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Review

Pharmacogenetic implications in the management of metabolic diseases in Brazilian populations

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Dyslipidemia, diabetes, obesity and hypertension are common metabolic diseases. In the last decades, unhealthy lifestyle and aging have leads to an increased incidence of these diseases, increasing morbidity and mortality by cardiovascular causes. The treatment of metabolic diseases includes life-style interventions as healthy diet and physical exercise, as well as pharmacological interventions. Several drugs are available for the management of metabolic diseases including among others lipid-lowering antidiabetics and antihypertensive drugs. Variability in response to these drugs is influenced by both genetic and non-genetic factors. Polymorphisms in genes related to drug pharmacokinetics and pharmacodynamics have been shown to influence drug efficacy and safety. This review is focused on pharmacogenetic studies related to the management of metabolic diseases in samples of the Brazilian population. Associations of variants in drug metabolizing enzymes and transporters, drug target and metabolism-related genes with the efficacy and safety of lipid-lowering, antidiabetic and antihypertensive drugs are described. Most pharmacogenetic studies in Brazil have focused in pharmacological response to a small group of drugs, as statins and some antihypertensives, while there are almost no studies on antidiabetic and antiobesity drugs. Some studies reported significant associations of gene polymorphisms with drug response confirming previous data from other populations, whereas other works did not replicate, which may relay on the genetic admixture of our population. In conclusion, further studies are necessary considering larger sample sizes, new unexplored drugs and more genetic variants to obtain stronger conclusions to explore clinical applications of pharmacogenetic studies in our population.

Keywords: Pharmacogenetics. Metabolic diseases. Gene polymorphism. Drug response.

INTRODUCTION

Metabolic diseases are interrelated disorders that contribute to the development of cardiovascular disease, which have experienced a notable increase in their rates in the last decades due to several contributing factors as ageing and mainly those related to life-style changes (unhealthy dietary pattern, physical inactivity and sedentary lifestyle, smoking, among others) which are reflected in high prevalence of obesity, type 2 diabetes (T2D) and, lately, metabolic syndrome (MetS) worldwide; including Brazil with a prevalence of MetS of almost 30% (De Carvalho Vidigal *et al*., 2013).

The origin of metabolic disorders can be explained by a number of conditions that lead to a proinflammatory status, such as over nutrition/obesity, insulin resistance, dyslipidemia and hypertension. Among them, obesity is a well-known risk factor conducting to atherosclerosis by increasing glucose levels, blood pressure and impairing lipid profile. Moreover, the increase of inflammatory mediators related to the expansion of adipose tissue and the changes observed in adipose tissue in response to over nutrition/obesity induce insulin resistance and oxidative stress, with the potential to impair several biological pathways that contributes to the establishment of insulin resistance and further development of atherosclerosis and cardiovascular diseases (Yoo, Choi, 2014).

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Changes in life-style are the first line treatment for the management of metabolic diseases. Dietary changes and physical activity improve metabolic parameters, mainly by changing anthropometric measures related to body composition as the reduction of fat mass related to visceral obesity. Nevertheless, when dietary changes are not enough to maintain patients with metabolic diseases at a low cardiometabolic risk, pharmacological intervention is necessary.

The pharmacological management of metabolic diseases has become a challenge due to the multifactorial components of these diseases, in which many times insulin resistance/T2D, hypertension and dyslipidemia coexist. Moreover, aging of the population and the increasing young age at which these alterations occurs result in long term exposure to the therapeutical drugs (Gouni-Berthold, Berthold, 2014). Moreover, it is well known that drug response, as effectiveness, safety and adverse drug reactions, depends on genetic and non-genetic factors, such as environmental/nutritional factors, drug interactions and drug metabolism, that could determinate the individual response to the therapeutical drugs.

Several pharmacogenetic studies have been performed in different populations around the world, in order to elucidate the influence of gene polymorphisms on the response to drugs used in the management of hyperglycemia, high blood pressure (BP), dyslipidemia and other metabolic diseases. In this way, Brazilian populations have been proposed as an interesting subject to be evaluated due to the difficulty to use an extrapolation of pharmacogenetic studies from other populations. The extensive miscegenation resulted in a genetic admixture from three major ethnical components, Europeans, Africans and Amerindians. The complex ancestral component of our population has important implications for pharmacogenetic studies and their applications (Cerda, Hirata, Hirata, 2014).

This review is focused on the pharmacogenetic studies that investigate the influence of gene polymorphisms on response to drugs used for treatment of metabolic diseases in Brazilian populations.

PHARMACOGENETICS AND DYSLIPIDEMIA

Dyslipidemia

Dyslipidemia is an important risk factor for coronary artery disease (CAD) and stroke. Several long-term prospective studies have consistently shown that characteristic alterations in lipid profile observed in dyslipidemia, such as hypercholesterolemia and hypertriglyceridemia (isolated or mixed if both are present), as well as low levels of high-density lipoprotein (HDL) cholesterol, have increased incidence of cardiovascular disease (CVD). These alterations in the lipid profile are etiologically classified as primary dyslipidemia, when the cause is of genetic origin; or secondary, if the alteration in the lipid profile is a consequence of inadequate life-style, some morbid conditions or as an adverse reaction to drugs (Faludi *et al*., 2017).

Prevention and a proper and timely management of dyslipidemia can markedly reduce morbidity and mortality due to cardiovascular causes. The treatment of dyslipidemia includes non-pharmacological strategies as a first line intervention, being recommended to modify life-style through nutritional therapy, weight-loss, reduction of alcohol intake, physical activity, among others. In high cardiovascular risk patients, as well as those patients with moderate risk who do not reach the therapeutic goals with lifestyle modifications, pharmacological intervention should be prescribed (Faludi *et al*., 2017).

Several drugs are available for the treatment of dyslipidemia and the choice of a specific medicine will depend on the type of dyslipidemia according to the altered parameter in lipid profile. Regarding cholesterol-lowering, statins are the most common drugs, with an important body of evidence supporting their benefits in preventing CVD in hypercholesterolemic patients. Also the ezetimibe (an inhibitor of cholesterol absorption) and resins (bile acid sequestrants) could be used in patients with statin intolerance or even could be used in association in patients at a high cardiovascular risk. Regarding treatment of hypertriglyceridemia, fibrates are the first choice, but also niacin and omega-3 fatty acids are available pharmacological strategies (Gryn, Hegele, 2014; Faludi *et al*., 2017).

Cholesterol-lowering drugs

Statins are the main focus of the pharmacogenomic studies on lipid-lowering therapy probably because they are very effective to treat hypercholesterolemia and to reduce the cardiovascular risk of patients with metabolic diseases. Statins also have pleiotropic effects that help improve endothelial function, stabilize plaques, and decrease inflammation contributing for primary and secondary prevention of cardiovascular and cerebrovascular diseases. Non-statin drugs, used as mono- or combined therapy, are becoming also focus of recent pharmacogenetic studies, mainly for patients with severe hypercholesterolemia, and/or who experienced lack of response or statin-induced muscular events (Gryn, Hegele, 2014; Alfonsi, Hegele, Gryn, 2016).

Statins are cholesterol synthesis inhibitors that competitively block 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the enzyme limiting the *de novo* synthesis of cholesterol in the liver. Statins are effective, well-tolerated and safe lipid-lowering drugs, but some patients do not respond to treatment and others experience adverse events, such as myopathy. The variability in the response to statins is attributed to genetic and non-genetic factors, such as lifestyle, drug interactions, intolerance or lack of adherence to pharmacotherapy (Gryn, Hegele, 2014; Patel *et al*., 2014; Alfonsi, Hegele, Gryn, 2016).

Pharmacogenetic studies of statins have focused mainly on genes in pharmacokinetic and pharmacodynamic pathways, as well as genes involved in lipid metabolism. Polymorphisms in these genes have been associated mainly with variability in statins efficacy and safety and with risk for cardiovascular events (Patel *et al*., 2014; Alfonsi, Hegele, Gryn, 2016; Leusink *et al*., 2016; Ruaño *et al*., 2016).

Pharmacokinetics-related genes

Several studies have reported that polymorphisms in genes encoding drug metabolizing enzymes influence the liver metabolism of specific statins and can cause a relevant effect on therapeutic response and the risk of adverse effects (Gelissen, McLachlan, 2014). Results from studies in Brazilian sample populations that investigated the influence of pharmacokinetics-related genes on response to statins are summarized in Table I.

Drug metabolizing enzymes and transporters

Cytochrome p450 (CYP) enzymes, such as CYP3A4 and CYP3A5, are involved in the metabolism of several classes of drugs including statins. Polymorphisms in *CYP3A4* and *CYP3A5* genes have been shown to influence the response to statins, including resistance to pharmacotherapy in other populations (Gelissen, McLachlan, 2014; Alfonsi, Hegele, Gryn, 2016).

Two studies investigated *CYP3A4* polymorphisms in Brazilian subjects with hypercholesterolemia. *CYP3A4*1B* (g.-392A>G), *CYP3A4*22* (g.15389C>T) alleles were not associated with cholesterol-lowering response and risk for adverse drug reactions (ADR) after long term treatment with simvastatin (Fiegenbaum *et al*., 2005a). Similarly, our group reported that *CYP3A4*1B* did not influenced the serum lipids reduction after short term treatment with atorvastatin (Wilrrich *et al*., 2013).

CYP3A5 polymorphisms were also evaluated in Brazilian samples. The *CYP3A5*3C* and **1D* alleles did not influence the response to simvastatin (Fiegenbaum *et al*., 2005a) and atorvastatin (Willrich *et al*., 2013). Interestingly, our group observed that carriers of the haplotype *CYP3A5*3A*, a combination of *3C and *1D alleles, showed reduced efficacy of atorvastatin compared to non-carriers (Willrich *et al*., 2008). Moreover, the *CYP3A5* AGT haplotype, which includes the *3C allele, was associated with lower basal *CYP3A5* mRNA expression in peripheral blood mononuclear cells (Willrich *et al*., 2013).

Adenosine triphosphate (ATP)-binding cassette (ABC) transporters are a family of efflux transporters that are involved in the bioavailability of several drugs and some statins. The most commonly studied is the ABCB1, also known as P-glycoprotein (P-gp) and multidrug-resistant protein 1 (MDR1). Polymorphisms in the *ABCB1* were shown to influence the cholesterol-lowering response to statins and the risk for statin-related muscular adverse events, such as myalgia in several studies (Gelissen, McLachlan, 2014; Gryn, Hegele, 2014; Patel *et al*., 2015; Alfonsi, Hegele, Gryn, 2016).

Three variants of the *ABCB1* (1236C>T, c.2677G>T/A and c.3435C>T) were studied in Brazilian hypercholesterolemic (HC) subjects treated with simvastatin and atorvastatin. Fiegenbaum *et al.* reported that carriers of c.1236T and c.2677non-G alleles had increased response to simvastatin long-term treatment. Moreover, three alleles of *ABCB1* (c.1236T, c.2677non-G and c.3435T) conferred lower risk for statin-induced ADR-induced (Fiegenbaum *et al*., 2005a). Our group described that HC subjects carrying *ABCB1* T/T haplotype have high basal serum concentrations of total and low-density lipoprotein (LDL) cholesterol but the *ABCB1* variants did not influence the response to short-term treatment with atorvastatin (Rodrigues *et al*., 2005). In a larger sample of HC subjects, we found that c.2677A allele is associated with greater LDL cholesterol reduction induced by atorvastatin (OR: 5.69, CI95%: 1.28-25.24, p=0.022). Interestingly, the c.2677T/A allele was also associated with reduction of *ABCB1* mRNA in PBMC (Rebecchi *et al*., 2009).

The variant 2012G>T of the *ABCC1*, which encodes the multidrug resistance-associated protein 1 (MRP1), was also investigated by our group. The 2012T allele carriers had low basal HDL cholesterol levels, but this variant did not influence the response to atorvastatin (Rebecchi *et al*., 2009).

Uptake transporters, such as the organic anion transporter polypeptides (OATP), play also an important role in the efficacy and safety of statins. Polymorphisms in the *SLCO1B1*, which encodes the organic anion-

TABLE I - Pharmacogenetics of statins in Brazilian sample populations: Pharmacokinetics-related genes

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/follow up]	Main findings [Outcomes]	Reference
CYP3A4	*CYP3A4*1B* (rs2740574; c.-392A>G), *CYP3A4*22 (*rs35599367; g.15389C>T)	*1B: 2.7%	Prospective cohort study	116 HC	Simvastatin, 20 mg/day, 6 months	*CYP3A4* *1B allele was not associated with cholesterol lowering response and ADR.	Fiegenbaum *et al.*, 2005a
		*1B: 20.0% *22: 1.0%	Prospective cohort study	119 HC	Atorvastatin, 10 md/day, 4 weeks	*CYP3A4* polymorphisms were not associated with serum lipids response to atorvastatin treatment	Willrich *et al.*, 2013
CYP3A5	*CYP3A5*3C* (rs776746; g.6986A>G), *CYP3A5*1D* (rs15524; g.31611C>T), *CYP3A5*6* (rs10264272, g.19787G>A) *CYP3A5*3A (*3C+*1D)*	*3: 91.1%	Prospective cohort study	116 HC	Simvastatin, 20 mg/day, 6 months	*CYP3A5* *3C allele was not associated with cholesterol lowering response or ADR.	Fiegenbaum *et al.*, 2005a
		*3C: 84.9%, *1D: 84.8%, *6: 0.0%, *3A: 82.6 %	Prospective cohort study	139 HC	Atorvastatin, 10 md/day, 4 weeks	*CYP3A5* *3A allele was associated with lower reduction of serum TC, LDL-c and apoB in response to atorvastatin treatment.	Willrich *et al.*, 2008
		*3C: 29.0% *1D: 26.0%	Prospective cohort study	119 HC	Atorvastatin, 10 md/day, 4 weeks	*CYP3A5* variants and haplotypes were not associated with serum lipids in response to atorvastatin treatment. AGT haplotype (*CYP3A5*3C* carrier) was associated with lower basal *CYP3A5* mRNA expression in PBMC.	Willrich *et al.*, 2013
ABCB1	c.1236C>T (rs1128503) c.2677G>T/A (rs2032582) c.3435C>T (rs1045642)	c.1236T: 42.2% c.2677non-G: 46.9% c.3435 T: 52.62%	Prospective cohort study	116 HC	Simvastatin, 20 mg/day, 6 months	*ABCB1* c.1236T and c.2677 non-G alleles were associated with greater reduction in serum TC and LDL-c after simvastatin treatment. *ABCB1* c.1236T, c.2677non-G, and c.3435T alleles were associated with lower risk for ADR.	Fiegenbaum *et al.*, 2005a
		c.2677T: 38.4% c.2677A: 3.6% c.3435T: 46.4%	Prospective cohort study	69 HC	Atorvastatin, 10 mg/day, 4 weeks	*ABCB1* T/T haplotype was associated with high basal TC and LDL-c. *ABCB1* variants did not influence the atorvastatin response.	Rodrigues *et al.*, 2005
		c.2677T: 33.0% c.2677A: 4.0% c.3435T: 45.0%	Prospective cohort study	136 HC	Atorvastatin, 10 mg/day, 4 weeks	*ABCB1* c.2677A allele was associated with atorvastatin-induced LDL-c reduction (OR: 5.69, CI95%: 1.28-25.24, p=0.022) c.2677T/A allele was associated with reduction of *ABCB1* mRNA expression. in PBMC after atorvastatin treatment.	Rebecchi *et al.*, 2009
ABCC1	2012G>T (rs45511401)	2012T: 4.0%	Prospective cohort study	136 HC	Atorvastatin, 10 mg/day, 4 weeks	*ABCC1* 2012T allele was associated with low basal serum HDL-c, but not with response to atorvastatin treatment.	Rebecchi *et al.*, 2009

TABLE I - Pharmacogenetics of statins in Brazilian sample populations: Pharmacokinetics-related genes (cont.)

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/follow up]	Main findings [Outcomes]	Reference
SLCO1B1	c.388A>G (rs2306283) c.463C>A (rs11045819) c.521T>C (rs4149056)	c.388G: 32.0% c.463A: 16.0% c.521C: 12.0%	Prospective cohort study	136 HC	Atorvastatin, 10 mg/day, 4 weeks	*SLCO1B1* c.388GG genotype was associated with higher LDL-c reduction after atorvastatin treatment (OR: 3.2, CI95%: 1.3-8.0, p=0.012). c.463A and c.521T>C variants and *SLCO1B1*15* haplotype (c.521C and c.388G) did not influence the atorvastatin response.	Rodrigues *et al*., 2011
		c.388G: 48.4% c.463A: 15.3% c.521C: 16.0%	Prospective cohort study	216 HC	Simvastatin, 20 mg/day, 6 months	*SLCO1B1* c.388G allele was associated with greater reduction of TC and LDL-c after simvastatin treatment. *SLCO1B1* c.463C>A and c.521T>C variants were not associated with response to simvastatin.	Sortica *et al*., 2012
		c.388G: 26.2% c.521C: 14.0%	Prospective cohort study	143 HC	Atorvastatin, 20/40/60/80 mg/day, 12 months Ezetimibe, 10 mg/day, 12 months (90 heterozygous FH)	*SLCO1B1* polymorphisms and haplotypes were not associated with ADR induced by cholesterol-lowering drugs.	Santos *et al*., 2012
SLCO2B1	c.-71T>C (rs2851069)	c.-71C: 53.0%	Prospective cohort study	136 HC	Atorvastatin, 10 mg/day, 4 weeks	*SLCO1B2* c.-71T>C polymorphism was not associated with response to atorvastatin.	Rodrigues *et al*., 2011
NR1I2	c.-1663T>C (rs1523130) c.-22-7659T>C (rs2472677)	T: 37.5% C: 38.8%	Prospective cohort study	240 HC	Simvastatin or atorvastatin, patient-adjusted dose, 1 year	*NR1I2* variants did not influence the lipid-lowering efficacy and safety of statins.	Lima *et al*., 2013
NR1I3	c.540C>T (rs2307424) c.238+1099A>G (rs2501873)	T: 31.4% G: 57.9%	Prospective cohort study	240 HC	Simvastatin or atorvastatin, patient-adjusted dose, 1 year	*NR1I3* variants did not influence the lipid-lowering response to statins. *NR1I3* c.540TT genotype was associated with lower risk for statin-induced liver or muscle ADR.	Lima *et al*., 2013
PPARA	c.484C>G (rs1800206)	CC genotype: 85.8%	Prospective cohort study	240 HC	Simvastatin or atorvastatin, patient-adjusted dose, 1 year	*PPARA* variant did not influence the lipid-lowering efficacy and safety of statins.	Lima *et al*., 2013
RXRA	*Indel* -/A (rs11381416)	-/- genotype: 81,2%	Prospective cohort study	240 HC	Simvastatin or atorvastatin, patient-adjusted dose, 1 year	*RXRA* variant did not influence the lipid-lowering efficacy and safety of statins.	Lima *et al*., 2013

ADR: adverse drug reaction; FH: familial hypercholesterolemia; HC: hypercholesterolemics; ApoB: apolipoprotein B; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TC: total cholesterol; OR: odds ratio; CI: confidence interval; PBMC: peripheral blood mononuclear cells.

transporting polypeptide 1B1 (OATP1B1), are important predictors of the clinical response to statins, mainly the risk for statin-related muscular events (Gelissen, McLachlan, 2014; Gryn, Hegele, 2014; Patel *et al*., 2015; Alfonsi, Hegele, Gryn, 2016; Leusink *et al*., 2016). Based on the clinical evidence of simvastatin-induced myopathy, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend dose adjustments in carriers of the *SLCO1B1* rs4149056 C allele (c.521T>C) (Ramsey *et al*., 2014).

The *SLCO1B1* c.388A>G, c.463C>A and c.521T>C variants were studied in Brazilian HC subjects. Our research group reported that *SLCO1B1* c.388GG genotype carriers are more likely to have greater LDL cholesterol response to atorvastatin (OR: 3.2, CI95%: 1.3-8.0, p=0.012) but the c.463C>A and c.521T>C variants did not influence the atorvastatin response (Rodrigues *et al*., 2011). Similar results were described by Sortica *et al*, with the *SLCO1B1* c.388G allele associated with greater reduction of total and LDL cholesterol after long term treatment with simvastatin (Sortica *et al*., 2012). *SLCO1B1* c.388A>G and c.521T>C variants were also investigated in a sample of heterozygous Familial Hypercholesterolemic (FH) subjects treated with atorvastatin (20-80 mg/day) and ezetimibe (10mg/day) for 12 months. *SLCO1B1* polymorphisms and haplotypes were not associated with ADR induced by cholesterol-lowering drugs (Santos *et al*., 2012).

The variant c.-71T>C of the *SLCO2B1*, which encodes the membrane transporter OATP2B1, was also studied by our group, but no association was found with the lipid response to atorvastatin (Rodrigues *et al*., 2011).

Pregnane X receptor (PXR), constitutive androsterone receptor (CAR), peroxisome proliferator-activated receptor alpha (PPAR-alpha) and other nuclear receptors regulate the expression of major drug metabolizing enzymes and transporters upon induction by xenobiotics and pharmacological drugs. Polymorphisms in genes encoding PXR (*NR1I2*), CAR (*NR1I3*), PPAR-alpha (*PPARA*) and retinoic X receptor alpha (RXR-alpha, *RXRA*) have been suggested to influence variability in CYP3A expression and activity and they may influence drug response (Klein, Zanger, 2013).

One study investigated the influence of polymorphisms within the *NR1I2*, *NR1I3*, *PPARA* and *RXRA* on simvastatin or atorvastatin response in Brazilian HC patients treated during one year. *NR1I2* (c.-1663T>C, c.-22-7659T>C), *NR1I3* (c.540C>T, c.238+1099A>G), *PPARA* (c.484C>G) and *RXRA* (Indel -/A) did not influence lipid-lowering response to these statins. *NR1I3* c.540TT genotype carriers had lower risk for statin-induced liver or muscle ADR, but the other variants were not associated with safety of statins (Lima *et al*., 2013).

Pharmacodynamics-related genes

Polymorphisms in the *HMGCR*, which encodes the target of statins, and other genes involved in the cholesterol homeostasis and lipid metabolism have been proposed as predictors of the statin response. Studies that investigated the influence of pharmacodynamics-related genes on response to statins in Brazilian populations are depicted in Table II.

Some variants of the *HMGCR* were associated with the response to statins. *HMGCR* haplotype H2 and H7 carriers experienced a 5% to 20% lower reduction of LDL cholesterol after treatment with simvastatin. *HMGCR* variants rs17244841 (SNP12) and rs17238540 (SNP29) were associated with lower LDL cholesterol reduction in response to pravastatin and atorvastatin. The *HMGCR* rs1724481, rs10474433 and rs17671591 polymorphisms were also associated with response to various statins (Gelissen, McLachlan, 2014; Gryn, Hegele, 2014; Patel *et al*., 2014; Alfonsi, Hegene, Gryn, 2016).

One study investigated the *HMGCR* SNP29 in Brazilian HC patients taking long term treatment with simvastatin or atorvastatin (10-80 mg/day), but no association was found with oxidative stress biomarkers, such as plasma malondialdehyde, oxidized LDL and total antioxidant activity, and plasma tocopherol (Botelho *et al*., 2012).

LDL receptor mediates the uptake of LDL particles in the cell surface by binding to the apolipoprotein B (ApoB), the structural protein of the very low-density lipoprotein (VLDL) and LDL. Variants in the LDL receptor encoding gene, *LDLR*, were described to be associated with increased plasma lipids, reduced response to several statins and high risk for cardiovascular events (Gelissen, McLachlan, 2014; Gryn, Hegele, 2014; Leusink *et al*., 2016; Postmus *et al*., 2014; Alfonsi, Hegele, Gryn, 2016; Ruaño *et al*., 2016).

Our group investigated the influence of three variants of the *LDLR* (Val653Val/AvaII, Asn591Asn/HincII and g.42716A>G/PvuII) in HC subjects. *LDLR* AvaII (A+A+) and PvuII (P1P1) genotypes were associated with high basal total cholesterol, LDL cholesterol and apoB plasma concentrations and reduced response of these lipids to fluvastatin (Salazar *et al*., 2000). Further we reported that the *LDLR* c.*52G>A variant, located in the 3´UTR, was associated with lower risk of hypercholesterolemia (OR: 0.58, 95%CI: 0.34-0.99, p=0.043) but not with response to atorvastatin (Zambrano *et al*., 2015).

TABLE II - Pharmacogenetics of statins in Brazilian sample populations: Pharmacodynamics-related genes

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/follow up]	Main findings [Outcomes]	Reference
HMGCR	g.27506T>G (SNP29, rs17238540)	n.i.	Cross-sectional study	55 HC	Simvastatin or atorvastatin (10-80 mg/day), 6 months	*HMGCR* SNP29 was not associated with oxidative stress biomarkers (plasma malondialdehyde, oxidized LDL, total antioxidant activity) and plasma tocopherol.	Botelho *et al*., 2012
LDLR	Val653Val (rs5925T>C, AvaII) Asn591Asn (rs688C>T, HincII) g.42716A>G (rs2569542, PvuII)	C (A+): 58.2% C (H+): 56.4% G (P1): 78.2%	Prospective cohort study	55 HC	Fluvastatin, 40 and 80 mg/day, 4 months	*LDLR* AvaII (A+A+) and PvuII (P1P1) genotypes were associated with high basal TC, LDL-c and apoB and reduced response to fluvastatin (TC, LDL-c and apoB).	Salazar *et al*., 2000
	c.*52G>A (3´UTR, rs14158)	A: 18.5%	Prospective cohort study	89 HC	Atorvastatin, 10 mg/day, 4 weeks	*LDLR* A allele carriers had lower risk of hypercholesterolemia (OR=0.58, 95%CI=0.34-0.99, p=0.043) but not with atorvastatin response.	Zambrano *et al*., 2015
	Null mutation Defective mutation	Null: 25.6% Defective: 37.8% Non-identified mutation: 36.6%	Prospective cohort study	156 heterozygous FH No *APOB* and *PCSK9* mutations	Atorvastatin associated or not with ezetimibe or adjuvant lipid-lowering medications. Doses were prescribed by the physician to reach LDL-c target values. Follow-up 12 months.	Carriers of null mutations had higher CT and LDL-c reduction after lipid-lowering treatment. *LDLR* mutations were associated with high likelihood of not reaching LDL-c target values after treatment (OR=9.07, 95%CI=1.41-58.16, p=0.02). Null and defective mutations were not associated with statin-induced muscle ADR.	Santos *et al*., 2014b
APOB	c.7545C>T (rs693, XbaI) c.12451G>A (rs1042031, EcoRI) c.35_43delTGGCGCTGC (5´Indel, rs17240441)	Ins (I): 61.6% c.7545C: 62.9% c.12451A: 14.0%	Prospective cohort study	104 HC (54 treated)	Fluvastatin, 40 and 80 mg/day, 4 months	*APOB* c.7545C>T variant was associated with high levels of plasma TC and LDL-c. *Indel* II genotype carriers had greater reduction of LDL-c in response to fluvastatin treatment.	Guzman *et al*., 2000
		n.i.	Prospective cohort study	157 HC	Atorvastatin, 10 mg/day, 4 weeks	*APOB* c.7545T allele was associated with hypercholesterolemia (OR: 2.20, CI95%: 1.48-3.20, p=0.0001), but not with response to atorvastatin.	Rodrigues *et al*., 2013
PCSK9	c.2009A>G (Gly670Glu, rs505151), c.1420A>G (Val474Ile, rs562556), c.137G>T (Arg46Leu, (rs11591147)	c.2009G:14.7% c.1420G: 19.1% c.137T: 0.3%	Prospective cohort study	128 HC	Atorvastatin, 10 mg/day, 4 weeks	*PCSK9* c.2009G allele was associated with high basal plasma LDL-c. *PCSK9* genotypes or haplotypes did not influence the LDL-c reduction in response to atorvastatin.	Anderson *et al*., 2014
	c.*614C>T (3´UTR, rs17111557)	T: 6.1%	Prospective cohort study	89 HC	Atorvastatin, 10 mg/day, 4 weeks	*PCSK9* 3´UTR polymorphism was not associated with atorvastatin response.	Zambrano *et al*., 2015

TABLE II - Pharmacogenetics of statins in Brazilian sample populations: Pharmacodynamics-related genes (cont.)

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/follow up]	Main findings [Outcomes]	Reference
MYLIP	c.1025G>A (p.N342S, rs9370867)	A: 39.7%	Prospective cohort study	156 heterozygous FH	Atorvastatin, 20/40/60/ 80 mg/day, 12 months Ezetimibe, 10 mg/day, 12 months (89 HF)	*MYLIP* AA genotype was associated with better response to cholesterol-lowering drugs, in patients carrying *LDLR* mutations.	Santos *et al*., 2014
SREBF1	c.-36del>G (rs796641934)	G+: 49.6%	Prospective cohort study	146 HC (99 treated)	Simvastatin, 20 mg/day, 6 months	*SREBF1* c.-36del>G was not associated with plasma lipids response to simvastatin	Fiegenbaum *et al.*, 2005c
		G+: 54.2%	Prospective cohort study	59 HC	Atorvastatin, 10 mg/day, 4 weeks	*SREBF1* c.-36del>G was not associated with plasma lipids response to atorvastatin.	Arazi *et al*., 2008
SREBF2	c.1784G>C (rs2228314)	A: 27.0%	Prospective cohort study	146 HC (99 treated)	Simvastatin, 20 mg/day, 6 months	*SREBF2* 1784G>C was not associated with plasma lipids response to simvastatin	Fiegenbaum *et al.*, 2005c
SCAP	2386A>G (rs12487736)	G: 48.4%	Prospective cohort study	146 HC (99 treated)	Simvastatin, 20 mg/day, 6 months	*SCAP* 2386G allele was associated with high basal plasma TC and increased response of TC and TG to simvastatin.	Fiegenbaum *et al.*, 2005c
		G: 54.2%	Prospective cohort study	59 HC	Atorvastatin, 10 mg/day, 4 weeks	*SCAP* 2386AA genotype was associated with reduction of SCAP mRNA expression in PBMC but not with lipid response to atorvastatin.	Arazi *et al*., 2008
APOE	*APOE*2/*3/*4* Generated by Arg112Cys (rs7412) and Cys158Arg (rs429358)	*2: 1.5%, *3: 81.3%, *4: 17.2%	Prospective cohort study	146 HC (99 treated)	Simvastatin, 20 mg/day, 6 months	*APOE* variants did not influence variation in serum lipids after treatment.	Fiegenbaum *et al.*, 2005b
		*2: 1.7%, *3: 80.9%, *4: 17.3%	Prospective cohort study	181 HC	Atorvastatin, 10 mg/day, 4 weeks	*APOE* *2 allele carriers had lower risk for hypercholesterolemia (OR= 0.27; CI95%= 0.01-0.85, p=0.025). *APOE* polymorphism did not influence plasma lipids after atorvastatin treatment.	Cerda *et al*., 2011b
		*2: 4.0%, *3: 79.0%, *4: 17.0%	Prospective cohort study	87 HC postmenopausal women	AT group (17): atorvastatin (10 mg) HT group (34): estradiol (2 mg) and estradiol+ NETA (1 mg) AT+HT group (36): estradiol+atorvastatin and estradiol+NETA+ atorvastatin. Daily doses, 3 months	*APOE* genotypes were not associated with serum lipids in response to atorvastatin combined or not with HT. *APOE*3*3* genotype was associated with greater reduction of *APOE* mRNA PBMC after treatment with atorvastatin.	Issa *et al*., 2012

TABLE II - Pharmacogenetics of statins in Brazilian sample populations: Pharmacodynamics-related genes (cont.)

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/follow up]	Main findings [Outcomes]	Reference
APOE	g.4798T>G (-219G>T, rs405509)	n.i.	Cross-sectional study	55 HC	Simvastatin and atorvastatin (10-80 mg/day), 6 months	*APOE* g.4798T>G was not associated with oxidative stress biomarkers (plasma malondialdehyde, oxidized LDL, total antioxidant activity) and plasma tocopherol.	Botelho *et al.*, 2012
LIPC	g.4765G>A (-250G>A, rs2070895)	A: 29.8%	Prospective cohort study	146 HC (99 treated)	Simvastatin, 20 mg/day, 6 months	*LIPC* -250G>A variant did not influence variation in plasma lipids after treatment	Fiegenbaum *et al.*, 2005b
	g.4501C>T (-514C>T, rs1800588)	n.i.	Prospective cohort study	157 HC	Atorvastatin, 10 mg/day, 4 weeks	*LIPC* -514C allele was associated with better response to atorvastatin treatment (OR: 0.27, CI95%: 0.08-0.90, p=0.03)	Rodrigues *et al.*, 2013
ABCA1	c.-327C>T (rs1800977) c.-418C>T (rs56064613) c.656G>A (Arg219Lys, (rs2230806)	c.-327T: 35.0% c.-418T: 2.0% c.656A: 42.0%	Prospective cohort study	224 HC	Atorvastatin, 10 mg/day, 4 weeks	*ABCA1* c.-418T and c.656A alleles were associated with high basal serum HDL-c and low TG and VLDL-c. *ABCA1* variants were not associated with lipids response to atorvastatin.	Genvigir *et al.*, 2008
APOA1	-75G>A (rs560) 83C>T (rs5069)	-75A: 16.0% 83T: 6.0%	Prospective cohort study	150 HC	Atorvastatin, 10 mg/day, 4 weeks	*APOA1* -75A allele was associated with high basal serum TG and VLDL-c in HC men. *APOA1* -75GG/83CC haplotype was associated with higher reduction of TG and VLDL-c after atorvastatin treatment in HC women.	Sorkin *et al.*, 2005
CETP	g.5454G>A (rs708272, Taq1B)	B1: 49.5% B2: 50.5%	Prospective cohort study	146 HC (99 treated)	Simvastatin, 20 mg/day, 6 months	*CETP* B2B2 genotype was associated with increase in HDL-c after simvastatin treatment.	Fiegenbaum *et al.*, 2005b
		n.i.	Cross-sectional study	55 HC	Simvastatin or atorvastatin (10-80 mg/day), 6 months	*CETP* Taq1B was not associated with differences in plasma tocopherol and oxidative stress biomarkers (malondialdehyde, oxidized LDL, total antioxidant activity).	Botelho *et al.*, 2012
SCARB1	c.4G>A (rs4238001) c.726+54C>T (rs61932577) c.1050C>T (rs5888)	c.4A: 12.0% c.726+54T: 7.0% c.1050T: 40.0%	Prospective cohort study	147 HC	Atorvastatin, 10 mg/day, 4 weeks	*SCARB1* c.1050C allele was associated with lower change in TC, LDL-c and apoB plasma levels after treatment with atorvastatin.	Cerda *et al.*, 2010
		n.i.	Prospective cohort study	123 HC	Atorvastatin, 10 mg/day/ 4 weeks (98 HC)	*SCARB1* c.726+54T allele was associated with high basal plasma LDL-c and apoB, and low *SCARB1* mRNA expression in PBMC before and after atorvastatin treatment.	Cerda *et al.*, 2011a
CD36	g.16417A>G (rs1984112)	n.i.	Prospective cohort study	157 HC 147 controls	Atorvastatin, 10 mg/day, 4 weeks	*CD36* g.16417A>G was associated with hypercholesterolemia (OR: 3.7, CI95%: 1.9-7.0, p=0.0002), but not with response to atorvastatin.	Rodrigues *et al.*, 2013

TABLE II - Pharmacogenetics of statins in Brazilian sample populations: Pharmacodynamics-related genes (cont.)

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/follow up]	Main findings [Outcomes]	Reference
PON1	c.575A>G (Gln192Arg, rs662) c.163T>A (Leu55Met, rs854560)	192Arg (C allele): 33.2% 55M (T allele): 33.6%	Prospective cohort study	433 HC	Simvastatin (360) and atorvastatin (73), standard dose 10.3 ± 4.6 mg/day, 6 months	*PON1* 192Arg and 55Met alleles were associated with higher probability of achieving HDL-c goals after long term treatment with statins (OR =2.81, CI95% =1.35–5.85, P =0.006).	De Souza *et al.*, 2015
	Gln192Arg	n.i.	Cross-sectional study	55 HC	Simvastatin and atorvastatin (10-80 mg/day), 6 months	*PON1* Gln1292Arg was not associated with plasma tocopherol and oxidative stress biomarkers (malondialdehyde, oxidized LDL, total antioxidant activity).	Botelho *et al.*, 2012
ESR1	g.190510T>C (rs2234693) g.448305T>C (rs3798577)	C allele: 43.0% C allele: 45.0%	Prospective cohort study	495 HC	Simvastatin (421) and atorvastatin (74), standard dose 10.2 ± 4.6 mg/day, 6 months	*ESR1* g.448305T allele was associated with greater reduction of plasma TC and TG and g.190510CC genotype was associated with increase in plasma HDL-c after treatment with statins in HC women.	Smiderle *et al.*, 2016
MTHFR	c.677C>T (rs1801133)	CC genotype: 52.0%	Prospective cohort study	25 obese women	Simvastatin, 20 mg/day, 6 weeks	*MTHFR* T allele was associated with reduction of homocysteine and increase of nitrite in plasma after simvastatin treatment	Villela *et al.*, 2014
NOS3	-786T>C (rs3918161)	n.i.	Prospective cohort study	30 heathy men	Atorvastatin, 10 mg/day, 14 days	*NOS3* CC genotype carriers had increased blood nitrite and reduced plasma malondialdehyde, after treatment with atorvastatin. *NOS3* polymorphism was not associated with cholesterol-lowering response to atorvastatin.	Nagassaki *et al.*, 2006
		n.i.	Prospective cohort study	30 heathy men	Atorvastatin, 10 mg/day, 14 days	*NOS3* CC genotype was associated with reduction of plasma sCD40-L, sVCAM, sP-selectin and MMP-9 after treatment with atorvastatin.	Souza-Costa *et al.*, 2007
		TT genotype:40.0%	Prospective cohort study	25 obese women	Simvastatin, 20 mg/day, 6 weeks	*NOS3* -786C allele modulated the increase of blood nitrite but not the reduction of plasma malondialdehyde, after treatment with simvastatin.	Andrade *et al.*, 2013
SOD2	c.47T>C (Val16Ala, (rs4880)	C allele: 50.0%	Prospective cohort study	122 HC	Rosuvastatin, 20 mg/day, 4 months	*SOD2* VV (TT) genotype was associated with less effective plasma lipids (TC, LDL-c and HDL-c), anti-inflammatory and anti-fibrinolytic responses to rosuvastatin treatment.	Duarte *et al.*, 2016

ADR: adverse drug reaction; FH: familial hypercholesterolemia; HC: hypercholesterolemics; ApoB: apolipoprotein B; HDL-c: high-density lipoprotein cholesterol; HT: hormone therapy; LDL-c: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; VLDL-c: very low-density lipoprotein cholesterol, NETA: norethisterone acetate; ni: not informed; OR: odds ratio; CI: confidence interval; PBMC: peripheral blood mononuclear cells.

Santos et al investigated the influence of *LDLR* mutations on response to long term (12 months) treatment with cholesterol-lowering drugs (atorvastatin associated or not with ezetimibe or adjuvant lipid-lowering drugs). Carriers of null mutations showed higher reduction of total and LDL cholesterol plasma levels after treatment. *LDLR* mutations were associated with greater likelihood of not reaching LDL cholesterol target values after treatment (OR: 9.07, 95%CI: 1.41-58.16, p=0.002). In addition null and defective mutations were not associated with statin-induced muscle ADR (Santos *et al*., 2014b).

APOB encodes ApoB, the ligand of LDL particles to the LDL receptor in the surface of the cells. Polymorphisms in *APOB* are associated with plasma ApoB and LDL cholesterol levels and risk of cardiovascular diseases (Benn, 2009).

The *APOB* c.7545C>T, c.12451G>A and 5´Indel polymorphisms have been studied in Brazilian samples. The c.7545C>T variant, also named XbaI, was associated with high levels of plasma total and LDL cholesterol (Guzman *et al*., 2000) and with hypercholesterolemia (OR: 2.2, 95%CI: 1.48-3.2, p=0.0001) (Rodrigues *et al*., 2013). The insertion/deletion variant, located at the 5´of the *APOB*, was associated with greater reduction of plasma LDL cholesterol after long term treatment with fluvastatin (4 months), however c.7545C>T and c.12451G>A (EcoRI) did not influence the response to fluvastatin (Guzman *et al*., 2000) or short term treatment with atorvastatin (Rodrigues *et al*., 2013).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that degrades the LDL receptor, and contributes to the cholesterol intracellular homeostasis. Functional polymorphisms (gain in function) in *PCSK9* have been associated with a lower response to statins (Gelissen, McLachlan, 2014; Gryn, Hegele, 2014; Alfonsi, Hegele, Gryn, 2016). Whereas non-functional (loss of function) variants were related to increased statin response, which was the basis of the development of the PCSK9 inhibitors (Burke *et al*., 2017).

Four variants of the *PCSK9* (c.2009A>G, c.1420A>G, c.137G>T and c.*614T>C) were analyzed in Brazilian HC subjects, but no one was associated with response to short term treatment with atorvastatin (Anderson *et al*., 2014; Zambrano *et al*., 2015). Interestingly, carriers of the c.2009G allele had higher basal plasma LDL cholesterol (Anderson *et al*., 2014).

The myosin regulatory light chain-interacting protein (MYLIP), also named E3-ubiquitin ligase, is a cytoskeletal effector protein that links actin to membrane-bound proteins at the cell surface. MYLIP causes the ubiquitination of the LDL receptor cytoplasmic domain, thereby promoting its degradation and rising plasma LDL cholesterol. Polymorphisms in *MYLIP* have been associated with variability in plasma cholesterol and response to statins (Gelissen, McLachlan, 2014).

Santos *et al*. investigated the influence of *MYLIP* c.1025G>A variant on plasma lipids in heterozygous FH patients. They showed that AA genotype was associated with better response to long term treatment with atorvastatin and ezetimibe, a cholesterol absorption inhibitor, in subjects carrying *LDLR* mutations (Santos *et al*., 2014a).

Cholesterol homeostasis-related genes

Sterol regulatory element-binding factors (SREBFs) and SREBF cleavage-activating protein (SCAP) are important regulators of the cholesterol homeostasis, mostly by activating hepatic synthesis of fatty acids and cholesterol. SREBFs are activated by low level of intracellular cholesterol, in a sequence of steps including the SCAP-mediated transfer from endoplasmic reticulum to the Golgi. Activated SREPFs are transferred to nucleus to induce the transcription of the cholesterogenic genes, such as *HMGCR* and *LDLR* that results in normalization of the intracellular cholesterol level. Polymorphisms in the SREBF1, SREBF1 and SCAP encoding genes have been implicated in the variability of plasma lipids and in the response to lipid-lowering drug (Gryn, Hegele, 2014).

The influence of the *SRBEF1*, *SREBF2* and *SCAP* polymorphisms on lipid-lowering response to statins were evaluated in two studies with Brazilian HC subjects. *SRBEF1* c.-36del>G and *SREBF2* c.1784G>C variants were not associated with plasma lipids response to simvastatin (Fiegenbaum *et al*., 2005c). We also did not find relationship between *SRBEF1* c.-36del>G and the atorvastatin cholesterol-lowering response (Arazi *et al*., 2008). HC subjects carrying the G allele of the *SCAP* 2386A>G polymorphism had high plasma total cholesterol and increased response of total cholesterol and triglycerides to simvastatin treatment for six months (Fiegenbaum *et al*., 2005c). Our research group reported that *SCAP* 2386GG genotype carriers had reduction of *SCAP* mRNA expression in PBMC, but the polymorphism did not influence the lipid response to atorvastatin (Arazi *et al*., 2008).

Lipid metabolism-related genes

Apolipoprotein E (ApoE) has an important role in the liver uptake of the triglyceride-rich lipoproteins, such as VLDL and its remnant, via LDL and lipoprotein receptor-related protein (LRP) receptors. The gene encoding the ApoE (*APOE*) has three main alleles (ε2,

ε3, and ε4), which encodes ApoE isoforms with different affinities for cell surface receptors. Candidate genes and genome-wide association studies have suggested that *APOE* polymorphism is as a robust marker of statin-induced cholesterol lowering response, but there is not a clear association with cardiovascular events (Gelissen, McLachlan, 2014; Gryn, Hegele, 2014; Patel *et al*., 2014; Postmus *et al*., 2014; Leusink *et al*., 2016; Ruaño *et al*., 2016).

Four studies evaluated of *APOE* polymorphism in Brazilian HC patients treated with statins. *APOE* alleles did not influence plasma lipids after long term treatment with simvastatin (Fiegenbaum *et al*., 2005b) and short term treatment with atorvastatin (Cerda *et al*., 2011b). We also reported no association between *APOE* genotypes and lipid-lowering response to atorvastatin combined or not with hormonal therapy for three months in postmenopausal HC women (Issa *et al*., 2012). As reported by previous studies, we found an association of *APOE* *2 allele with lower risk for hypercholesterolemia (OR: 0.27, CI95%; 0.01-0.85, p=0.025) (Cerda *et al*., 2011b). Interestingly, *APOE* *3*3 genotype carriers had greater reduction of *APOE* mRNA levels in PBMC after atorvastatin treatment (Issa *et al*., 2012). Another study investigated the *APOE* g.4798T>G in subjects with statin-controlled dyslipidemia and did not find association with oxidative stress biomarkers and plasma tocopherol (Botelho *et al*., 2012).

Hepatic lipase, encoded by *LIPC*, has an important role in lipid metabolism by hydrolyzing triglycerides and phospholipids in plasma lipoproteins and by acting as a bridging factor for receptor-mediated lipoprotein uptake. Variants of LIPC have been associated with response to statins (Leusink *et al*., 2016).

Two studies investigated the influence of *LIPC* polymorphisms in Brazilian HC patients treated with statins. Fiegenbaum *et al* reported lack of association between *LIPC* -250G>A and variability in plasma lipids after long term treatment with simvastatin (Fiegenbaum *et al*., 2005b). Whereas, our group described that C allele carriers of the *LIPC* -514C>T are more likely to have better response to atorvastatin (OR: 0.27, CI95%: 0.08-0.90, p=0.003) (Rodrigues *et al*., 2013).

Reverse cholesterol transport-related genes

ABCA1 and ABCG1 are membrane transporters involved in the cholesterol efflux from cells to lipid poor apolipoprotein A-I (ApoA-I) in nascent discoidal HDL. In this way ABCA1and ABCG1 transporters and ApoA-I as well play important roles in the biogenesis of HDL and the reverse transport of cholesterol from the cells to the liver. Polymorphisms in the gene cluster encoding apolipoproteins *A1-C3-A4-A5-BUD13* were reported to affect triglycerides and LDL cholesterol responses to statins (Gryn, Hegele, 2014).

Our group investigated the influence of three *ABCA1* polymorphisms (c.-327C>T, c.-418C>T and c.656G>A) and two *APOA1* variants (-75G>A and 83C>T) on short term atorvastatin treatment. Carriers of *ABCA1* c.-418T and c.656A alleles had high basal serum HDL cholesterol and low triglycerides and VLDL cholesterol, but *ABCA1* variants were not associated of with response to atorvastatin (Genvigir *et al*., 2008). *APOA1* -75A allele was associated with high basal serum triglycerides and VLDL cholesterol in HC men, and *APOA1* -75GG/83CC haplotype was associated with higher reduction of triglycerides and VLDL cholesterol after atorvastatin treatment in HC women (Sorkin *et al*., 2005).

Cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl ester for triglycerides between HDL and the apoB-containing lipoproteins VLDL and LDL. Polymorphisms in *CETP* have been associated with variability in HDL cholesterol levels and cardiovascular events in patients treated with statins (Patel *et al*., 2014; Alfonsi, Hegele, Gryn, 2016; Leusink *et al*., 2016; Ruaño *et al*., 2016).

The influence of the *CETP* Taq1B (g.5454G>A) polymorphism in HC treated with statins was reported in two Brazilian studies. *CETP* B2B2 genotype was shown to increase the HDL cholesterol after long term of simvastatin treatment (Fiegenbaum *et al*., 2005b). Whereas *CETP* Taq1B variant was not associated with differences in plasma tocopherol and oxidative stress biomarkers, such as malondialdehyde, oxidized LDL and total antioxidant activity, in a study with HC subjects treated with simvastatin or atorvastatin (Botelho *et al*., 2012).

The scavenger receptor BI (SR-BI) has also an important role in the final step of the reverse cholesterol transport, by mediating the liver uptake of the HDL-associated cholesterol esters, which are excreted through the bile. Several polymorphisms in genes involved in the cholesterol lowering pathway were investigated for modification of the effectiveness of statins in reducing the risk for myocardial infarction. *SCARB1* variants had the most significant interaction with statin effectiveness (Peters *et al*., 2011).

Three polymorphisms (c.4G>A, c.726+54C>T, c.1050C>T) in the *SCARB1*, which encodes the SR-BI, were investigated by our group, in HC subjects treated with atorvastatin during 4 weeks. Carriers of *SCARB1* c.1050C allele had less reduction of total cholesterol, LDL cholesterol and apoB plasma levels in response to atorvastatin (Cerda *et al.*, 2010). *SCARB1*

c.726+54T allele was associated with high basal plasma LDL cholesterol and apoB, and low *SCARB1* mRNA expression in PBMC before and after atorvastatin treatment (Cerda *et al*., 2011a). *SCARB1* variants were not associated with plasma lipids or *SCARB1* mRNA expression in PBMC of HC subjects after treatment with ezetimibe (10 mg/day/4weeks) and simvastatin (10mg/day/8weeks) monotherapies and combined therapy (ezetimibe+simvastatin: 10mg/day/4weeks) (Cerda *et al*., 2011a).

Cluster determinant 36 (CD36), also named fatty acid translocase (FAT), is a membrane glycoprotein with various cellular functions, including oxidized LDL receptor (scavenger receptor type B), mechanisms of angiogenesis and gustatory perception of fatty acids. Using a candidate gene approach, we investigated the effects of polymorphisms in *CD36* and other genes related to lipid metabolism and atherosclerosis in a sample of Brazilian population. *CD36* g.16417A>G was associated with hypercholesterolemia (OR: 3.7, CI95%: 1.9-7.0, p=0.0002), but not with response to short term treatment with atorvastatin (Rodrigues *et al*., 2013).

Paraoxonase 1 (PON1) is an enzyme with important roles in the detoxification of the oxidized LDL and prevention of the HDL lipid peroxidation. PON1 has been suggested to be a cardioprotective agent in atherosclerosis and related vascular diseases (Cerda, Hirata, Hirata, 2012). The polymorphisms c.575A>G (Gln192Arg) and c.163T>A (Leu55Met) in the *PON1* were studied in a sample of Brazilian HC subjects. Carriers of *PON1* 192Arg and 55Met alleles are more likely of achieving HDL cholesterol goals after long term treatment with simvastatin and atorvastatin (OR: 2.81, CI95%:1.35-5.85, P =0.006) (De Souza *et al*., 2015). On the other hand *PON1* Gln192Arg was not associated with differences in plasma tocopherol and oxidative stress biomarkers, in HC subjects treated with simvastatin or atorvastatin for six months (Botelho *et al*., 2012).

Estrogen receptor alpha, encoded by *ESR1*, is a ligand-activated transcription factor involved in the signaling of the estrogen physiological effects in the female body, including the regulation of genes involved in the metabolism of HDL and other lipoproteins. Two variants in the *ESR1* (g.190510T>C and g.448305T>C) were studied in a large sample of HC Brazilian subjects. g.448305T>C was associated with greater reduction of plasma total cholesterol and LDL cholesterol after treatment with simvastatin and atorvastatin for six months, in HC women. Moreover, carriers of g.190510CC genotype showed increased HDL cholesterol in response to statins (Smiderle *et al*., 2016).

Endothelial function-related genes

Methylenetetrahydrofolate reductase (MTHFR) is involved in the methyl cycle generating 5-methylhydrofolate used for conversion of homocysteine to methionine. Endothelial dysfunction can be caused by hyperhomocysteinemia, which has been considered an independent risk factor for cardiovascular diseases. Polymorphisms in *MTHFR* and other genes were suggested to be predictors for slow atorvastatin metabolism (León-Cachón *et al*., 2016). A Brazilian study reported the association of *MTHFR* c.677C>T polymorphism with homocysteine reduction and nitrite in plasma after simvastatin treatment, in obese women (Villela *et al*., 2014).

The endothelial nitric oxide synthase (eNOS) produces the vasodilator nitric oxide (NO), which regulates the vascular system by inhibition of platelet aggregation, leukocyte adhesion and smooth muscle proliferation. Variants in the eNOS encoding gene (*NOS3*) have been associated with myotoxicity of statins (Gryn, Hegele, 2014; Ruaño *et al*., 2016).

Three studies investigated the *NOS3* -786T>C polymorphism was studied in Brazilian subjects. This variant was not associated with short term treatment with short term treatment with atorvastatin in health men, but blood nitrite was increased and plasma malondialdehyde was reduced in carriers of the *NOS3* -786CC genotype (Nagasaki *et al*., 2006). The CC genotype was also associated with reduction of plasma sCD40-L, sVCAM, sP-selectin and MMP-9 in response to atorvastatin, in health men (Souza-Costa *et al*., 2007). *NOS3* -786C allele was also associated with the increase in blood nitrite but not with the reduction of plasma malondialdehyde in obese women treated with simvastatin (Andrade *et al*., 2013).

Manganese-dependent superoxide dismutase (SOD2) is an antioxidant enzyme that prevents the deleterious effects of the superoxide anion, a reactive oxygen specie that is involved in the pathophysiology of atherosclerosis and other vascular diseases. The influence of *SOD2* Val16Ala (c.47T>C) on plasma lipids was evaluated in Brazilian HC patients. The VV (TT) genotype carriers had less intense reduction of plasma total and LDL cholesterol, anti-inflammatory and anti-fibrinolytic markers in response to long term treatment with rosuvastatin (Duarte *et al*., 2016).

PHARMACOGENETICS AND DIABETES

The increasing prevalence of obesity worldwide in the last decades have become this disease one of the most important public health problems nowadays, positioning to

obesity-related metabolic diseases and CVD as one of the main causes of death in developed as well as developing countries (Bastien *et al*., 2014).

In this way, T2D has been considered a major health problem, affecting more than 415 million people. Several classes of antidiabetic drugs are currently prescribed, including mainly biguadines, sulfonylureas, meglitidines and thiazolidinediones (Chamberlain *et al.*, 2017). The treatment strategy is mostly based on efficacy of oral antidiabetic drugs assessed by the level of fasting or postprandial glycaemia and/or glycated hemoglobin (HbA1c). Pharmacogenetic studies have proposed several genes involved in the response to antidiabetic drugs (Singh, Usman, Banerjee, 2016).

Curiously, in Brazilian population the influence of genetic variants in genes participating in pharmacokinetics/pharmacodynamics of oral antidiabetic drugs are almost inexistent. We identified only one study from our research group that evaluated the role of polymorphisms in the genes encoding the tumor necrosis factor alpha (*TNF*) and interleukin 6 (*IL6*) in 53 T2D patients treated with pioglitazone, an antidiabetic drug that enhances the expression of the peroxisome proliferator-activated receptor-gamma (PPARγ), leading to improved sensitivity to insulin but that also can induce bone loss. *TNF* -308G>A (g.4682G>A, rs1800629) and *IL6* -174G>C (c.-237C>G, rs1800795) polymorphisms were not associated with pioglitazone response regarding glycemic control, however the *TNF* -308A allele carriers had lower values of total alkaline phosphatase (tALP) in T2D patients after pioglitazone treatment (Himelfarb *et al*., 2011).

Regarding the treatment of obesity, in the last years Brazilian studies have mainly focused in the evaluation of the role of genetic variation on the response to surgical treatment of obesity (Nicoletti *et al*., 2017); however, the influence of genetic polymorphisms on pharmacological strategies for weight loss have not been evaluated until now.

Evaluating the pharmacogenetic implications of antidiabetic and antiobesity drugs in Brazilian populations is challenge due to the scarce information in the scientific literature. Further studies are necessary in order to elucidate the contribution of genetic background of our population to the pharmacological response regarding the treatment of the most prevalent diseases related to cardiovascular risk.

PHARMACOGENETICS AND HYPERTENSION

Hypertension is a very important public health issue, because it affects about one billion adult globally and is the most important risk factor to *causa mortis* in the contemporary society: coronary artery diseases, stroke, renal dysfunction and heart failure (Savoia *et al*., 2017).

A small subset of the hypertensive population is affected by monogenic disease; however the majority of cases of hypertension are multifactorial and polygenic. There is a complex trait of etiology involving an intricate network between homeostasis of extracellular body fluid, vascular tone regulated by renal system, cardiac contractility, neuroendocrine system and others factors such as age, weight, ethnicity, lifestyle and diet (Savoia *et al*., 2017).

Currently, the most commonly used antihypertensives are: (i) angiotensin I-converting enzyme (ACE) inhibitors, such as enalapril; (ii) angiotensin II-receptor blockers (ARBs), such as losartan; (iii) β-blockers, for example, atenolol; (iv) calcium-channel blockers, such as nifedipine; and (v) diuretics, such as spironolactone or hydrochlorothiazide. Even though these antihypertensive drugs are effective and well tolerated, only about half of patients with treated hypertension achieve appropriate BP control (Savoia *et al*., 2017). This variability is caused by genetic and non-genetic factors, which are known can cause primary and secondary hypertension (Cooper-DeHoff, Johnson, 2016).

The pharmacogenetic approaches in Brazilian population have involved primary (majority) hypertensive patients (HP), resistant hypertensive patients (RHP), gestational hypertensive (GHP) and preeclamptic patients (PP). The studies including GHP and PP were recently and very well reviewed by Luizon *et al.* (2017). The main results of the pharmacogenetic studies with HP and RHP are described in this review.

HP have been defined as systolic BP (SBP) ≥140 mmHg and diastolic BP (DBP) ≥90 mmHg, with BP measurement obtained from the average of three BP readings on at least two office visits with the individuals in the seated position. RHP have been defined according to the Statement of American Heart Association as all subjects with BP that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes (ideally among them, a diuretic) in optimal doses. Also the definition includes patients whose BP is controlled using four or more antihypertensive medications (Malachias *et al*., 2016). By the way, the use of multiple drugs is an inherent limitation of the pharmacogenetic studies with RHP. The mechanisms of resistance to antihypertensive treatment are not fully elucidated, but have been associated to excess sodium and fluid retention, increased activation of the renin-angiotensin-aldosterone system (RAAS), heightened activity of the sympathetic nervous system,

endothelial dysfunction, arterial stiffness, left ventricular hypertrophy, microalbuminuria and deregulation of inflammatory adipokines (Hwang *et al*., 2017).

The pharmacogenetic studies of antihypertensive drugs in samples of the Brazilian population are listed in the Table III.

Pharmacokinetics-related genes

Two Brazilian studies investigated the influence of polymorphisms in genes encoding drug metabolizing and transporters on response to antihypertensive therapy, including hydralazine.

Hydralazine is a vasodilator metabolized by an acetylation reaction mediated by *N*-acetyltransferase 2 (NAT2), a drug metabolizing enzyme. Several alleles of the *NAT2*, which encodes NAT2 enzyme, are associated with slow acetylation phenotypes (191A, 341C, 590A, 857A). Spinasse *et al* investigated 15 different *NAT2* polymorphisms, including two new variants (30T>A and 824T>C), in Brazilian RHP prescribed with a therapeutic scheme containing hydralazine. In a subset of 61 patients, significant BP reductions were observed in the carriers of slow acetylator alleles. Four of RHP patients had hydralazine-induced adverse effects, and three of them were slow NAT2 acelylators (Spinasse *et al*., 2014).

The influence of *ABCB1* polymorphisms on antihypertensive response was also investigated in Brazilian subjects. *ABCB1* c.3435C>T (rs1045642) was not associated with resistance to antihypertensive treatment. Interestingly, in RHP, c.3435CC genotype was associated with higher BP (Lacchini *et al.,* 2014).

Pharmacodynamics-related genes

The components of the RAAS pathway, such as ACE, angiotensinogen, angiotensin II receptor type 1 (AT1 receptor) and aldosterone, play an important role in BP control. The polymorphisms in the genes encoding RAAS proteins and other pharmacodynamics-related genes can influence the response to antihypertensive drugs. Results from pharmacogenetic studies in Brazilian HP are shown in Table III.

ACE has a 287 bp insertion/deletion (g.16457_16458insG, *Indel*, rs1799752) polymorphism in intron 16 that is the most well-known variant**.** The *ACE del* variant has been associated with increased plasma levels of ACE, which potentially increases the BP (Thorn *et al.,* 2010). Previous studies have analyzed the influence of the variant on the pharmacological response with contradictory results (Thorn *et al.,* 2010). In Brazilian older women, no association was found between the *ACE Indel* and the amplitude of the reduction of BP in response to antihypertensive drugs (Moraes *et al*., 2008). Likewise, *ACE* rs1799752 was not a genetic risk factor for resistant hypertension (Yugar-Toledo *et al.,* 2011).

Polymorphisms in the *AGT*, which encodes the angiotensinogen, such as the Met268Thr (rs699), have not been associated with differences in BP reduction after treatment with ACE inhibitors or ARBs (Konoshita *et al*., 2011). Interestingly, in individuals from Brazil treated with combinations of antihypertensive drugs (which is the case in RHP), there was an association between *AGT* Met268Thr polymorphism and increased risk for resistant hypertension. The 268Thr carriers presented an increased risk, especially if they were older than 50 years (Yugar-Toledo *et al*., 2011).

Polymorphisms in the gene encoding AT1 receptor (*AGTR1*) have been shown to be associated with differences in response to antihypertensive drugs (Fontana, Luizon, Sandrim, 2015). The *AGTR1* c.*86A>C (rs5186) variant, that is located in the 3´UTR and may affect gene transcription, was studied in a sample of Brazilian older women, but no association was found with BP reduction.

Bradykinin is a potent vasoactive peptide that induces vasodilation, releases of NO and promotes water and sodium excretion, which are mediated by bradykinin receptors (BDKRs). Variants in the gene encoding BDKR type B2 (*BDKRB2*) were associated with the risk of hypertension (Luo, Kang, Xu, 2015). Two polymorphisms in *BDKRB2*, c.-192C>T (-58C>T) and *Indel* exon 1 (BE1 +9/-9), have been studied in Brazilian hypertensive patients. *BDKRB2* -58TT genotype was associated with poor response to enalapril, an ACE inhibitor. Moreover, -58CC genotype was associated with better response depending on presence of *NOS3* -786TC genotype (Silva *et al*., 2013). On the other hand, no association was found between *BDKRB2*, -58C>T and the response to enalapril in another sample of Brazilian HP subjects (Oliveira-Paula *et al.*, 2017). The *Indel* BE1 9-bp repeat sequence was also not associated with the response to antihypertensive therapy in HP subjects (Silva *et al*., 2013; Oliveira-Paula *et al*., 2017).

Aldosterone synthase is a member of the cytochrome P450 family responsible for the final step of aldosterone synthesis in the adrenal cortex. The gene encoding aldosterone synthase, *CYP11B2*, is the hot spot for essential hypertension susceptibility genes (Chen *et al*., 2015). The results of association studies between the *CYP11B2* c.-344C>T (rs1799998) polymorphism and essential hypertension, or aldosterone levels, are controversial. In Brazilian individuals, this SNP was not

TABLE III - Pharmacogenetics of antihypertensive drugs in Brazilian sample populations

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/ follow up]	Main findings [Outcomes]	Reference
Pharmacokinetics-related genes							
NAT2	29G>A (rs72466456), 30T>A, 33C>A, 191G>A (rs1801279), 282C>T (rs1041983), 341T>C (rs1801280), 403C>G (rs12720065), 481C>T (rs1799929), 590G>A (rs1799930), 609G>T (rs45618543), 766A>G (rs55700793), 803A>G (rs1208), 824T>C, 838G>A (rs56393504), 857G>A (rs1799931)	*Slow acetylators* 191A: 2.1% 341C: 36.6% 590A: 19.2% 857A: 3.9% *Fast and intermediate acetylators* 29A: 0.3% 30A: 1.5% 33A: 3.3% 282T: 31.0% 403G: 1.5% 481T: 34.6% 609T: 0.6% 766G: 0.9% 803G: 42.6% 824C: 0.6% 838A: 0.6%	Case-control study	169 RHP (61 with results of before and after treatment)	Therapeutic scheme containing hydralazine 50-300 mg/day	*NAT2* slow acetylators had significant blood pressure reduction in response to hydralazine. Three out of four RHP patients with hydralazine-induced adverse effects were slow acetylators.	Spinasse *et al.*, 2014
ABCB1	c.3435C>T (rs1045642)	c.3435T: 38%	Case-control study	105 CS 137 HP 83 RHP	Not specified	*ABCB1* c.3435CC genotype was associated with higher blood pressure in RHP c.3435C>T was not associated with resistance to antihypertensive treatment.	Lacchini *et al.*, 2014
Pharmacodynamics-related genes							
ACE	g.16457_16458insG (*Indel*, rs1799752)	In: 47%	Prospective cohort study	169 HP (older women)	Not specified. The patients were followed for up to 20 months	*ACE Indel* was not associated with the amplitude of the reduction of blood pressure in response to antihypertensive therapy.	Moraes *et al.*, 2008
		In: 43%	Case-control study	70 CS 80 HP 70 RHP	Not specified. The patients were followed for up to 20 months	*ACE Indel* was not associated with resistance to antihypertensive therapy.	Yugar-Toledo *et al.*, 2011
AGT	c.803T>C (Met268Thr, M235T, rs699)	268Met: 43%	Case-control study	70 CS 80 HP 70 RHP	Not specified. The patients were followed for up to 20 months	*AGT* 268Thr carriers have increased risk for resistant hypertension, especially if they were older than 50 years.	Yugar-Toledo *et al.*, 2011
AGTR1	c.*86A>C (1166A>C, rs5186)	*86C: 22%	Prospective cohort study	169 HP (older women)	Not specified. The patients were followed for up to 20 months	*AGTR1* c.*86A>C was not associated with the amplitude of the reduction of blood pressure in response to antihypertensive therapy.	Moraes *et al.*, 2008

TABLE III - Pharmacogenetics of antihypertensive drugs in Brazilian sample populations (cont.)

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/ follow up]	Main findings [Outcomes]	Reference
BDKRB2	c.-192C>T (-58C>T, rs1799722) *Indel* exon 1 (BE1 +9/-9)	-58T: 39% *Del* (-9): 47%	Prospective cohort study	106 HP	Enalapril 10 or 20 mg/day, 2 months	*BDKRB2* -58TT genotype was associated with poor response to enalapril. -58CC genotype was associated with response depending on *NOS3* -786T>C polymorphism.	Silva *et al.*, 2013
		-58T: 39% *Del* (-9): 47%	Prospective cohort study	104 HP	Enalapril 10 or 20 mg/day, 2 months	Single-locus analyses showed no relationship with antihypertensive response.	Oliveira-Paula *et al.*, 2017
CYP11B2	c.-344C>T (rs1799998)	c.-344C: 35%	Case-control study	110 CS 140 HP 88 RHP	No specified. The patients were followed for at least 6 months	*CYP11B2* c.-344C>T was not associated with resistance to antihypertensive treatment.	Lacchini *et al.*, 2009
		c.-344C: 35%	Cross-sectional study	62 RHP	Not specified	*CYP11B2* c.-344TT genotype and use of spironolactone were independent predictors of aldosterone levels in RHP.	Fontana, Luizon, Sandrim, 2014
NOS2	(CCTTT)n, g.3975G>T (-1026C>A, rs2779249), g.35959C>T (2087G>A, rs2297518),	$(CCTT)_{n<12}$: 41% -1026A: 37% 2087A: ni	Case-control study	113 CS 115 HP 82 RHP	Not specified. The patients were followed for up to 6 months	*NOS2* $(CCTT)_{n<12}$CA haplotype was associated with lower risk of resistant hypertension.	Oliveira-Paula *et al.*, 2013
NOS3	g.6933C>T (-786T>C, rs2070744), Asp298Glu (c.894T>G, rs1799983), 4b/4a VNTR	-786C: 36% 298Asp: 33% 4a: 18%	Case-control study	111 CS 116 HP 100 RHP	Not specified. The patients were followed for up to 2 years	*NOS3* polymorphisms or haplotypes were not associated with resistance to antihypertensive treatment.	Sandrim *et al.*, 2006
		298Asp: 38%	Case-control study	70 CS 80 HP 70 RHP	Not specified. The patients were followed for up to 20 months	*NOS3* Asp298Glu was not associated with resistance to antihypertensive treatment.	Yugar-Toledo *et al.*, 2011
		-786C: 34% 298Asp: 25% 4a: 19%	Prospective cohort study	106 HP	Enalapril 10 or 20 mg/day for 2 months	*NOS3* -786C allele was associated with better response to enalapril.	Silva *et al.*, 2013
	g.19635C>A (rs3918188), g.7030C>T (rs3918226), g.23769G>A (rs743506)	g.19635A: 35% g.7030T: ni g.23769G: 41%	Prospective cohort study	101 HP	Enalapril 10 or 20 mg/day for 2 months	*NOS3* g.19635A allele and CAG haplotype were associated with worse antihypertensive responses, while the *NOS3* g.7030T allele and TCA haplotype were associated with better responses to enalapril.	Oliveira-Paula *et al.*, 2016
		-786C: 35% 298Asp: 25% 4a: 19% g.7030T: 8%	Prospective cohort study	104 HP	Enalapril 10 or 20 mg/day for 2 months	*NOS3* -786TC genotype was associated with better response to enalapril.	Oliveira-Paula *et al.*, 2017

TABLE III - Pharmacogenetics of antihypertensive drugs in Brazilian sample populations (cont.)

Gene	Polymorphism	Allele Frequency	Study design	Sample population [n]	Treatment [drug/dose/ follow up]	Main findings [Outcomes]	Reference
NR3C2	c.538G>A (Val180Ile, rs5522), c.-2G>C (rs2070951)	180Val: 9% c.-2C: 48%	Cross-sectional study	122 HP 181 RHP	Not specified. The RHP were followed for up to 6 months	*NR3C2* polymorphisms were not associated with resistance to antihypertensive treatment. Val180Ile variant was associated with left ventricular hypertrophy and increased plasma aldosterone in RHP. 180Val/c.-2G haplotype also was associated with higher plasma aldosterone in RHP.	Ritter *et al.*, 2016
PRKCA	g.285520C>T (rs887797), g.393521T>C (rs1010544), g.494902G>A (rs16960228)	g.285520T: 36% g.393521C: 29% g.494902A: 13%	Prospective cohort study	104 HP	Enalapril 10 or 20 mg/day for 2 months	*PRKC*A g.393521C allele (TC+CC genotypes) was associated with better response to enalapril, whereas g.494902A allele and CTA haplotype were associated with poor response. g.494902GG genotype was associated with response to therapy depending on the *NOS3* rs2070744 and *BDKRB2* rs1799722 variants.	Oliveira-Paula *et al.*, 2017
VEGFA	g.3437C>A (-2578C>A, rs699947), c.-1154G>A (rs1570360) c.-634G>C (rs2010963)	-2578A: 36% c.-1154A: 27% c.-634C: 35%	Case-control study	101 CS 82 HP 89 RHP	Not specified. The patients were followed for up to 2 years	*VEGFA* polymorphisms and haplotypes were not associated with resistance to antihypertensive treatment.	Sandrim *et al.*, 2013
		-2578A: 39% c.-1154A: 21% c.-634C: 34%	Prospective cohort study	102 HP	Enalapril 10 or 20 mg/day for 2 months	*VEGFA* -2578C>A polymorphism was associated with response to enalapril (20 mg/day). The *VEGFA* AGG haplotype was associated with more intense decrease in blood pressure after treatment with 20 mg/day, while the opposite was found to be associated with CGG haplotype.	Oliveira-Paula *et al.*, 2015
Other genes							
ADIPOQ	g.4012C>G (-11377C>G, rs266729), c.214+62G>T (276G>T, rs1501299)	-11377G: 29% 276T: 33%	Cross-sectional study	109RHP	Not specified. The patients were followed for up to 6 months	*ADIPOQ* variants were not associated with the response to antihypertensive treatment. Carriers of the -11377G and 276T alleles had lower and higher adiponectin concentrations, respectively.	de Faria *et al.*, 2015
LEP	g.2453G>A (-2548G>A, rs7799039)	-2548A: 37%	Cross-sectional study	125 HP 109 RHP	Not specified. The patients were followed for up to 6 months	*LEP* -2548G>A was not associated with resistance to the antihypertensive treatment. RHP carriers of the -2548AA genotype had worse metabolic profile.	de Faria *et al.*, 2017
LEPR	c.668A>G (Gln223Arg, rs1137101)	c.668G: 46%	Cross-sectional study	125 HP 109 RHP	Not specified. The patients were followed for up to 6 months	LEPR c.668A>G was not associated with resistance to the antihypertensive treatment. In RHP, carriers of the c.668AA genotype had worse metabolic profile.	de Faria *et al.*, 2017
MMP2	g.3457G>A (-1575 G>A, rs243866), g..3726C>T (-1306C>T, rs243865), g.4297C>T (-735C>T, rs2285053)	-1575A: 16% -1306T: 16% -735T: 14%	Cross-sectional study	136 HP 119 RHP	Not specified. The patients were followed for up to 6 months	*MMP2* -735C allele and GCC haplotype was associated with increased risk to resistant hypertension. Conversely, GCT haplotype is a protective genetic factor for this resistance.	Sabbatini *et al.*, 2017

CS: control subjects; HP: hypertensive patients; ni: not informed; RHP: resistant hypertensive patients.

associated with resistant hypertension (Lacchini *et al*., 2009); nevertheless the c.-344TT genotype and use of spironolactone were independent predictors of aldosterone levels in RHP (Fontana *et al.,* 2014).

The inducible oxide nitric synthase (iNOS, NOS2) is calcium-independent and generates more NO than the constitutive members, neuronal (nNOS, NOS1) and endothelial (eNOS, NOS3) isoforms. The regulation of NOS2 expression is stimulated by multiple factors including inflammatory cytokines and stress signals (Sorokin, 2016). Three variants in *NOS2*, the microsatellite (CCTTT)n, g.-1026C>A (rs2779249) and g.2087G>A (rs2297518), were investigated in Brazilian individuals. The results showed that $(CCTT)_{n<12}CA$ haplotype was associated with lower risk of resistant hypertension (responsiveness to antihypertensive therapy) (Oliveira-Paula *et al*., 2013).

NOS3, constitutively expressed in vascular endothelium, is the most important isoform for NO formation in the cardiovascular system (Sorokin, 2016). *NOS3* variants have been the most studied in pharmacogenetic approaches with Brazilian hypertensive patients. The -786T>C (rs2070744) polymorphism was not associated with resistance to antihypertensive therapy (Sandrim *et al*., 2006), but it seems to be related to a better therapeutic response to enalapril (Silva *et al*., 2013; Oliveira-Paula *et al.*, 2017). Likewise, the *NOS3* rs3918226T allele and TCA haplotype of the tagSNPs (rs3918188, rs3918226 and rs743506) were associated with better response, whereas the rs3918188A allele and CAG haplotype were associated with worse antihypertensive response to enalapril 10 and/or 20mg/day (Oliveira-Paula *et al*., 2016). The *NOS3* Asp298Glu (rs1799983) and 4b/4a VNTR polymorphisms were not associated with responsiveness to therapy (Silva *et al*., 2013; Oliveira-Paula *et al.*, 2017) or with resistance to treatment (Sandrim *et al*., 2006; Yugar-Toledo *et al*., 2011) in Brazilian individuals.

The mineralocorticoid receptor (MR) or nuclear receptor subfamily 3, group c, member 2 (NR3C2) belongs to the nuclear receptor superfamily and functions as a ligand-dependent transcription factor that mediates the effects of aldosterone on a variety of target tissues. Variants in *NR3C2*, which encodes MR, affected BP response to enalapril treatment in Chinese hypertensive patients (Luo *et al*., 2014). In Brazilian individuals, the *NR3C2* Val180Ile and c.-2G>C (rs2070951) polymorphisms were not associated with resistance to antihypertensive therapy. Interestingly, in RHP, increased levels of aldosterone and more prevalent left ventricular hypertrophy were associated with Val180Ile polymorphism. 180Val/c.-2G haplotype also was associated with higher plasma aldosterone in RHP (Ritter *et al*., 2016).

Protein kinase C (PKC) signaling is involved in the vascular control mechanisms of BP. A genome wide association study (GWAS) revealed an intronic SNP, g.494902G>A (rs16960228), in gene encoding of the isoform PKC alpha (*PRKCA*) as an important predictor of hydrochlorothiazide and atenolol response. The rs16960228 A allele carriers had a greater hydrochlorothiazide BP response compared to GG carriers; however, an opposite direction of effect was found in participants treated with a β-blocker, atenolol (Cooper-DeHoff, Johnson, 2016). Three variants in *PRKCA* (rs887797, rs1010544 and rs16960228) were investigated in 104 Brazilian HP. *PRKCA* g.393521 (rs1010544) C allele was associated with better response to enalapril therapy, whereas the rs16960228 A allele and CTA haplotype had the opposite effect. Moreover, the rs16960228 GG genotype combined with *BDKRB2* -58CC (rs1799722) and *NOS3* -786TC or TT (rs2070744) genotypes were associated with good or poor response to treatment, respectively (Oliveira-Paula *et al*., 2017).

Vascular endothelial growth factor (VEGF) has many biological roles, including migration and proliferation of endothelial cells and increase of vascular permeability. VEGF by stimulating NOS expression and NO activity also has a significant role in BP control (Mazidi *et al*., 2017). Because ACE inhibitors seem to up-regulate VEGF expression, Oliveira-Paula *et al.* (2015) investigated the influence of three *VEGFA* variants in Brazilian HP treated with enalapril. The authors found that after treatment with enalapril 20 mg/day, the -2578C>A (rs699947) polymorphism predisposed to better antihypertensive response. Moreover, the haplotype AGG (-2578C>A, c.-1154G>A and c.-634G>C polymorphisms) was associated with more intense decrease in BP, while the opposite was found to be associated with the CGG haplotype. Conversely, these *VEGFA* polymorphisms were not associated with resistance to antihypertensive treatment in another sample of the Brazilian population (Sandrim *et al*., 2013).

Other genes

Polymorphisms in genes encoding adipokines, such as leptin (*LEP*), leptin receptor (*LEPR*) and adiponectin (*ADIPOQ*), have been also studied in Brazilian sample population due to the relationship of alterations in these proteins with hypertension (Table III). *ADIPOQ* (-11377C>G and 276G>T), *LEP* (-2548G>A) and *LEPR* (c.668A>G) were not associated with the response

to antihypertensive therapy in RHP (de Faria *et al.*, 2015; de Faria *et al.*, 2017). Interestingly, carriers of *ADIPOQ* -11377G and 276T alleles had lower and higher adiponectin concentrations, respectively (de Faria *et al*., 2015). Moreover, RHP carrying the *LEP* -2548AA or *LEPR* c.668AA genotypes, compared to GG, presented a worse metabolic profile (de Faria *et al*., 2017).

Matrix metalloproteinases (MMPs) comprise a family of zinc and calcium-dependent proteases that degrade different components of the extracellular matrix, both in physiological and in pathophysiological conditions (Pulkoski-Gross, 2015). Previous review has showed the importance of MMP-2 in hypertension (Belo, Guimarães, Castro, 2015). The association of the three SNPs located in the promoter region of *MMP2* (-1575G>A, -1306C>T and -735C>T), with resistant hypertension was evaluated in Brazilian individuals (Table III). The -735C allele and GCC haplotype carriers showed increased risk to resistant hypertension, whereas the GCT haplotype had an opposite effect (Sabbatini *et al*., 2017).

CONCLUSIONS AND FUTURE PERSPECTIVES

Metabolic disorders represent an important group of pathologies and risk factors related to the development of CVD and the pharmacological and non-pharmacological management of these conditions are closely related to the high rates of morbidity and mortality by non-communicable diseases in our population. Genetic admixture of Brazilian populations is a challenge for genetic approaches to study complex disorders and multifactorial events, including pharmacogenetics, and frequently the data from well-defined ethnic groups are not applicable to Brazilian populations.

Pharmacogenetic studies of metabolic diseases in Brazilian population have explored a number of cardiovascular drugs for the treatment of dyslipidemia and hypertension; however, evaluating the role of genetic variability in response to antidiabetic drugs and pharmacological management of weight loss is still a challenge in this population. Considering that obesity and insulin resistance/T2D are the most prevalent diseases related to cardiovascular risk in developing countries, further pharmacogenetic studies are necessary in order to elucidate the contribution of genetic background of our population for effectiveness and safety of these drugs.

Pharmacogenetic studies of dyslipidemia have evaluated almost exclusively the response to statins, being necessary to expand the scope of pharmacogenetics to other lipid-lowering drugs. In the same line, it is also important to spread out the repertory of gene variants implicated in pharmacological response of cholesterol-lowering drugs to new mechanism of drug actions, mainly due to the broad applications of statin-induced pleiotropic effects.

Regarding pharmacogenetic studies of anti-hypertensive drugs, here the influence of genetic variants on HP and HRP in Brazilian populations was reviewed. Genetic causes of inadequate response to antihypertensive therapy are of great importance, mainly by the fact that a small proportion of these individuals achieve BP levels according to recommendations. Results from Brazilian studies demonstrated that response to antihypertensive drugs could be affected by the variability of diverse genes, including genes implicated in pharmacokinetics/pharmacodynamics as also genes that not necessarily are directly involved in drug action. These studies have shown limitations in number and sample size, which make difficult to establish strong conclusions about their impact in our population.

In conclusion, although several pharmacogenetic studies evaluating drug response of metabolic diseases have been performed in Brazilian populations, a small sample size has been a constant in these studies, which limits the conclusions and clinical applications in our populations.

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