Pharmacogenetics of osteoporosis
Francesca Marini and Maria Luisa Brandi*

Address: Metabolic Bone Unit, Department of Internal Medicine, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy
* Corresponding author: Maria Luisa Brandi (m.brandi@mi.unifi.it)
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Abstract
Osteoporosis is a complex bone disorder with a strong genetic basis. The genetics of osteoporosis encompasses two main areas: genetics of disease susceptibility and pharmacogenetics of drug response. The former has been widely studied in the past few decades, while the latter is still largely untouched. This review will provide an overview of the pharmacogenetics of osteoporosis, focusing on the major recent advances in the past two years.

Introduction and context
Osteoporosis is the most common and serious skeletal disorder of the elderly, characterized by a reduced density and quality of bone leading to weakness of the skeleton and increased risk of bone fragility and spontaneous fractures, which are associated with up to a three-fold increase in mortality in both sexes [1]. Osteoporosis affects all ethnic groups, with a lifetime risk of hip, forearm, or vertebral fractures being over 40% [2]. Today osteoporosis represents a global public health problem, affecting over 200 million people worldwide, with important implications for healthcare costs, morbidity, and mortality. Osteoporosis is a complex multifactorial disease, but it is now understood that genetic factors play a central role in its pathogenesis [3].

The genetics of osteoporosis comprises two main areas: genetics of disease susceptibility and pharmacogenetics of drug response. The genetics of osteoporosis predisposition has been widely studied and the results of numerous association studies between polymorphisms of more than 40 candidate genes and bone quantitative and qualitative traits have been published in the literature, although the results of these studies are controversial and no convincing conclusions have emerged yet. Conversely, the study of the pharmacogenetics of osteoporosis is still largely untouched and only a few studies have been published in the past decade. Pharmacogenetics represents the utilization of individual genetic data to predict the outcome of a drug treatment with respect to both beneficial and adverse effects [4-6]. The response of osteoporosis to pharmacotherapy is known to be highly variable between patients. Thus, the emerging field of pharmacogenetics could be very useful for refining and optimizing osteoporosis drug treatment, potentially allowing the identification of the most effective drug and dose for each patient, in terms of beneficial and adverse effects, based on the single genotype. The study of the pharmacogenetics of osteoporosis should include the understanding of molecular mechanisms of drug action, the identification of drug response candidate genes and their variants, and the expansion of clinical trials to include patients’ genetic profiling. All these approaches could provide useful tools to tailor decisions about osteoporosis drug treatments in order to maximize the health and well-being of osteoporotic patients.

Major recent advances
Very few data [7-23] are available to date on the pharmacogenetics of osteoporosis. Some major osteoporosis candidate genes, such as those encoding the vitamin D receptor (VDR), estrogen receptors alpha (ERα) and beta (ERβ), and collagen I alpha 1 (COL1A1), have been investigated with regard to anti-resorptive drug (i.e., hormone replacement therapy, raloxifene, and bisphosphonates) responses. Most of these studies associated variation in drug response, evaluated in
terms of bone mineral density (BMD) and bone turnover marker variation, with genetic polymorphisms. Never-
theless, the great majority of these studies have investi-
gated only genes that affect BMD and fracture risk and
these might be independent from genes that affect drug
responses. The variability in drug response is much more
complicated than simple variability in BMD or bone
turnover markers; thus, it will be very important to
define the phenotypes of antiresorptive drug response
and to enlarge pharmacogenetic studies to also include
genes involved in drug-specific pharmacokinetics and
pharmacodynamics.

Four novel studies have been published in the past two
years in the field of genetics of osteoporosis. In 2008,
Simsek et al. [7] evaluated the effects of the Sp1
polyorphism in intron 1 of the COL1A1 gene on
BMD response to at least 3 years of low-dose hormone
replacement therapy in 111 postmenopausal Turkish
women. The increase in spinal and femoral BMD was
higher in women with the SS genotype compared to
those with the Ss genotype.

In the same year, our research group [8] associated the A/
C rs2297480 polymorphism in intron 1 of the farnesyl
pyrophosphate synthase gene (FDPS), the molecular
target of amino-bisphosphonates in osteoclasts, with the
response to 2-year aminobisphosphonate treatment in
234 osteoporotic Danish women. We found that subjects
with the homozygous CC genotype showed a decreased
response by urinary Crosslips after 2 years, but not after
1 year, of amino-bisphosphonate therapy when com-
pared to the heterozygous AC and to the homozygous AA
genotypes.

In 2009, Kruk et al. [9] failed to find any association
between the V667M polymorphism (exon 9) and the
A1330V polymorphism (exon 18) of the low-density
lipoprotein receptor-related protein 5 gene (LRPS) and
BMD and bone turnover response to 1-year risedronate
treatment in a cohort of 249 osteoporotic or osteopenic
men.

Very recently, Choi et al. [10] analyzed the role of the
rs2297480 (intron 1) and rs11264361 (intron 8) poly-
morphisms of the FDPS gene and the rs3840452
(promoter region) and rs3841735 (intron 3) polymorph-
isms of the geranylgeranyl diphosphate synthase 1 gene
(GGPS1) and the response, in terms of changes in
lumbar spine and femoral neck BMD, to 1-year bisphos-
phonate treatment in 144 osteoporotic Korean women.
Women with two deletion alleles (-8188A del) of the
rs3840452 polymorphism of the GGPS1 gene presented a
significantly lower improvement in BMD than women
with only one deletion allele or no deletion alleles.
Women with two deletion alleles had a seven-fold higher
risk of non-response to bisphosphonates compared with
women with the other two genotypes, after adjusting for
baseline BMD.

Results from these studies seem to suggest that patient
genotyping could be useful to target osteoporosis drug
treatments to subjects most likely to respond in terms of
BMD and bone turnover marker variation. However,
association studies can have some limitations, such as
inadequate sample size or sampling errors, genetic
differences between different ethnic groups, the presence
of gene-gene and/or gene-environment interactions
acting as confounding factors, the complexity of genome
and gene regulation (epigenetic factors, somatic muta-
tions, microRNAs, and so on), and frequent accidental
statistical association not due to a real association
between genotype and phenotype. For all these reasons,
at the moment no definite gene variations have been
conclusively shown to be responsible for the regulation
of any anti-osteoporosis drug response.

Future directions
Patient genotyping could be useful for targeting osteo-
porosis drug treatments to subjects most likely to respond
well, avoiding suboptimal long-term treatments or
adverse reactions. The application of specific genetic
tests to identify subjects most likely to respond well and
not to develop adverse reactions before the beginning of
drug treatment is important mostly for those diseases,
such as osteoporosis, for which numerous and effective
therapies are available and, therefore, for which the
selection of the optimal therapy is foreseeable. Moreover,
the pharmacogenetics could help to map novel molecular
drug targets, with an impact on drug discovery, moving
from ‘one drug fits all’ to personalized therapy. Certainly,
the genes to be evaluated should always encompass those
encoding drug targets, drug metabolizing enzymes, and
drug transporters, and pharmacogenetics will need to
apply novel strategies in the search for gene variation, such
as genome-wide scan association studies, microarray
analysis, and the application of Bayesian methodology.
Moreover, pharmacogenetic association studies need to
be extended and confirmed in large cohorts, in different
ethnic groups and/or in multicentric studies, and all gene
variants positively correlated with drug response in
association studies will have to be validated by functional
in vitro, in vivo, and ex vivo studies.

Abbreviations
BMD, bone mineral density; COL1A1, collagen I alpha 1;
FDPS, farnesyl pyrophosphate synthase; GGPS1, ger-
anylgeranyl diphosphate synthase 1.
Competing interests
The authors declare that they have no competing interests.

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References


