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Pharmacogenetics of Metabolic Bone Diseases

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Abstract

Individual drug response results to be highly variable among treated patients for many of the most commonly prescribed drugs. Common sequence variants in the human genome are today believed to be the main cause of different individual drug response.

Pharmacogenetics applies the principles of both pharmacology and genetics, for the discovery and validation of functional gene polymorphisms that could be relevant in the modulation of the pharmacodynamics and pharmacokinetics of drugs, in order to be able to predict the personal response to drugs both in terms of beneficial and adverse effects.

A more and more growing number of pharmacogenetic studies have been performed in the last decade, but, to date, only few of them have validated clinical application. This is even more true in the field of bone disorders in which pharmacogenetic studies are still very limited.

This review will offer an overview on current pharmacogenetic applications, especially focusing on pharmacogenetic studies in the field of osteoporosis and metabolic bone diseases.

Keywords: Drug response; Pharmacogenetics; Pharmacogenomics; Genetic tests; Polymorphisms; Osteoporosis; Metabolic bone diseases

Introduction

Personal drug response is variable among treated subjects for all the currently available drugs. When a drug is administered to a patient it can present three main responses: A) none or ineffective drug effect, B) normal drug effect, C) pronounced or excessive drug effect. An additive (to condition A, B or C) development of adverse drug reactions (ADRs) in a number of treated patients is also a possibility, with variable degrees of severity. The lack of efficacy in all treated patients and the development of ADRs in a percentage of them have negative implications in terms of reduction of patient quality of life and in terms of hospitalization costs for Health Care Systems.

Individual drug response can be influenced by several factors, such as sex, age, ethnicity, disease severity, concomitant diseases, adherence to the therapy and prescription, possible interaction with other therapies, environmental influences (diet, smoke, alcohol, etc). Nevertheless, common polymorphic variants in genes that regulate drug transport and metabolism (pharmacokinetics) or in genes that codify drug targets (pharmacodynamics) are now recognized as the most important cause of individual variable drug responses.

Pharmacogenetics aims to investigate the genetic factors that modulate drug response. Pharmacogenetics represents the alternative to the current "one size fits all" prescribing. The analysis of individual gene variations, in genes involved in regulation of drug pharmacokinetics and pharmacodynamics, and the development of specific genetic tests to identify responders from non-responders or individuals at higher risk to develop ADRs can help to predict the outcome of drug treatment and potentially to determine the appropriateness and dosage of many of the most commonly prescribed drugs. In particular, this will be very helpful in complex disorders that require long-term drug treatments, such metabolic bone diseases, in order to make individual dose adjustment or to choose alternative drug therapy.

The last decades have seen considerable progress in understanding the role of gene variations in inter-individual drug response to various commonly used drugs, through the performing of pharmacogenetic single-gene association studies and genome-wide association studies. Pharmacogenetic results on about 114 drugs have now been included on Food and Drug Administration (FDA)-approved "Table of Pharmacogenomic Biomarkers in Drug Labels" (http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). The great majority of data included in this list concern genetic variations of CYP2D6, CYP2C19 and CYP2C9 genes that have been associated to different response to several drugs used for the treatment of various common diseases. These three drug–metabolizing P450 cytochromes are responsible of the most frequent variation in phase I metabolism of about 80% of all prescribed drugs today. The first clinical application of a pharmacogenetic test was approved by FDA in January 2005: the AmpliChip CYP450 test that includes genetic variants of CYP2D6 and CYP2C19 genes. Moreover, in June 2007 the FDA released an online "Guidance on pharmacogenetic tests and genetic tests for heritable markers" (available at

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm) which aimed to represent general guidelines for the performing and data handling of pharmacogenetics tests and for the rapid transfer of laboratory results to the clinical practice.

Pharmacogenetic tests could be easily performed on a blood sample and they do not need to be repeated during lifetime. Results

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of pharmacogenetic tests should become part of the patient medical records, with access to this information protected by medical privacy laws, and available, prior the choose of a therapy, to clinicians granted the official permission of the patient.

Pharmacogenetics and Metabolic Bone Diseases

Several differentially-acting effective drugs are available for the treatment of metabolic bone disorders, all of them not being effective in a variable percentage of treated patients or inducing ADRs in a number of them. Nevertheless, to date only few studies are available on the pharmacogenetics of metabolic bone disorders, mainly focused on the pharmacogenetics of osteoporosis, and no validated pharmacogenetic test is still available in this area.

Pharmacogenetics of Osteoporosis Therapies

The great majority of studies on pharmacogenetics of osteoporosis have analyzed the role of genetic variants of previously known osteoporosis candidate genes [i.e estrogen receptors alpha (*ERα*) and beta (*ERβ*), vitamin D receptor *(VDR)*, collagen I alpha 1 *(COL1A1)*, lipoprotein receptor-related protein 5 *(LRP5)*] in the modulation of response to commonly used anti-osteoporotic drugs, such as hormone replacement therapy (HRT) [1-8], raloxifene [9,10] and bisphosphonates (BPs) [11-16].

Many of published osteoporosis pharmacogenetics studies [1-13,16] showed positive statistical associations between common polymorphisms of osteoporosis major candidate genes and the response to anti-resorptive drugs in treated patients, valuated in terms of bone mineral density (BMD) changes and variations of serum and/or urinary bone turn-over markers (Table 1).

Three studies [2-4] seemed to indicate the PvuII polymorphism of the *ERα* gene as involved in the response to HRT in postmenopausal women of different ethnicity with the P allele associated, respectively, with a higher increase of spinal BMD, a reduced risk of fracture and a higher increase of total body, spinal and femoral BMD. The PP genotype has been also associated to a better lumbar spine BMD response after treatment with raloxifene in Brazilian postmenopausal women [10]. However, data about *PvuII* polymorphism was not confirmed in another study [5] that failed to find any association between polymorphism of *ERα* and HRT response in Japanese women.

In the same study, Authors evidenced a positive association between the TT genotype of the *TaqI* polymorphism of *VDR* gene and a higher increase of spinal BMD in Japanese woman receiving HRT [5]. Another polymorphism of *VDR* gene, *BsmI*, seemed to be a promising marker for the prediction of response to different anti-osteoporotic drugs. The BB genotype has been associated with a higher increase of spinal BMD in response to raloxifene [9], while the bb genotype to a lower increase of spinal BMD in response to bisphosphonates, alone or in combination with raloxifene or HRT [11,12].

Also the Sp1 polymorphism of *COL1A1* gene appeared involved in the modulation of response to anti-resorptive drugs with the SS genotype associated with a higher increase of spinal and femoral BMD in response to HRT [7] and with a higher increase of femoral BMD after treatment with bisphosphonates [13].

A study by Wang et al. [16], published in Chinese, investigated the association of polymorphisms (*A163G, T245G* and *T950C*) of the osteoprotegerin (*OPG*) gene with BMD changes in osteoporotic postmenopausal women receiving oral alendronate for 12 months. Patients with the G allele of *A163G* polymorphism and those with the G allele of *T245G* polymorphism showed a lower increase at vertebral L2-4, inter-troche and total hip BMD. Subjects with the AA genotype (*A163T*) and with the TT genotype (*T245G*) presented a better therapeutic effect to alendronate therapy.

Surely, these interesting data need to be validated in larger cohorts and functional studies.

Conversely, two studies reported no association. The first one [14] failed to find any association between the *RsaI* polymorphism of the *ERβ* gene and the response to alendronate, confirming *ERβ* as a not important genetic determinant of BMD and bone metabolism. The other one [15] failed to find any association between two *LRP5* polymorphisms (*V667M* and *A1330V*) and the response to risedronate in osteoporotic and osteopenic men. The absence of role of *LRP5* variations in the response to bisphosphonate therapy seems to be confirmed also by two other studies [17,18] that evaluated the effect of bisphosphonate administration in patients affected by osteoporosis-pseudoglioma syndrome, a rare disorder characterized by severe juvenile osteoporosis and congenital or infancy-onset visual loss, bearing homozygotic inactivating mutations of the *LRP5* gene. Both the studies evidenced that, despite the presence of LRP5 mutation, the administration of bisphosphonates resulted in an improving of lumbar spine BMD Z-score and a decreasing of bone pain [17] and in an increased BMD value and a decreased fracture rate [18]. Conversely, Kim et al. [8] demonstrated that the T allele of *LRP5 C3893T* and the G allele of *LRP5 A266G* polymorphisms were associated with a higher risk of non response, respectively in terms of lumbar spine and femoral neck BMD gain and only of lumbar spine BMD gain, in postmenopausal Korean women treated with HRT.

Out of the classical osteoporosis candidate genes, recently, three studies aimed to investigate possible genetic bases of personal variable response to BPs [19-21], focusing their attention on genes of the mevalonate pathway, the molecular target of amino-bisphosphonates (NBPs) in osteoclasts. Variations in genes encoding the enzymes of the mevalonate pathway may modulate the different response to NBPs. Two studies [19,20] on Caucasian women found association between polymorphisms of the farnesyl pyrophosphate synthase (*FDPS*) gene and the individual response to NBPs. One study [19] associated the *rs2297480* genotypes of *FDPS* gene with different response to long-term (two years) NBPs therapy in osteoporotic postmenopausal Danish women, measured in terms of variations in urinary bone turnover markers. The other study [20] associated the *rs2297480* and *rs11264359* alleles with different BMD changes in Spanish women, after NBP therapy for an average period of 2.5 years. These two studies seem to suggest that polymorphisms of the FDPS gene may influence the individual response to NBPs. Conversely, a study on Korean women failed to find any association between patient response to NBPs and *FDPS* genotypes [21], but associated the NBP response to variations in geranylgeranyl diphosphate synthase (*GGPS1*) gene. The apparently contradictory results on FDPS gene may be due to the ethnically different populations included in these studies, respectively Caucasians and Asians, in which these polymorphisms presents an opposite ethnic-related allelic variant distribution [22,23].

No pharmacogenetic studies have been performed, to date, on the response to parathyroid hormone-based drugs or other novel anti-osteoporotic drugs, such as monoclonal antibodies or strontium ranelate.

Sex and age of patients	Ethnicity of patients	Administered drug	Analyzed genes and their polymorphisms	Associations	Reference
Postmenopausal women; NA	Thai (Asian)	HRT	*ERα; PvuII*	P allele: higher increase of spinal BMD	[2]
Postmenopausal women; 47-56 years	Finnish (Caucasian)	HRT	*ERα; PvuII*	P allele: reduced risk of fracture	[3]
Postmenopausal women; 40-64 years	Japanese (Asian)	HRT	*ERα;* 18 intronic SNPs	IVS6 + 14144 GG genotype: higher increase of spinal BMD	[1]
Elderly postmenopausal women; 65-77 years	NA	HRT	*ERα*; *PvuII, and XbaI*	PP and XX genotypes: higher increase of total body, spinal and femoral BMD	[4]
Women; 40-64 years	Japanese (Asian)	HRT	*ERα*; *PvuII, XbaI VDR; TaqI, ApaI, FokI*	TT genotype: higher increase of spinal BMD	[6]
Postmenopausal women; 46-54 years	Turkish (Caucasian)	HRT	*COL1A1; Sp1*	SS genotype: higher increase of spinal and femoral BMD	[7]
Postmenopausal osteoporotic women, NA	Korean (Asian)	HRT	LRP5; A266G, C3893T	T allele of *C3893T:* higher risk of non response in terms of lumbar spine and femoral neck BMD gain; G allele of *A266G*: higher risk of non response, in terms of lumbar spine BMD gain	[8]
Postmenopausal women; NA	Italian (Caucasian)	Raloxifene	*VDR; BsmI*	BB genotype: higher increase of spinal BMD	[9]
Postmenopausal women; NA	Brazilian	Raloxifene	*ERα; PvuII, XbaI*	PP and xx genotypes: better lumbar spine BMD response	[10]
Postmenopausal women; 56-73 years	Slovenian (Caucasian)	Etidronate	*VDR; BsmI*	bb genotype: lower increase of spinal BMD	[11]
Postmenopausal women; NA	Italian (Caucasian)	Five treatment groups: 1) Alendronate plus raloxifene 2) Alendronate plus HRT 3) Alendronate alone 4) HRT alone 5) Raloxifene alone	*VDR; BsmI*	bb genotype: lower increase of spinal BMD	[12]
Early postmenopausal women; NA	NA	Etidronate	*COL1A1; Sp1*	SS genotype: higher increase of femoral BMD	[13]
Postmenopausal osteoporotic women; NA	Chinese (Asian)	Alendronate	*OPG; A163G, T245G, T950C*	G allele of A163G: lower increase at vertebral L2-4, inter-troche and total hip BMD. G allele of T245G:lower increase at vertebral L2-4, inter-troche and total hip BMD.	[16]

NA = not available

Table 1: Pharmacogenetic studies of osteoporosis.

Pharmacogenetics of Paget's Disease of Bone Therapy

Paget's disease of bone (PDB) is a metabolic bone disease characterized by accelerated bone resorption due to deregulation of osteoclast activity. NBPs are first-choice drugs for the treatment of Paget's disease of bone (PDB) diminishing bone resorption, inhibiting osteoclast proliferation and activity and inducing apoptosis. However, acquired resistance to consecutive NBP therapy has been described in some patients treated for PDB recurrences. A study by Mossetti et al. [24] has investigated the role of *BsmI*, *TaqI* and *FokI* polymorphisms of VDR gene in the acquired resistance (in terms of failure of total alkaline phosphatase serum levels to be suppressed) to intravenous clodronate administration in Caucasian patients with polyostotic PDB. The study evidenced that *bb* (*BsmI*) and *TT* (*TaqI*) *VDR* genotypes were significantly and independently associated with the development of resistance to clodronate. Another study [25] has assessed if genetic variations, in genes encoding proteins of the interleukin 1 (IL1) pathway, might be related to different responses to treatment with various BPS, evidencing that the CC genotype of the *-511 C/T* polymorphism of *IL1B* gene was associated with a greater resistance (calculated as number of treatment cycles with a positive bone response) to BP therapy in Spanish patients with PDB.

Pharmacogenetics of Bone Metastases Therapy

Intravenous high doses of NBPs are effective also for the treatment of bone metastases subsequent to prostate cancer, breast cancer or

multiple myeloma, but not without adverse effects in a percentage of treated patients. Since 2003, an increasing number of case reports and case series have associated the development of osteonecrosis of the jaw (ONJ) in a range of about 1-10 per 100 patients after a long-term intravenous use of high dose of zoledronic acid and, in more rare cases, of pamidronate [26]. The incidence of ONJ is very low in patients receiving oral NBPs for the treatment of PDB or osteoporosis [26]. The exact causes of bisphosphonate-related ONJ (BRONJ) are still unknown and numerous risk factors are suspected (i.e. poor dental hygiene, invasive dental procedures, maxillo-facial repeated irradiation, long-term corticosteroid and/or anti-angiogenic medications, etc) but none of them alone playing a pivotal role in the development of this complication. It has been hypothesized that genetic variants in genes regulating individual bone metabolism or in target genes of NBPs may confer susceptibility to BRONJ. Recently, a genome-wide association study, of over half a million of single nucleotide polymorphisms (SNPs) all along the entire human genome, has been carried out in two groups of patients affected by multiple myeloma and treated with intravenous NBPs (pamidronate or zoledronic acid), one who developed ONJ and the other one who did not present this complication after two years of therapy [27]. Four SNPs (*rs1341162 rs17110453, rs1934951* and *rs1934980*), that mapped within the cytochrome P450-2C gene (*CYP2C8*) showed a statistically significant different distribution between ONJ-positive and ONJ-negative subjects, indicating the polymorphisms of *CYP2C8* gene as promising ONJ genetic risk factors. Nevertheless, since NBPs do not undergo to any physical-chemical modification, polymorphisms in gene encoding CYP2C8 would not play a role in NBPs metabolism, but they could affect other biological pathways involved in BRONJ development. However, two association studies [28,29] did not confirm association between the *rs1934951* SNP of the *CYP2C8* gene and the development of BRONJ, respectively in 100 men receiving NBPs for bone metastatic prostate cancer and in 79 patients treated with zoledronic acid for bone metastases from multiple myeloma.

Another work [30] has evaluated the segregation of the A/C rs2297480 polymorphism in the intron 1 of the *FDPS* gene with the development of BRONJ in two cohorts of Caucasian patients, treated for two years with intravenous zoledronic acid for bone-metastatic multiple myeloma, prostate and breast cancer, one who developed BRONJ (ONJ group) and the other one who did not show this complication (control group). The study showed a statistically significant higher frequency of AA carriers in the ONJ group respect to control group, matched for sex, age, and kind of primary tumour. These results are in agreement with the previously described higher responsivity of the AC and AA genotypes to oral treatment with amino-bisphosphonates when compared to the CC genotype [19]. The presence of the A allele creates a putative binding site for the Runx1 transcription factor that may negatively modulate the expression of FDPS [31]. It could be assumed that the A allele segregates with the ONJ complication through a positive modulation of the response to a potent NBP, as zoledronic acid.

A recent work [32] studied polymorphisms of genes known to be related to bone metabolism and the risk of BRONJ. The study associated SNPs in five genes, *COL1A1 (rs1800012), RANK (rs12458117), MMP2 (rs243865), OPG (rs2073618)* and *OPN (rs11730582),* with ONJ development in multiple myeloma patients undergoing NBP therapy for over one year. The five SNPs have been considered together in the association analysis and the results suggest that multiple genes, rather than a single gene may be involved in BRONJ pathogenesis.

These studies above support the possibility to use pharmacogenetic tests to identify subjects at risk to develop BRONJ among tumour patients who are needed to take high dose of long-term NBP therapy for bone metastases. These preliminary data certainly need to be validated in prospective association studies from controlled clinical trials and by functional studies.

Conclusions and Future Perspectives

Metabolic bone disorders require chronic drug therapies. Different and effective treatments are available. Unfortunately, all drugs currently in use are non effective in a variable percentage of treated patients or may induce, in a variable number of them, various ADRs, that can range from moderate adverse effects, such as allergic reactions and transitory acute phase reaction, up to severe complications, such as BRONJ or atypical low-trauma femoral fractures.

Pharmacogenetics of metabolic bone diseases needs to be implemented, in the near future, with the final goal of designing specific genetic tests that can be performed prior to the administration of a drug, allowing the early identification of non-responders and of subjects at risk of ADRs and, thus, permitting to optimize treatment and to choose the best drug at the optimal dose for each single patient, based on the genotype.

Data from pharmacogenetics studies, performed to date, are in some cases inconclusive and/or contradictory, mainly because of study design limitations such as small sample sizes, reduced or absent follow up, different ethnicity of the analyzed populations, different evaluated clinical outcomes, etc. Moreover, these studies are characterized by no or limited analysis of gene-gene interactions or epigenetic factors and no or limited evaluation of environmental or other non-genetic cofactors, that could account for false positive associations. In addition, since studies showing positive associations are accepted for publication more frequently, negative associations are often hidden by this publication bias and they remain not available to the Scientific Community. Surely, pharmacogenetics studies on bone pharmacotherapies need to be implemented to avoid statistical and publication bias that could lead to false positive associations or to miss some important pharmacogenetic determinants. First step should be the extension and confirmation of genetic variants associated with different drug response in larger cohorts, different ethnical groups and multicentric studies preferentially from prospective controlled clinical trials, and then their validation by functional in vitro and in vivo studies. Next step should encompass analysis of genetic variations of genes encoding for drug targets, drug metabolizing enzymes and drug transporters, preferentially via multi-candidate gene approaches. Moreover, the application of high-throughput genome-wide techniques will allow to analyze genetic bases of drug response through a whole-genome point of view (pharmacogenomics), permitting to bypass all the limitations of the traditional single candidate gene approaches. Results from pharmacogenetic studies should be then integrated and validated by gene expression profiles, functional studies in cell and animal models, and proteomic analyses, before their translation into clinical practice.

However, since the expression of genes is under the control of epigenetic factors, pharmacogenetic studies should include also the analysis of the effects of epigenetic mechanisms on the regulation of expression of genes encoding drug metabolic enzymes, transporters and targets (pharmacoepigenomics) [33]. Epigenetic mechanisms may represent an explanation for the controversial results of pharmacogenetic

studies limited to the classical analysis of polymorphisms. There are growing evidences that the individual response to drugs cannot be attributed only to the genetic variants, and that many genes encoding drug metabolizing enzymes, drug transporters or drug targets are under epigenetic control (i.e. DNA methylation, histone modification or non-coding small RNAs) that could affect the drug response. MicroRNAs (miRNAs) are small non-coding RNAs that are important modulators of gene expression in several biological pathways by negative regulation of post-transcriptional gene expression, through the recognizing of specific sequences in the 3'UTR of target mRNAs. A polymorphism in the 3'UTR of the mRNA target could affect only one or few specific molecular pathways, while a polymorphism in mature miRNA may affect the expression of several genes involved in numerous molecular pathways. Polymorphisms mapping within the 3'UTR of mRNA targets, as well as those located in genes encoding miRNAs or proteins involved in miRNA biogenesis and maturation may potentially affect miRNA-mediated drug response. Thus, analysis of genetic variants in genes encoding for microRNAs and their mRNA targets should be routinely included in pharmacogenetic studies [34].

Finally, there are some non-scientific issues to be solved for pharmacogenetic translation into clinical practice such as economic, commercial, political, ethical and educational barriers among different states. A strong collaboration between regulatory agencies, university boards and hospitals for the establishment of International guidelines is needed; pharmacogenetic educational trainings and updates among health care professionals are strongly recommended.

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