Ethnic difference in osteoporosis-related phenotypes and its potential underlying genetic determination

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Abstract

Osteoporosis is a serious health problem in both Caucasians and Asians. Caucasians and Asians are two distinct major ethnic groups, which may have differential genetic determination underlying complex genetic diseases such as osteoporosis. However, to date, there has been no systematic review focusing on the aspect of ethnic difference in risk to osteoporosis and its potential underlying genetic determination between Asians and Caucasians. Here, we firstly review diverse aspects of osteoporosis-related differences, including the differences of epidemiology of osteoporotic fractures, peak bone mass, bone loss, bone area, bone geometry and drug treatment response between Asians and Caucasians. Then, we provide some potential genetic evidence on the different heritability and inheritance mode of bone phenotypes, the different osteoporosis candidate genes and the differential results in related molecular studies between them, to explain the above osteoporosis-related phenotypic differences. The results suggest that the osteoporosis-related phenotypic differences between Asians and Caucasians may be partially the result of the different ethnic genetic background. The present review may increase our understanding of potential different mechanisms related to ethnicity in pathogenesis of osteoporosis for effective and potentially customized treatments in different major ethnic groups.

Keywords: Osteoporosis, Bone Mineral Density, Osteoporotic Fracture, Asians, Caucasians

Osteoporosis, as a serious metabolic bone disease, is characterized by low mineral density (BMD) and poor bone quality, resulting in an increased risk for osteoporotic fractures. Osteoporosis constitutes a serious health problem both in Asians and Caucasians¹². In China, 6.97% of Chinese people (about 88 million) suffer from primary osteoporosis¹. To dissect the complex genetic determination of osteoporosis, BMD is a commonly used surrogate study phenotype due to their high correlation with osteoporosis. Caucasians and Asians are two distinct major ethnic groups and many studies have implicated the differential genetic determination of osteoporosis between the two populations¹⁴. However, to date, there has been no systemic review focusing on these aspects. Here, we attempt to integrate the recent progresses in osteoporosis research, with the aim of contributing to the understanding of the ethnic differential pathogenesis of osteoporosis and effective treatment of osteoporosis in different ethnic groups. In the following, we are going to review diverse aspects of osteoporosis-related differences between Asians and Caucasians, starting from phenotypes and then proceeding to genetic factors.

Osteoporosis-related phenotypic differences

Caucasians and Asians are two distinct major ethnic groups. Therefore, there are some potential differences in osteoporosis-related phenotypes including epidemiology of osteoporotic fractures, peak bone mass, bone loss, bone area, bone geometry and drug treatment response.

Epidemiology of osteoporotic fractures

The most serious clinical complication of osteoporosis is osteoporotic fracture. These fractures typically occur at the spine, hip and distal forearm. As far as vertebral fractures
are concerned, it is clinically difficult to definitely diagnose them due to the lack of universally accepted criteria, which may hamper the calculation and comparison of its incidence in epidemiological studies. However, from the limited preliminary data, the inconsistent incidence of vertebral fracture was found between Asians and Caucasians. Lau et al. concluded the prevalence of vertebral fracture was similar in Hong Kong Chinese (29%) and American Caucasians (25%). In contrast, both vertebral fracture prevalence and incidence were reported to be higher in Japanese women than American Caucasian women. Thus, we cannot make any confident conclusions about racial differences in vertebral fracture rates until standard morphometric definitions of vertebral fracture are employed.

Hip fractures are associated with significantly increased morbidity and mortality rates. Almost all of the studies consistently reported that the age and sex-adjusted annual rate of hip fracture was lower in Asians than in Caucasians. Lau et al. concluded the prevalence of vertebral fracture was similar in Hong Kong Chinese (29%) and American Caucasians (25%). In contrast, both vertebral fracture prevalence and incidence were reported to be higher in Japanese women than American Caucasian women. Thus, we cannot make any confident conclusions about racial differences in vertebral fracture rates until standard morphometric definitions of vertebral fracture are employed.

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As for forearm fractures, the international pattern is not well described. However, there is some evidence to suggest that forearm fracture is much less frequent in Asians than in Caucasians. Hagino et al. addressed the age- and gender-specific incidence rates of distal radius and proximal humerus fractures among Japanese were substantially lower than those of Caucasians living in North America or northern Europe, e.g., the incidences (per 100,000 person-years) of distal radius and proximal humerus fractures were 196 and 52 in the Japanese, 438 and 161 in the USA, as well as 766 and 211 in Sweden, respectively.

Many potential reasons may be responsible for the racial differences in fracture rates. The differential patterns of bone growth and bone loss after menopause among diverse ethnic populations are the two important factors responsible for the population variation in bone fragility. It has been reported that the differential bone growth is associated with racial differences in several structural features of Asian and Caucasian children. Evidence from twin and family studies has shown important genetic effects on skeletal growth in bone mass, size and structure. Thus, we may infer the genetic factors partially account for the different osteoporotic fracture incidence. It is well documented that family history of osteoporotic fracture reflects the influence of genetic factors on fracture occurrence.

Peak bone mass

The appearance of postmenopausal osteoporosis is correlated with the magnitude of peak bone mass (PBM) reached in the third or fourth decade of life and the extent of bone loss during later life. Bachrach et al. reported that Asian women had lower total hip BMD, femoral neck BMD, and whole body BMD than Caucasian subjects. A study from Wu et al. noted the differences of peak bone mineral density (PBMD) for Asian women at the femoral neck (0.805 g/cm² for Chinese and 0.828 g/cm² for Japanese) and total hip (0.875 g/cm² for Chinese and 0.908 g/cm² for Japanese) were lower than those for Caucasians (0.849 g/cm² and 0.942 g/cm²), respectively. Table 2 describes a little differential range of PBM with 0.974-1.055 g/cm² and 0.805-0.966 g/cm² in Asians, as well as 1.04-1.59 g/cm² and 0.821-1.36 g/cm² in Caucasians at the spine and femoral neck, respectively. However, we may not make a conclusion that PBM is signif-
Bone loss

Age-related bone loss occurs as the bone resorption phase outweighs the bone synthesis phase of bone metabolism. Wu et al.\textsuperscript{25} addressed the racial difference of bone loss. In that study, average T-scores for BMD loss were subsequently calculated in a 5-year study. T-score was defined by the World Health Organization as the number of standard deviations from the mean value of young adults, namely PBM\textsuperscript{26}. The age-related dynamic changes of T-scores are ideal for comparison of bone loss among populations since such changes with aging may reflect bone loss change relative to PBM. As shown in their reference curves of BMD, except at the femoral neck, the T-scores at different skeletal regions (including anteroposterior lumbar spine, lateral spine, trochanter, intertrochanter, Ward's triangle, total hip and ultradistal forearm) in Chinese and Japanese women were lower than those in Caucasian women\textsuperscript{25}.

Bone area and bone geometry

Asians have smaller bone area compared with Caucasians\textsuperscript{18,27}. As shown in Table 3, the Chinese have significantly smaller projected bone area than Caucasians at the spine and hip\textsuperscript{27}. Bone geometry parameters measuring various lengths are also significantly shorter in the Chinese than in Caucasians\textsuperscript{26-30}. Such a phenomenon is exemplified by the significant differences between Asian and Caucasian women in terms of hip axis length, femoral neck diameter and femoral neck length\textsuperscript{26-30} (Table 3). More importantly, these geometric characteristics of the femoral neck have been shown to predict the risk of hip fracture\textsuperscript{30}. Furthermore, the racial difference in bone area and geometric characteristics of the femoral neck may partially account for the different risk of hip fracture among Asians and Caucasians\textsuperscript{29,30}.

Drug treatment response

A systematical review was well addressed in the race-specific response to drug treatments between Asians and Caucasians\textsuperscript{31}. Massart\textsuperscript{31} summarized and compared the race-specific minimal efficacious doses of treatments based on vitamin D and estrogen, and found many clinical clues suggesting that the human race (Asians, Caucasian) plays a major role in determining bone treatment effectiveness. It seems that Asians are more "estrogen-resistant" and "vitamin D-sensitive" than Caucasians. These race-specific effects may depend at least on different allelic frequencies of drug target genes (e.g., VDR and ER\textgreek{a} genes) that potentially contribute to individual drug response\textsuperscript{31}.

The potential underlying genetic determination for the ethnic difference in osteoporosis-related phenotypes

What are responsible for the above osteoporosis-related phenotypic differences between Asians and Caucasians? The different ethnic genetic background may partially account for these differences between them. The following will provide some genetic evidence to elucidate the different ethnic genetic background.

Heritability of bone phenotypes

Bone phenotypes are determined by both genetic and environmental factors and their interactions. Rapidly accumulating data have unambiguously established that the genetic factors can explain about 50%-90% of total BMD variation\textsuperscript{32}. As for bone size, by general consensus, the heritabilities of bone size variation at the spine, hip, and wrist are over 50%\textsuperscript{33}. Table 4

Table 3. Differential bone area and bone geometry between Asian and Caucasian women.

<table>
<thead>
<tr>
<th></th>
<th>Asians Mean (SD)</th>
<th>Caucasians Mean (SD)</th>
<th>Asians vs. Caucasians</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone geometry parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip axis length</td>
<td>97.3 mm (4.7)</td>
<td>101.9 mm (6.0)</td>
<td>Significantly shorter (&lt;0.01)</td>
<td>29</td>
</tr>
<tr>
<td>Femoral neck diameter</td>
<td>30.5 mm (2.3)</td>
<td>33.6 mm (2.5)</td>
<td>Significantly shorter (&lt;0.01)</td>
<td>29</td>
</tr>
<tr>
<td>Femoral neck length</td>
<td>44.2 mm (4.1)</td>
<td>47.3 mm (5.2)</td>
<td>Significantly shorter (&lt;0.01)</td>
<td>29</td>
</tr>
<tr>
<td><strong>Bone projected area</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Hip</td>
<td>32.7 cm(^2) (3.1)</td>
<td>33.9 cm(^2) (3.1)</td>
<td>Significantly smaller (&lt;0.01)</td>
<td>27</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>4.5 cm(^2) (0.4)</td>
<td>5.1 cm(^2) (0.5)</td>
<td>Significantly smaller (&lt;0.01)</td>
<td>27</td>
</tr>
<tr>
<td>Trochanter</td>
<td>9.8 cm(^2) (1.2)</td>
<td>10.5 cm(^2) (1.1)</td>
<td>Significantly smaller (&lt;0.01)</td>
<td>27</td>
</tr>
<tr>
<td>Spine</td>
<td>53.9 cm(^2) (5.5)</td>
<td>58.5 cm(^2) (5.4)</td>
<td>Significantly smaller (&lt;0.01)</td>
<td>27</td>
</tr>
</tbody>
</table>
summarizes several heritabilities of BMD variation in Asians and Caucasians. However, the estimated heritabilities of bone phenotypes are inconsistent in the different ethnic samples, possibly because of the different statistical analyses and differential types of samples. To illustrate the differential genetic influence on BMD variation in Asian and Caucasian populations, we cited two studies by Jian et al. and Deng et al., which used the same estimation method and the same type of sample. Jian et al. obtained the estimates of heritabilities of 0.44 and 0.77 for the spine BMD and hip BMD in the Chinese, respectively, whereas those in Caucasians were 0.86 and 0.84, respectively. The differential heritabilities for bone phenotypes between Asians and Caucasians may be related to the different determination of osteoporosis.

Inheritance modes of osteoporosis-related phenotypes

Complex segregation analysis sheds light on the nature of genetic determination of complex traits by testing the transmission of a trait within pedigrees, which provides us with a valuable prelude to genetic analyses. In order to test whether there is a genetic locus with a major effect on bone phenotype variation, as well as to demonstrate the importance and magnitude of genetic determination, a series of complex segregation studies have been performed in different populations. For the hip, the existence of a major gene with additive effect on BMD in the Chinese population was consistent with several earlier segregation analyses in Caucasians. However, for the spine, the results in the Chinese did not support...
the conclusion of a major gene influencing BMD variation, while another study in eight Caucasian families found a major gene of codominant inheritance for spinal BMD. As reflected by the above results, the mode of inheritance for BMD may vary not only in different ethnic populations but also at specific skeletal sites. As for bone size, the study in the Chinese indicated a major gene of codominant inheritance, which may account for ~16.9% of spine bone size variation without consideration of potential covariate effects, whereas there was no evidence of a major gene influencing hip bone size. The different genetic mode of bone phenotype between Asians and Caucasians at specific skeletal sites might suggest another evidence for differential genetic determination in different major ethnic groups.

Osteoporosis candidate genes

A number of bone-related candidate genes, such as the estrogen receptor gene (ER) and vitamin D receptor gene (VDR), alpha2-HS-glycoprotein (AHSG) and parathyroid hormone (PTH), have been studied for their association with bone phenotypes by employing various polymorphic molecular markers. However, population and ethnic differentiation at the allele and genotype distributions for some bone-related candidate genes may be remarkable. Lei et al. performed a comparative study on the polymorphisms of four candidate BMD genes among Chinese and other populations, showing significant ethnic differentiation on four prominent candidate genes. For example, the frequencies of the high-fracture risk allele "s" at the Sp1 site of the collagen IA1 (COLIA1) gene were elevated in Caucasians (ranging from 0.15 to 0.32), but absent in East Asian populations tested. Dvornyk et al. also found the ethnic background of populations was of particular importance to the allelic distribution. Table 5 shows the frequency distributions of some polymorphisms within several prominent candidate genes among Asians and Caucasians, which intuitively describes the differential range of allelic and genotypic frequencies. For example, the "A" allele of VDR-ApaI marker was prevalent with a frequency of 64-83% in Asians and the "A" allele had a frequency of only 40-51% in Caucasians.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Marker loci</th>
<th>N</th>
<th>Populations</th>
<th>Phenotype and effect</th>
<th>p values</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>VDR</td>
<td>TaqI</td>
<td>125</td>
<td>Healthy Japanese girls aged 12-15</td>
<td>Spine BMD</td>
<td>NS</td>
<td>109</td>
</tr>
<tr>
<td>VDR</td>
<td>TaqI</td>
<td>68</td>
<td>Healthy Caucasian girls aged 7</td>
<td>Spine BMD (TT&gt;Tt&gt;tt)</td>
<td>0.038</td>
<td>110</td>
</tr>
<tr>
<td>VDR</td>
<td>FokI</td>
<td>125</td>
<td>Healthy Japanese girls aged 12-15</td>
<td>Spine BMD (ff&lt;FF)</td>
<td>&lt;0.05</td>
<td>109</td>
</tr>
<tr>
<td>VDR</td>
<td>FokI</td>
<td>38</td>
<td>Caucasian children aged 7.5-12</td>
<td>Total body BMD (FF&gt;ff)</td>
<td>0.03</td>
<td>111</td>
</tr>
<tr>
<td>VDR</td>
<td>T/C</td>
<td>110</td>
<td>Premenopausal Japanese women</td>
<td>Spine BMD (CC&gt;TT)</td>
<td>&lt;0.05</td>
<td>112</td>
</tr>
<tr>
<td>VDR</td>
<td>T/C</td>
<td>261</td>
<td>Pre/peri-menopausal white women aged 28-48</td>
<td>Spine BMD</td>
<td>NS</td>
<td>113</td>
</tr>
<tr>
<td>ER-α</td>
<td>PvuII</td>
<td>54</td>
<td>Premenopausal Chinese women</td>
<td>Femoral neck BMD (pp&lt;Pp&lt;PP)</td>
<td>&lt;0.05</td>
<td>114</td>
</tr>
<tr>
<td>ER-α</td>
<td>PvuII</td>
<td>253</td>
<td>Pre/peri-menopausal Caucasian women</td>
<td>Spine and total body (pp&gt;Pp&gt;PP); Femoral neck BMD</td>
<td>&lt;0.005; NS</td>
<td>86</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>T29→C</td>
<td>171</td>
<td>Postmenopausal Japanese women</td>
<td>Spine BMD (CC&gt;TT)</td>
<td>0.019</td>
<td>49</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>T29→C</td>
<td>116</td>
<td>Postmenopausal Japanese women</td>
<td>Spine BMD (CC&gt;CT,TT)</td>
<td>&lt;0.0001</td>
<td>49</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>T29→C</td>
<td>102</td>
<td>Postmenopausal German women</td>
<td>Spine BMD (TT&gt;CC)</td>
<td>0.02</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 6. Differential association results on BMD in Asians and Caucasians.
that the value of $F_{ST}$ was 0.103 and significantly different from zero ($p<0.01$). Thus, 10.3% of the total variability at these loci was due to the genetic differentiation between the two populations under study. Furthermore, they also found at least three loci where $F_{ST}$ significantly deviated from the average value: ER-XbaI, AHSG-SacI, and PTH-BstBI. This may be partially due to different evolutionary histories involving various types of natural selection such as disruptive and stabilizing natural selection.

Whether the observed ethnic differentiation of candidate genes is related to the different levels of bone phenotypes and fracture risk in different populations and ethnic groups awaits further studies. However, if the ethnic heterogeneity of the studied candidate genes is representative of the major genes underlying bone phenotype variation, this observation may implicate that the between-ethnic difference of osteoporosis-related phenotypes come from that observed between-ethnic differentiation of candidate genes. To verify the above hypothesis, Dvornyk et al.$^{45}$ comparatively investigated the association of six markers for five candidate genes with BMD variation in the Chinese and Caucasians, and found that ethnicity appears to influence both the association outcomes and the total population BMD variation in both genders. The definite conclusions, however, cannot be made due to the limited data and imperfect study designs.

Related molecular studies

Extensive molecular genetic studies have addressed the relationship between osteoporosis related phenotypes and candidate genes. The list includes ER, VDR, COLIA1, AHSG, PTH, collagen IA2 (COLIA2), bone Gla protein (BGP), transforming growth factor-$\beta$1 (TGF-$\beta$1), PTH receptor type I (PTH1R), interleukin-6 (IL-6)$^{44,46}$. However, the majority of these results are inconsistent. The contradictory discoveries for osteoporosis may arise from the complicated inheritance patterns, and different ethnic backgrounds.

Table 6 summarizes the association results on BMD in Asians and Caucasians. The association results differ not only in the existence of association (i.e., non-significant or significant), but also in the direction of association (i.e., which allele is associated with lower or higher BMD) (Table 6). As shown in Table 6, the VDR polymorphism (TaqI), which was associated with spinal BMD for healthy Caucasian girls (aged 7, $p=0.038$), showed no evidence of such association in a similar group of Japanese girls aged 12-15. The $TT$ genotype for the T29 -$C$ polymorphism in signal sequence region of TGF-$\beta$1 gene was associated with higher BMD in estrogen-deficient postmenopausal German women$^{48}$, whereas the same polymorphism in Japanese women exhibited an opposite effect such that the $CC$ genotype was associated with higher BMD$^{49}$.

By now, two meta-analyses have appeared showing that the Sp1 polymorphism is associated with differences in osteoporotic fracture risk as well as BMD variation to a certain extent$^{50,51}$. However, the importance of the COLIA1 gene on BMD may not be explained by the Sp1 polymorphism in the Chinese because it is absent in the Chinese population.$^{1}$ Recently, Zhang et al.$^{52}$ found that a $-1997G/T$ polymorphism near COLIA1 Sp1 polymorphism had important effects on BMD variation in a large sample of Chinese nuclear families.

Summary

While the above different results are not conclusive, they indeed suggest that the differences in osteoporosis-related phenotypes between Asians and Caucasians may be partially the result of the different ethnic genetic background.

On the other hand, environmental and lifestyle factors cannot be ignored. According to a national survey, the average dietary calcium intake in the Chinese population was less than 35% of that in western people$^{53}$. There was a similar finding in a study of 131 Asian and Caucasian girls$^{54}$. Ethnic differences also exist for other lifestyle factors, such as sunlight exposure, smoking, exercise, and alcohol consumption.

However, it should be highlighted that the differentiation of Asians and Caucasians at bone mass candidate genes, the different inheritance mode of major gene effects, plus the different results of association studies on bone phenotypes supports that the genetic mechanisms leading to osteoporosis in Asians and Caucasians may not be entirely the same. Yet, more data are needed to justify such a point.

In summary, the present review may help contribute to the understanding of the genetic basis of osteoporosis under different ethnic backgrounds. It also suggests different treatment of osteoporosis according to the specific genetic background in diverse ethnic populations such as Asians and Caucasians. In general, however, it should be emphasized that these two major ethnic groups share the vast majority of osteoporosis genetics and most of the related knowledge we have accumulated is applicable to both ethnic groups.

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