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Pharmacogenetics of osteoporosis

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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. Nevertheless, the great majority of these studies have investigated 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* polymorphism 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 Crosslaps after 2 years, but not after 1 year, of amino-bisphosphonate therapy when compared 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 (*LRP5)* and BMD and bone turnover response to 2-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) polymorphisms of the *FDPS* gene and the *rs3840452* (promoter region) and *rs3841735* (intron 3) polymorphisms 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 bisphosphonate 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 mutations, 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 osteoporosis 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, geranylgeranyl diphosphate synthase 1.

Competing interests

The authors declare that they have no competing interests.

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