromosomes with replication of some QTL across different strains, and replication of some human BMD QTL (Koller et al. 2005). These studies have also shown that the genes that regulate BMD in mice have effects that are site-specific and gender-specific (Beamer et al. 2001; Orwoll et al. 2001). To date, only one gene that regulates BMD, the Alox15 gene, has been identified, by studies in mice (Klein et al. 2004). In this study a QTL for the regulation of BMD was identified on mouse chromosome 11 by linkage in a cross of DBA/2 and C57BL/6 mice, and subsequent microarray analysis has shown that the parental DBA2 strain of mice (low BMD) has a 20-fold increase in expression of the Alox15 mRNA when compared with C57BL/6 (high BMD) mice. From this observation the authors had suspected that Alox15 might act as a negative regulator of bone mass and they have confirmed this hypothesis by finding that Alox15-knock-out mice have increased BMD and that inhibition of Alox15 protects against ovariectomy-induced bone loss. The mechanism by which Alox15 reduces BMD is unclear, but the gene encodes a lipoxigenase enzyme that converts arachidonic and linoleic acids into ligands for the transcription factor PPARγ, which is thought to regulate differentiation of mesenchymal cells into adipocytes and osteoblasts. Recent studies have shown that genetic variation in a human homologue of Alox15 accounts for some of the heritable component of spine BMD regulation in man (Ichikawa et al. 2006).

**Candidate gene studies**

Candidate gene association studies have identified several polymorphisms that are associated with BMD, bone loss or osteoporotic fractures. Some of the most important candidate genes that have been implicated in the pathogenesis of osteoporosis will be discussed.

**Vitamin D receptor**

The vitamin D receptor (VDR) was the first candidate gene to be studied in relation to BMD regulation and most attention has focused on polymorphisms situated on the 3’ flank of VDR recognised by the restriction enzymes BsmI, Apal and TaqI. A meta-analysis of association studies that have genotyped the BsmI polymorphism have concluded that there is evidence of an association between spine BMD and the BsmI polymorphism, equivalent to approximately 0.15 Z-score units, between the BB genotype and the other genotypes (Thakkinstian et al. 2004). Another polymorphism affecting exon 2 of VDR has been identified that creates an alternative translational start site, resulting in the production of two isoforms of the VDR protein that differ in length by three amino acids (Gross et al. 1997). This polymorphism has been associated with BMD in some studies, but functional studies have yielded inconclusive results (Gross et al. 1998). A polymorphism has been identified in the promoter of VDR at a binding site for the transcription factor Cdx-2 that has been associated with BMD in Japanese subjects and appears to be functional (Arai et al. 2001). This polymorphism has been associated with fracture in other populations, but not with BMD (Fang et al. 2003). The most comprehensive study of VDR alleles in relation to osteoporosis has been in the Rotterdam study in which haplotype-tagging single-nucleotide polymorphisms of VDR were analysed in 6418 subjects (Fang et al. 2005). Alleles were identified in the promoter region and 3’ untranslated region that were shown to be associated with an increased risk of fracture, and a subgroup of individuals who carried risk alleles at both sites were found to have an increased risk of fracture when compared with control subjects. Functional studies have also shown that the promoter haplotype that increases fracture risk is associated with reduced VDR expression in reporter assays whereas the 3’ UTR risk haplotype is associated with increased degradation of VDR mRNA. The data would be consistent with a model whereby the combination of risk haplotypes results in a lower VDR mRNA level as a result of decreased transcription and increased degradation. Interestingly, the risk alleles for fracture identified in this study were not associated with differences in BMD. In view of this finding, the mechanism by which these polymorphisms predispose to fracture is unclear. Moreover, if correction had been applied for all the combinations of VDR haplotypes tested in this study in relation to fracture, the association would not have been significant.

**Collagen type I α1**

COLIA1, the gene encoding the α1 chain of type I collagen, is an important functional candidate for the pathogenesis of osteoporosis, as type I collagen is the major protein of bone. Extensive studies have been conducted on a polymorphism that lies within intron 1 of the COLIA1 gene at a Sp1 binding site (Grant et al. 1996). The thymidine-containing allele of this polymorphism has been associated with reduced bone density (Grant et al. 1996; Uitterlinden et al. 1998) and other osteoporosis-related phenotypes such as post-menopausal bone loss (Harris et al. 2000; MacDonald et al. 2001), bone geometry (Qureshi et al. 2001), bone quality (Mann et al. 2001) and bone mineralization (Stewart et al. 2005). Functional analysis has shown that the osteoporosis-associated T allele (‘s’) of the Sp1 polymorphism is associated with increased DNA–protein binding, increased transcription from the T allele and abnormally increased production of the collagen type I α1 mRNA and protein (Mann et al. 2001). It is thought that the resulting imbalance between the α1 and α2 chains of collagen type I may contribute to impairment of bone strength and reduced bone mass in carriers of the T allele by subtly affecting bone mineralization (Stewart et al. 2005). Meta-analyses of published studies (Efstathiadou et al. 2001; Mann et al. 2001; Mann & Ralston, 2003) have
concluded that carriage of the T allele is associated with reduced BMD at the lumbar spine and femoral neck and with vertebral fractures. More recently, two polymorphisms (−1997G/T and −1663delT) have been identified in the COL1A1 promoter region and have been associated with BMD (Garcia-Giralt et al. 2002). These polymorphisms are in linkage disequilibrium with the Sp1 polymorphism, and functional studies have shown that the polymorphisms influence COL1A1 transcription in promoter–reporter assays (Garcia-Giralt et al. 2005). The −1997G/T promoter polymorphism has been studied in relation to BMD in other populations and in family-based studies (Liu et al. 2004; Yamada et al. 2005; Zhang et al. 2005) with mixed results, although most of these studies have been of limited sample size. Current evidence indicates that the promoter polymorphisms and the Sp1 polymorphism interact to regulate BMD in women (Stewart et al. 2006), indicating that the previously-reported associations between the Sp1 polymorphism and osteoporosis-related phenotypes may in fact be driven by an extended haplotype involving the Sp1 and promoter polymorphisms.

Oestrogen receptor α

The oestrogen receptor α, encoded by the ESR1 gene, is another important functional candidate for the regulation of bone mass. A large number of investigators have looked for evidence of an association between ESR1 alleles and BMD, mostly focusing on two polymorphisms within intron 1, recognised by the XbaI and PvuII restriction enzymes. There is some evidence to suggest that these polymorphisms regulate ESR1 transcription and that they may therefore be functionally important (Herrington et al. 2002). A meta-analysis of published studies performed up until 2001 (Ioannidis et al. 2002) has shown an association between the XbaI polymorphism, BMD and fractures, with higher BMD values and reduced fracture risk in ‘Xc’ homozygotes. Recently, a large prospective analysis in the Genetic Markers for Osteoporosis Project has confirmed that XX homozygotes have a reduced risk of fracture (Ioannidis et al. 2004), but no association with BMD was observed, indicating that ESR1 might influence fracture risk by mechanisms that are independent of BMD. One possible mechanism might be through effects on bone quality or bone turnover, since ESR1 alleles have recently been associated with ultrason sound properties of bone and rates of post-menopausal bone loss (Albagha et al. 2005).

Transforming growth factor β1

Several polymorphisms of the TGFBI gene that encodes the growth factor transforming growth factor β-1 have been identified and some of them have been associated with BMD and/or osteoporotic fracture in various studies (Langdahl et al. 1997; Yamada et al. 2001). The best functional candidate is a C/T polymorphism that causes a proline to leucine amino acid substitution at position 10 in the transforming growth factor β-1 signal peptide that has been associated with circulating transforming growth factor β-1 levels. However, this polymorphism is in strong linkage disequilibrium within other polymorphisms in the TGFBI promoter and effects on transcription are also possible (Shah et al. 2005). Although many association studies have been performed, most are of limited sample size and further large-scale studies will be required to confirm or refute the status of TGFBI as a true susceptibility gene for osteoporosis.

Lipoprotein receptor-related protein 5

Inactivating mutations of the lipoprotein receptor-related protein (LRP) 5 gene are the cause of the rare recessive disorder osteoporosis pseudoglioma syndrome (Gong et al. 2001), whereas activating mutations in the same gene cause autosomal dominant inheritance of high bone mass (Little et al. 2002). The involvement of LRP5 in these rare monogenic bone disorders led several investigators to evaluate the role of LRP5 as a candidate gene for BMD regulation in the normal population. Six studies have now been published showing evidence of an allelic association between polymorphisms in LRP5 and BMD (Ferrari et al. 2004; Koay et al. 2004; Koh et al. 2004; Mizuguchi et al. 2004; Urano et al. 2004; van Meurs et al. 2006). Many variants have been studied, but the most likely functional candidate is an alanine to valine amino acid substitution at position 1330 (A1330V). The mechanism by which this variant affects LRP5 signalling has not been investigated, but evidence of an interaction between the LRP5 A1330V variant and a coding polymorphism of LRP6 (1062V) has been gained in the Rotterdam study (van Meurs et al. 2006), in which polymorphisms of both genes were found to interact to affect fracture susceptibility. One consistent feature to emerge from these studies is that the association between LRP5 alleles and BMD is stronger in males (Ferrari et al. 2004; Koay et al. 2004), which suggests that LRP5 may regulate bone mass in a gender-specific manner.

Sclerostin

Mutations affecting the SOST gene, which encodes sclerostin, are the cause of the sclerosing bone dysplasias Van Buchem disease and sclerosteosis (Balemans et al. 2001, 2002b; Brunkow et al. 2001). Polymorphisms of SOST have been evaluated in relation to BMD in two studies. In one study (Balemans et al. 2002a) no association between SOST polymorphism and BMD was found in perimenopausal women using a case–control design, whereas in another study of older women (Uitterlinden et al. 2004) evidence of an association with BMD was observed in men and women, with effects that increase with age. These data suggest that SOST polymorphisms may regulate BMD, especially in older individuals.

TCIRG1

The TCIRG1 gene encodes the APT6i subunit of the osteoclast-specific proton pump (Frattini et al. 2000). Inactivating mutations in TCIRG1 are responsible for a subset of patients with recessive osteopetrosis. Recent work indicates that polymorphisms of TCIRG1 might contribute to regulation of BMD in the normal population;
a study by Frattini (Sobacchi et al. 2004) has shown evidence of an association between a polymorphism affecting an activator protein 1-binding site in the TCIRG1 promoter and BMD in peri-menopausal women. However, functional studies need to be performed to identify the mechanisms that underlie this association and to replicate the finding in other populations.

**CLCN7**

The CLCN7 gene encodes a chloride channel that is highly expressed in osteoclasts and essential for acidification of the resorption lacuna. Homozygous inactivation mutations in CLCN7 cause a severe form of recessive osteopetrosis whereas heterozygous missense mutations of CLCN7 cause autosomal dominant osteopetrosis (Balemans et al. 2005). Prompted by this observation Pettersson et al. (2005) have looked for evidence of an association between polymorphisms of CLCN7 and BMD in normal individuals and have found that a common polymorphism in exon 15 of CLCN7 that results in a methionine to valine amino acid change is associated with BMD in normal women. Further studies will be required to determine whether this polymorphism is functionally important and to replicate the observation in other populations.

**Gene–environment interactions**

Several studies have been performed in which interactions have been sought between environmental factors and polymorphic variants in candidate genes. For the most part, these studies have been underpowered and conflicting results have been obtained. The most widely studied gene–environment interaction is between VDR alleles and Ca or vitamin D intake. An early study (Krall et al. 1995) has shown faster rates of post-menopausal bone loss in women with the BB genotype of VDR than in women with other genotype groups, but have found that Ca supplements (500 mg daily) abolish this difference. Another study (Ferrari et al. 1995) has shown that change in lumbar spine bone density is associated with Ca intake in elderly subjects who have the VDR ‘Bb’ genotype group, but not in other genotypes. The largest study of VDR alleles in relation to bone mass, bone loss and Ca intake is that of MacDonald et al. (2006) who found little evidence of an interaction between Ca intake, VDR alleles and bone mass or bone loss. A functional polymorphism at position 677 (C677T) in the methylene tetrahydrofolate reductase gene has been associated with BMD and fracture in various studies (Miyao et al. 2000; Jorgensen et al. 2002; Abrahamsen et al. 2003; Bathum et al. 2004), but the results have been inconsistent, since in some studies (Abrahamsen et al. 2003; Bathum et al. 2004) the T allele has been associated with osteoporosis and in others (Jorgensen et al. 2002) the C allele has been associated with osteoporosis. Recent work has suggested that folate status (McLean et al. 2004) or riboflavin status (MacDonald et al. 2004) might influence the association between methylene tetrahydrofolate reductase alleles and BMD.

**Conclusions**

Many advances have been made in understanding the role of genetic factors in osteoporosis over the past 10 years, but a great deal of additional research is required to identify the genes that regulate BMD and other phenotypes relevant to the pathogenesis of osteoporotic fractures. Until recently, most of the studies in the area of osteoporosis genetics have been underpowered, leading to results that have seldom been replicated (Ioannidis, 2003). It has now become clear that large-scale studies need to be assembled to evaluate the true role of genetic polymorphisms in osteoporosis and other complex diseases (Ioannidis et al. 2006). It is likely that large-scale studies, when combined with technological advances such as genome-wide association, will assist in identifying and validating the role of candidate gene polymorphisms in the regulation of BMD and other markers of osteoporosis susceptibility.

**References**


S. H. Ralston


Langdahl BL, Knudsen JY, Jensen HK, Gregersen N & Eriksen EF (1997) A sequence variation: 713–8 eCL in the transforming growth factor-beta 1 gene has higher prevalence in osteoporotic women than in normal women and is associated with very low bone mass in osteoporotic women and increased bone turnover in both osteoporotic and normal women. *Bone* 20, 289–294.


