Osteoporosis is the most common and serious skeletal disorder of the elderly; it is characterized by reduced bone mass and deterioration of bone microarchitecture, with an increased risk of low-trauma fractures. Genetic factors are important predisposing elements influencing individual bone strength variability and susceptibility to osteoporosis and related complications. The genetics of osteoporosis encompasses two main areas: disease susceptibility and pharmacogenetics of drug response. The former has been widely studied while the latter is still largely untouched. Pharmacogenetics is the study of relationships between genetic variations and inter-individual differences in drug response in terms of efficacy and adverse effects, representing an opportunity to identify new biomarkers for drug development and drug response. However, pharmacogenetic approaches to osteoporosis are still in their infancy, needing to be developed further and combined with functional studies. This article provides an overview on the current basic research applications in the pharmacogenetics of osteoporosis and their implications for clinical practice.

**Keywords:** gene variation • individual drug response • osteoporosis • pharmacogenetics

**Pharmacogenetics of osteoporosis**

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Pharmacogenetics represents the utilization of individual genetic data to predict the outcome of drug treatment with respect to both beneficial and adverse effects. Drug response is known to be highly variable among treated patients and when a drug is administered to a patient it can present with one of the four following possibilities: normal drug effect; no or reduced drug effect; pronounced drug effect; and adverse drug reactions (ADRs). Personal drug response is affected by many factors, such as age, sex, ethnicity, concomitant diseases and/or pharmacological therapy, but although these nongenetic variants can be very important, sequence variants in the human genome are now considered the principal cause of different drug responses, both in terms of efficacy and toxicity. Sequence variation in drug absorption and drug deposition genes can alter the pharmacokinetics of a drug, while sequence variations in drug-metabolizing genes or drug-target genes can change the pharmacodynamics of a drug. Given the great complexity of the human genome, it is very difficult to identify an optimal pharmacogenetic biomarker since genome variations and gene-expression regulating elements are not only limited to single nucleotide polymorphisms, but also to variability of shot sequence repeats, insertions, deletions,
epigenetic changes, noncoding RNAs, miRNAs and gene–gene interactions. Moreover, gene–environment interactions should also be taken into account.

The pharmacogenetic analysis of a specific drug response first requires the knowledge of both genetic and nongenetic factors that can affect drug pharmacokinetics and pharmacodynamics. The identification of a specific biomarker is usually made by genome-wide association studies and/or association studies of specific genetic variants in selected treated populations from prospective controlled clinical trials. Moreover, once identified, a genetic biomarker requires, before its application to clinical practice, additional validation works, including in vitro and/or animal model functional studies, randomized clinical trials to evaluate the clinical utility of the pharmacogenetic test, the development of guidelines for the clinical applications of the pharmacogenetic test and the supply of specific pharmacogenetic education to healthcare professionals.

Pharmacogenetic studies have made significant progress in the past 10 years, and genetic results on approximately 50 drugs have now been included on US FDA-approved drug labels [5]. The validated genomic biomarkers on drug labels can be found at the FDA website [102]. Only a few pharmacogenetic tests are currently used in clinical practice, and none of them are in the field of bone diseases [6]. Almost all of the currently approved tests are primarily based on genetic variations in a single gene; however, with the constant improvement of human genome analysis approaches, these single-gene tests will soon be replaced by diagnostic tests of a panel of genes associated with drug efficacy and/or toxicity.

**Pharmacogenetics of osteoporosis**

Despite the growing evidence of genetic influence in the efficacy and safety of drugs in other chronic diseases, very few data are available on the pharmacogenetics of osteoporosis. In the last 10 years, some bone metabolism-related genes have been investigated with regard to response to antiresorptive agents, such as hormone-replacement therapy (HRT), raloxifene and bisphosphonates, or to vitamin D and calcium supplementation (Table 1). Data from these studies demonstrated that individual response to antifracturative drugs is variable among treated patients, with a range of 5–10% of patients not responding to the therapy and a percentage of patients developing ADRs [7], suggesting a genetic involvement in the modulation of different inter-individual responses to anti-osteoporotic agents. However, all genetic variants associated with different drug responses need to be confirmed in larger cohorts, in different ethnic groups and/or in multicentric studies, and then validated by functional in vitro, in vivo and ex vivo studies, and by randomized clinical trials in humans. No pharmacogenetics studies are currently available on parathyroid hormone-based drugs or other novel anti-osteoporotic drugs, such as strontium ranelate or monoclonal antibodies.

**Pharmacogenetics of the response to HRT**

In the last 10 years, a few association studies [8–15] have investigated the genetic variants associated with differing response to HRT and have tried to offer a possible explanation of why approximately 8% [16] of treated women do not exhibit a favorable response to HRT. In particular, these studies have been focused on the analysis of XbaI and PvuII polymorphisms in intron 1 of the estrogen receptor-α (ERα) gene, which is largely expressed in bone tissue and is the most probable determinant of HRT response. Ongphaphanakul et al. demonstrated in 124 Thai postmenopausal women that the ERα PvuII polymorphism was associated with HRT response in vertebral bone mineral density (BMD) [10]. The increase of vertebral BMD was significantly higher in women bearing at least one P allele with respect to those without the P allele, but this association was significant only with low estrogen doses. No association was found in the response of femoral BMD and bone turnover markers. Salmén et al. confirmed these results in a cohort of 331 nonosteorporotic early postmenopausal Caucasian women treated with HRT in association with vitamin D and calcium supplementation [11]. The pp genotype has been associated with a greater fracture risk, with respect to the presence of at least one P allele, and it seemed to be a relatively estrogen-insensitive genotype. Recently, Yahata et al. have characterized a total of 18 single nucleotide polymorphisms of the ERα gene in a cohort of 84 osteopenic and osteoporotic Japanese postmenopausal women in association to the response to 3-year treatment with HRT [8]. They evidenced a strong association between the GG genotype of the IVS6 +14144 polymorphism in intron 6 and a higher increase of lumbar BMD, with respect to GA or AA genotypes. More recently, Rapuri et al. have evaluated the effect of XbaI and PvuII polymorphisms on BMD, bone turnover biochemical markers, rate of bone loss and response to HRT in 79 postmenopausal women [9]. They found a higher response of total body, spinal and femoral BMD to the HRT in women with PP and XX genotypes than with the pp and the xx genotypes.

Two studies by Kurabayashi et al. also investigated the possible association of the vitamin D receptor (VDR) genotype with the response to HRT [12,13]. In the most recent study, the authors carried out a retrospective association study between the VDR and ERα genotypes and the response of spinal BMD to 3–5 years of HRT treatment on 81 osteopenic and osteoporotic Japanese women [13]. Results from this study demonstrated a better response of spinal BMD to 1-year HRT treatment in women with the TT genotype (Taql polymorphism of the VDR gene) versus women with the Tt genotype.

Very recently, Simsek et al. evaluated the effects of the Sp1 polymorphism in the intron 1 of the COLIA1 gene on the BMD response to HRT in a cohort of 111 Turkish postmenopausal women, showing a lower BMD increase in patients with the SS genotype compared with the SS genotype [15].

**Pharmacogenetics of the response to selective estrogen receptor modulators**

Only two studies are available for the bone response to raloxifene, a selective estrogen receptor modulator with estrogen-like effects on bone used for both the prevention and the treatment of postmenopausal osteoporosis. The first is a study by Palomba et al. that investigated the influence of the BsmI polymorphism on the 3’ untranslated region of the VDR gene in a cohort of 75 Italian
postmenopausal osteoporotic women treated with raloxifene for 1 year [17]. They found a higher increase in spinal BMD and a more pronounced decrease in serum and urinary levels of bone turnover markers in women with the BB genotype than in those with the bb genotype. Women with the heterozygote Bb genotype demonstrated an intermediate percentage change of spinal BMD and serum and urinary bone turnover markers. The second is a study by Heilberg et al., that investigated whether XbaI and PvuII polymorphisms of the ERα gene could predict the response of BMD in 28 postmenopausal Brazilian women on hemodialysis with marked osteopenia or osteoporosis, randomized to receive raloxifene or placebo for 1 year [18]. Results

| Table 1. Pharmacogenetic studies in osteoporosis. |
|-----------------------------------------------|
| **Anti-osteooporotic drug** | **Gene** | **Polymorphisms** | **Subjects** | **Polymorphism–drug response association** | **Ref.** |
| Hormone-replacement therapy | | | | | |
| Conjugated equine estrogen/medroxyprogesterone acetate | ERα | PvuII | 124 Thai women | P allele: higher increase of spinal BMD | [10] |
| Estradiol valerate/cyproterone acetate | ERα | PvuII | 331 Finnish women | P allele: reduced risk of fracture | [11] |
| Conjugated equine estrogen/medroxyprogesterone acetate | ERα | 18 intronic SNPs | 84 Japanese women | IVS6 +14144 GG genotype: higher increase of spinal BMD | [8] |
| Conjugated equine estrogen/medroxyprogesterone acetate | ERα | PvuII, XbaI | 79 women (ethnicity not available) | PP and XX genotypes: higher increase of total body, spinal and femoral BMD | [9] |
| Conjugated equine estrogen/medroxyprogesterone acetate | ERα | VDR | 79 women (ethnicity not available) | TT genotype: higher increase of spinal BMD | [12] |
| Conjugated equine estrogen/medroxyprogesterone acetate | COL1A1 | Sp1 | 111 Turkish women | SS genotype: higher increase of spinal and femoral BMD | [15] |
| Selective estrogen receptor modulators | | | | | |
| Raloxifene hydrochloride | VDR | Bsml | 75 Italian women | BB genotype: higher increase of spinal BMD | [17] |
| Raloxifene | ERα | PvuII, XbaI | 28 Brazilian women | PP and xx genotypes: better lumbar spine BMD response | [18] |
| Bisphosphonates | | | | | |
| Etidronate | VDR | Bsml | 24 Slovenian women | bb genotype: lower increase of spinal BMD | [19] |
| Five treatment groups: 1) Alendronate/raloxifene 2) Alendronate/conjugated equine estrogen/medroxyprogesterone acetate 3) Alendronate 4) Conjugated equine estrogen/medroxyprogesterone acetate 5) Raloxifene | VDR | Bsml | 222 Italian women 220 Italian women 220 Italian women 219 Italian women 219 Italian women | bb genotype: lower increase of spinal BMD | [20] |
| Alendronate | ERβ | RsaI | 79 Slovenian women | No significant association | [21] |
| Etidronate | COL1A1 | Sp1 | 52 women (ethnicity not available) | SS genotype: higher increase of femoral BMD | [22] |
| Alendronate or ibandronate | FDPS | rs2297480 | 234 Danish women | CC genotype: lower decrease of urinary cross-laps | [23] |
| Alendronate | FDPS | rs2297480 rs11264361 rs3840452 rs3841735 | 144 Korean women | rs3840452 -8188Adel: reduced spinal and femoral BMD improvements | [24] |
| Risedronate | LRP5 | V667M, A1330V | 249 Caucasian osteoporotic men | No significant association | [25] |

BMD: Bone mineral density; SNP: Single nucleotide polymorphism.
from this study evidenced that after 1 year of raloxifene treatment, postmenopausal osteoporotic women on chronic hemodialysis, with the homozygote PP or xx genotypes exhibited a better lumbar spine BMD response and decreased serum pyridinoline values compared with heterozygous Pp or Xx women.

**Pharmacogenetics of the response to bisphosphonates**

In the last decade, some studies have analyzed the role of genetic variants of bone-related genes in the modulation of individual response to bisphosphonate treatment [19–25] in order to dissect the possible genetic bases responsible for nonresponse in approximately 5–10% of treated patients [26] or for the development of ADRs [27–29]. The first study was performed in 1999 by Marc et al. [19]. The authors investigated the association between the BsmI VDR polymorphism and the response to 1-year etidronate treatment in 24 Slovenian postmenopausal osteoporotic women, finding that lumbar spine BMD increased significantly more in women with the BB and the Bb genotypes compared with those with the bb genotype, while serum osteocalcin level decreased significantly more in the bb genotype with respect to the BB genotype. In 2005, Palomba et al. evaluated the association between the BsmI polymorphism of the VDR gene and the response to alendronate alone or in combination with HRT or raloxifene in cohorts of approximately 220 Italian osteoporotic postmenopausal women [20]. They found that alendronate and HRT (together or alone) have a weak response in terms of BMD increase in women with the bb genotype. Conversely, the association of alendronate and raloxifene induced a strong gain in BMD in women with the BB genotype and a slight effect on BMD improvement in women with the bb genotype. Qureshi et al. studied the association between the Sp1 polymorphism of the COL1A1 gene and the response to 2-year etidronate treatment in 52 Caucasian postmenopausal women with osteopenia [22]. The SS genotype was associated with a better response in femoral neck BMD, but not in lumbar spine BMD, than the Ss and the ss genotypes.

A study by Arko et al. failed to detect any association between the Ral1 polymorphism of the estrogen receptor-β (ERβ) gene and the response to alendronate treatment in 79 Slovenian postmenopausal osteoporotic women [21]. In 2008, a study by our research group [23] investigated the association between the polymorphism A/G rs2297480 in intron 1 of the farnesyl pyrophosphate synthase (FDPS) gene, the molecular target of amino-bisphosphonates in osteoclast cells, and the response to 2-year alendronate or ibandronate treatment in a cohort of 234 osteoporotic Danish women. We found an association between the CC genotype, compared with the AC and AA genotypes, and a reduced response of urinary cross-laps after 2 years of treatment. No association has been evidenced after only 1 year of treatment.

More recently, a study by Choi et al. analyzed the association between four polymorphisms in the molecular target of bisphosphonates (rs2297480 in intron 1 and rs11264361 in the intron 8 of the FDPS gene, and rs3840452 in the promoter region and rs3841735 in the intron 3 of the geranylgeranyl diphosphate synthase 1 [GGPS1] gene) and the response to 1-year treatment with bisphosphonates in 144 Korean osteoporotic women [24]. The study demonstrated that the response rate, in terms of lumbar spine and femoral neck BMD improvements, of women with two deletion alleles (-8198A del) of the rs3840452 polymorphism of the GGPS1 gene was significantly lower than that of women with only one deletion allele or without a deletion allele. Women with two deletion alleles had a sevenfold higher risk of nonresponse to bisphosphonates compared with women with the other two genotypes, after adjusting for baseline BMD. The other analyzed polymorphisms of the GGPS1 and FDPS genes were not associated with a different response in lumbar spine or femoral neck BMD variations. Finally, a study by Kruk et al. evaluated the correlation between the V667M polymorphism in the exon 9 and the A1330V polymorphism in the exon 18 of the lipoprotein receptor-related protein 5 (LRP5) gene and the response to 2 years of risedronate treatment in a cohort of 249 Caucasian osteoporotic or osteopenic men [25]. They found no association between LRP5 allelic variations and the response to bisphosphonate therapy both in terms of BMD gain or reduction of biochemical markers of bone turnover.

**Expert commentary & five-year view**

Data from the aforementioned studies suggest that patients’ genotyping could be useful to target osteoporosis drug treatments to subjects most likely to respond in terms of BMD improvement and bone turnover marker variations, avoiding suboptimal long-term treatments or ADRs. This is very important for chronic diseases, such as osteoporosis, for which different effective therapies are available and, therefore, the selection of the best therapy for each single patient is foreseeable. In particular, the study of pharmacogenetics of osteoporosis should include the understanding of molecular mechanisms of drug action, the identification of drug-response candidate genes (including genes encoding for drug targets, drug-metabolizing enzymes and drug transporters) and of their variants and the expansion of clinical trials to include patients’ genetic profiling. Moreover, the pharmacogenetic approach could help to identify novel anti-osteoporotic drug molecular or genetic targets, with an impact on novel drug discovery and development, moving from ‘one drug fits all’ to a personalized therapy.

The constant development of novel tools and technologies for the study of functional genomic and molecular biology will be very useful for the understanding of single gene functions and for the comprehension of how these genes interact to generate the whole patterns of drug response. Currently, genome-wide scan analysis and DNA microarrays represent two powerful approaches to address the identification of genetic variants involved in the regulation of drug response and the simultaneous expression analysis of thousands of genes, respectively. In addition, since gene expression can also be modulated at post-transcriptional level, a complementary approach to DNA and RNA analyses is proteomics, which consists of the global analysis of protein expression. Proteomics can measure expression changes, independently by RNA modifications, including post-transcriptional regulation of gene expression (i.e., miRNAs), post-translational modification and
protein–protein interactions. These novel techniques are now applied to the discovery of new drug targets and to the study of drug response, but, so far, no data have yet been reported in the field of pharmacogenetics and/or pharmacoproteomics of anti-osteoporotic drug response.

The ultimate goal of pharmacogenetic studies is their application to clinical practice leading to the design of specific and valid genetic tests that allow the identification of subjects for which a specific medication will produce the desired therapeutic response or will develop adverse effects. The application of specific genetic tests, that could be easily performed on a blood sample just before the initiation of a specific therapy, will allow the tailoring of drug therapies and choice of the correct agent at the adequate dose for every patient based on the genotype, which will be important and beneficial in terms of patients’ quality of life and healthcare system costs.

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Key issues

• Osteoporosis is the most common chronic bone disease in the elderly, characterized by excessive bone resorption and deterioration of normal bone microarchitecture with subsequent very high risk of spontaneous fractures. Osteoporosis requires long-term continuous treatment with antiresorptive agents to be initiated as early as possible in order to reduce the progressive bone mass loss and to prevent fragility fractures that represent the major cause of morbidity and mortality of this disease.

• Anti-osteoporotic pharmacotherapy encompasses several approved and effective treatments such vitamin D and calcium supplements and antifracture drugs such as hormone-replacement therapy, selective estrogen receptor modulators (i.e., raloxifene), bisphosphonates, calcitonin, parathyroid hormone and strontium ranelate.

• Most of these drugs, except for parathyroid hormone, acts as antiresorptive agents on osteoclast cells, decreasing bone loss and reducing fracture risk. In addition, new forms of treatment are appearing on the horizon, such as nitrates, β-blockers, kathespin K inhibitors and monoclonal antibodies.

• A common feature of all these anti-osteoporosis pharmacological treatments is that their efficacy and safety are highly variable among treated patients, ranging from good to little or no response. A variable percentage of approximately 5–10% of patients do not respond, in terms of bone mineral density increase or variations in biochemical markers of bone turnover, to a specific anti-osteoporotic therapy. In addition, some treated patients develop significant adverse drug reactions to the therapy.

• Pharmacogenetic approaches to osteoporosis could help in drug efficacy and safety improvement by the identification of genetic markers that differentiate responder from nonresponder patients, as well as patients who may develop adverse drug reactions. Greater benefits could be obtained by the application of genetic and molecular profiling to anti-osteoporosis drug discovery, development and administration.

• Few pharmacogenetic studies have been performed to date in the field of osteoporosis, some of them evidencing associations between genetic polymorphisms in bone-related genes and response to anti-osteoporosis treatment. These preliminary data suggested the possibility to use patient genotyping to target osteoporosis drug treatments to subjects most likely to respond in terms of bone mineral density and bone turnover markers variations, avoiding suboptimal long-term treatments.

• The pharmacogenetics of osteoporosis certainly need to be applied and improved in the near future. The genes to be evaluated should encompass those encoding for drug targets, drug-metabolizing enzymes and drug transporters. Moreover, all genetic variants identified by association studies will have to be validated by functional \textit{in vitro}, \textit{in vivo} and ex vivo studies and by controlled clinical trials in humans.

• Genome-wide scan analysis, DNA microarrays and proteomics techniques should be applied to the pharmacogenetics of osteoporosis for the better understanding of genetic and molecular bases of individual drug response and also for the identification of novel molecular targets for the design of new effective therapies.

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