Published in final edited form as:

Curr Atheroscler Rep. 2007 September ; 9(3): 187–194.

Pharmacogenetics of Response to Statins

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Abstract

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are among the most commonly prescribed drugs worldwide. On average, statins improve lipid profiles and have been shown to have ancillary beneficial effects on inflammation, platelet activity, and endothelial function. However, variability in drug response exists regardless of the measured phenotype, and genetic variability may be a contributing factor. Recently, there has been an interesting shift in statin pharmacogenetic studies. Novel study designs have been employed and nontraditional candidate genes have been investigated in relation to both lipid and nonlipid responses to statins. This review outlines earlier pharmacogenetic studies and highlights newly published findings that expand on previous work. Furthermore, a framework is provided in which the necessary next steps in research are described, with the ultimate goal of translating pharmacogenetic findings into clinically meaningful changes in patient care.

Introduction

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are among the most effective and widely used drugs for the primary and secondary prevention of cardiovascular disease (CVD) and its complications. Statins confer their cardioprotective effects largely through reduction in low-density lipoprotein (LDL) cholesterol, a well-known modifiable CVD risk factor. Specifically, the available statin agents undergo extensive hepatic uptake whereupon they block hepatic cholesterol biosynthesis via inhibition of the mevalonate pathway. As a consequence, hepatic LDL receptors are upregulated and circulating LDL and other apolipoprotein (apo) B-containing lipoproteins are removed from the systemic circulation to restore hepatic cholesterol equilibrium. In addition, statins have modest effects on high-density lipoprotein (HDL) cholesterol, perhaps due to inhibition of hepatic lipase activity.

Variability in both the lipid-modifying and CVD risk-reducing effects of statins has been described. For example, several groups have shown that for a given statin drug and dose, heterogeneity in the total cholesterol-lowering, LDL-lowering, and triglyceride-lowering and HDL-raising effects exists; this has been demonstrated in various patient populations, even at the highest available statin doses [1,2]. In addition, there has been a description of a range of drug-response phenotypes among statin-treated patients that includes responders, nonresponders, and response losers (ie, those whose initial responses diminish over time) [3]. More importantly, whereas statins lower the risk for mortality and CVD-associated

morbidity, the relative attenuation of risk is approximately 30% compared with placebo. In other words, in approximately 70% of patients who received statins in the clinical trial experience, modification of CVD risk was no different than in placebo-treated patients [4].

Because millions of individuals worldwide are prescribed statins, elucidation of the causes of statin response variability and incorporation of this information into practice may prove to be an important public health accomplishment. As such, researchers have become increasingly interested in identifying the contributors to variable drug response. Although these factors undoubtedly include social and environmental influences, there has been a push to investigate the contribution of genetic variants (ie, polymorphisms) to variability in the drug response through pharmacogenetics. Previous evidence behind statin pharmacogenetics has been comprehensively reviewed [5–8]. However, in recent years, there has been an interesting shift in statin pharmacogenetic studies. Most notably, novel study designs have been employed and nontraditional candidate genes (ie, not necessarily related to drug metabolism or lipid transport) have been investigated in relation to both lipid and nonlipid responses to statins. This review outlines earlier pharmacogenetic studies and highlights newly published findings that expand on previous work. Furthermore, a framework is provided in which the necessary “next steps” in research are described, with the ultimate goal of translating pharmacogenetic findings into clinically meaningful changes in patient care.

Variants in Statin Disposition Genes

A common working hypothesis is that variability in genes responsible for statin absorption, distribution, metabolism, and/or excretion could potentially explain several drug-related phenotypes. Specifically, because transport proteins partially mediate statin oral absorption, uptake to their site of action (ie, the hepatocyte), and biliary and renal clearance of some statins, it has been put forth that polymorphisms in genes of the organic anion transporter (OAT) polypeptide family and other endogenous molecule/xenobiotic transporters may influence drug disposition and pharmacodynamic responses to statins.

There has been a major focus on the OATs in statin pharmacogenetics. However, although there have certainly been signals that OAT polymorphisms may be important contributors to variable statin pharmacokinetics (ie, systemic drug exposure), there have been few significant findings regarding their contribution to pharmacodynamic (ie, clinical endpoint) variability. Because it is a well-characterized substrate of OATs, most OAT-statin pharmacogenetic studies have used pravastatin. Although polymorphisms in *SLCO2B1* (formerly OATP-B), *SLCO1B1* (formerly OATP-C), *SLC22A8* (formerly OAT-3), *ABCB1* (formerly MDR1 or P-glycoprotein), and *ABCC2* (formerly MRP2) have been studied, only *SLCO1B1* polymorphisms seem to be consistently associated with pravastatin pharmacokinetic variability [6,7]. Differences in pravastatin area-under-the-curve (AUC), total clearance, and nonrenal clearance have been seen between wild-type homozygous individuals and individuals carrying variant alleles or haplotypes. The diminished transporter activity resulting in increased drug concentrations seems to be driven by a nonsynonymous single nucleotide polymorphism (SNP), 521T>C, which results in a Val174>Ala amino acid change, although a second 388G>A (Asn130>Asp) SNP may also contribute.

Because diminished hepatic transport activity is seen with the codon 174 variant, it is hypothesized that individuals with the variant allele will have a diminished lipid-lowering response to statins; this has been recently tested in several studies. Tachibana-Iimori et al. [9] tested the association between 521T>C and the lipid-lowering effect of statins in a retrospective study of 66 Japanese patients with dyslipidemia. Patients were treated with pravastatin, atorvastatin, or simvastatin. As hypothesized, those with the T/C genotype (ie, decreased hepatic uptake and potentially decreased drug effect) had attenuated reductions in total cholesterol compared with T/T wild-type homozygotes (−16.5% vs −22.3%; $P < 0.05$). There was also a trend toward attenuated LDL response that paralleled the total cholesterol response (−12.4% vs −29%; $P = 0.09$). There were no genotype-related differences in HDL or triglyceride response to the statins. Although limited by its retrospective nature and small sample size, this observation provides interesting supportive evidence for a role of *SLCO1B1* polymorphisms in the lipid-modulating effects of statins. Two additional studies have investigated *SLCO1B1* genotype combinations (ie, haplotypes derived from consideration of both the 521T>C and 388G>A SNPs) as correlates of drug response. In a small, prospective study of white healthy volunteers, Niemi et al. [10] demonstrated that carriers of the *17 haplotype ($n = 3$), which is comprised of three SNPs (−11187G>A, 388A>G, and 521T>C), exhibited diminished pravastatin-induced plasma lathosterol and lathosterol:cholesterol ratio reduction (surrogates for cholesterol biosynthesis) compared with nonvariant carriers ($n = 38$) [10]. Despite being a single-dose study, this study again adds to the growing evidence of *SLCO1B1* as a candidate gene in statin pharmacogenetics with publication of subsequent supportive reports [11]. Of interest, a recent study has extended the findings of *SLCO1B1*-associated differential statin-lipid response to include HDL cholesterol [12].

The usefulness of considering *SLCO1B1* polymorphisms to guide statin treatment decisions is debatable. For example, the body of evidence regarding *SLCO1B1* is largely pharmacokinetic in nature, and even within the pharmacokinetic literature data have been conflicting. Inter- and intra-racial differences in statin disposition have been shown to result with little or no contribution from *SLCO1B1* polymorphisms [13]. In addition, most *SLCO1B1* pharmacogenetic studies have been small in size and some have been retrospective. What is unknown is to what extent the body of evidence in support of *SLCO1B1* is a function of publication bias (ie, the number of neutral associations is unknown). Furthermore, the magnitude of the genetic association is likely to be influenced by the particular statin studied because the degree of affinity for *SLCO1B1* differs among the statins; this has recently been shown in a pharmacokinetic analysis where the *SLCO1B1* genotype was associated with variable pharmacokinetics of pravastatin but not of the lipophilic fluvastatin [14]. Furthermore, the role of *SLCO1B1* polymorphisms in statin pharmacogenetics is further complicated with added consideration of effects on disposition of statin hydroxy metabolites compared with lactone forms [15]. Finally, it is unclear if any genetic contribution to attenuated responses can be overcome simply by increasing the drug dose. Encouragingly, some of the findings described by these studies have been replicated in the Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS) pharmacogenetic evaluation [16••], which is the largest statin pharmacogenetic analysis to date. New data continue to emerge implicating other transporters in statin pharmacokinetics

and pharmacodynamic responses [17–19]. As such, the statin-transporter-genotype axis is likely to be a continued line of investigation.

Once in the liver, most statins are metabolized via the cytochrome P450 (CYP) enzyme system. To the extent that CYP metabolism is the major mode of statin clearance for almost all the statins, pharmacogenetic studies of *CYP* polymorphisms have been performed since 1997. The major candidate genes are *CYP3A4/5*, although pharmacogenetic studies of *CYP2D6* and *CYP2C9* are also available [20–24]. Early studies focused on the role of *CYP2D6* in simvastatin responses, demonstrated conflicting results, and are of limited value because *CYP2D6* is not a major route of statin metabolism. Other studies have investigated the influence of *CYP2C9* polymorphisms on cholesterol responses to various statins [22]. Although carriers of *CYP2C9* variant alleles demonstrate greater exposure to fluvastatin as measured by AUC, no relationship was found between *CYP2C9* genotype and any cholesterol parameter. Because commonly used statins such as atorvastatin and simvastatin are metabolized by the CYP3A system, more relevant studies would examine the effects of *CYP3A5* or *CYP3A4* on pharmacokinetics and pharmacodynamics.

Kajinami et al. [21] investigated *CYP3A4* polymorphisms and response to atorvastatin. The effects of the *CYP3A4* –290A>G promoter polymorphism and two nonsynonymous SNPs were studied in over 300 patients with dyslipidemia. Genotypes were not associated with variable response to atorvastatin in multivariable analyses. Additionally, *CYP3A4* and *CYP3A5* polymorphisms have not been associated with variable lipid responses to pravastatin, although this is not surprising given that pravastatin is not significantly metabolized via CYP enzymes [25••].

Kivisto et al. [26] investigated the relationship between *CYP3A5* polymorphisms and the lipid-modifying effects of atorvastatin, lovastatin, and simvastatin. This was a pooled retrospective study of 69 white subjects, most with established CVD. Individuals that carried at least one copy of the *CYP3A5**1 allele (which results in CYP3A5 expression and potentially increased statin metabolism) had an attenuated total cholesterol and LDL response to statins. The *CYP3A5**3 allele (associated with no CYP3A5 expression and potentially decreased statin metabolism) was associated with enhanced LDL-lowering response to atorvastatin among whites in the ACCESS study, which enrolled 2735 subjects [16••]. Interestingly, these findings are not consistent for all statins; *CYP3A5* genotype was not found to be correlated to therapeutic response for simvastatin or pravastatin.

The findings relative to atorvastatin support the hypothesis that certain statins are metabolized by *CYP3A5*, and that expressors of the CYP3A5 isoenzyme (ie, *CYP3A5**1 carriers) may metabolize statins to a greater degree than nonexpressors, resulting in differences in drug response. This has led to the hypothesis that *CYP3A* may be relevant in adverse drug reactions to statins. A recent case-control analysis of statin-treated patients at the Marshfield clinics demonstrated that among those who experienced statin-induced myopathy, those with two copies of the *CYP3A5**3 allele had the highest creatine kinase (CK) levels, an intracellular marker of muscle damage [27•]. This observation would be consistent with higher systemic exposure to statins resulting from diminished activity of the *CYP3A5**3 allele.

As knowledge of the CYP family continues to grow, novel insights into the role of *CYP* genetic variants in statin response variability will likely grow in parallel. For instance, not only are they involved in statin disposition, but CYP family members such as *CYP7A1*, which encodes cholesterol 7 α -hydroxylase, are important in lipid homeostasis and are promising pharmacodynamic candidates for statin pharmacogenetic studies [28–31].

Variants in Genes that Modulate Drug Target Physiology

We have previously listed over 40 candidate genes for statin pharmacogenetic studies, most of which have been genes in which polymorphisms may conceivably alter physiologic processes modulated by statins (eg, cholesterol biosynthesis and lipid transport) [7]. Most pharmacogenetic studies investigating pharmacodynamic-related genes have limited their investigations to single genes. However, two relatively large pharmacogenetic analyses of statin-lipoprotein response variability as a function of multiple genes have been conducted and published. In a retrospective analysis of the Pravastatin Inflammation/CRP Evaluation (PRINCE) study, Chasman et al. [25••] investigated whether any of nearly 150 SNPs (and their associated haplotypes) in 10 candidate genes were associated with variable lipoprotein responses in approximately 1500 participants. Pharmacodynamic genes included *ABCG5*, *ABCG8*, *APOB*, *APOE*, *CETP*, *FDFT1*, *HMGCR*, and *LDLR*. Of the polymorphisms studied, SNPs in *HMGCR*, which encodes the pharmacodynamic target of statins (HMG CoA reductase), were associated with variable total cholesterol and LDL responses to 40 mg/d of pravastatin. In the previously mentioned ACCESS study, Thompson et al. [16••] assessed 43 SNPs in 16 candidate genes. Despite analyzing data from nearly twice as many patients as in the PRINCE study, the *HMGCR* association could not be replicated for any of the statins studied [16••].

Two of the most extensively studied drug target genes in statin pharmacogenetics include *APOE* and *CETP*. The triallelic *APOE* polymorphism (ϵ 2/ ϵ 3/ ϵ 4) has been evaluated in over a dozen pharmacogenetic studies, and its association with variable lipid-lowering response was the only previously reported association subsequently replicated in the ACCESS dataset [7,16••]. With respect to *CETP*, the well-studied TaqIB polymorphism has been investigated as both a disease susceptibility polymorphism and statin-drug response variant in over 13,000 patients [32].

The *APOE* polymorphism offers a very interesting case study in the importance of defining drug response phenotype in pharmacogenetic analyses. The association between *APOE* polymorphisms and variable LDL reduction by statins has been well described. It is known that *APOE* ϵ 2 carriers have the greatest reductions in LDL, with ϵ 4 carriers exhibiting the most attenuated responses. However, genetic epidemiology analyses suggest that the ϵ 4 allele is associated with excess CVD risk, and clinical trial data show that despite attenuated cholesterol responses to statins, it is precisely the ϵ 4 carriers that experience the greatest reduction in hard endpoints when treated with statins [33]. The disconnect between *APOE* genotype associations with lipids and angiographic parameters has also been noted [34,35].

To the extent that *CETP* is involved in reverse cholesterol transport from peripheral tissues, this gene is a candidate for HDL and triglyceride responses to statins, as well as

angiographic and CVD clinical endpoints. *CETP* TaqIB genotype seems to be associated with modified HDL response; individuals with the B1B1 genotype have been reported to display the greatest HDL increases in response to statins in multiple studies [36,37]. Initial data have also suggested that pravastatin is most beneficial in B1 carriers in terms of angiographic outcomes and is similar to placebo in effect on angiographic disease progression in patients with the B2B2 genotype. However, as data on the role of *CETP* genotypes, CETP protein concentrations, CVD risk, and contributions to statin drug responses continue to emerge [17,38–40], a retrospective analysis of the Cholesterol and Recurrent Events (CARE) study [41] and a recent 13,677 person meta-analysis [32] suggest no robust relationship between TaqIB genotypes and lipoprotein or endpoint responses to pravastatin. The totality of data regarding *APOE* and *CETP* highlight some of the major limitations of not only statin pharmacogenetic studies, but pharmacogenetic studies in general to date. The limitations include the following: 1) studies are generally concerned with single genes (despite drug response likely to be a polygenic complex “trait”); 2) surrogate markers are used in lieu of “hard” CVD endpoints; and 3) results may not be able to be generalized to all drugs within a class [7].

New Directions in Statin Pharmacogenetic Studies

Although the main mechanism of statin action is LDL lowering, it is increasingly accepted that statins confer part of their disease-modifying effects through immunomodulation and improved endothelial function, and perhaps through antioxidant effects. As such, statin pharmacogenetic studies have taken a new and interesting direction by 1) increasingly investigating inflammation- and endothelium-related genes and 2) studying genetic contributors to the nonlipid effects of statins. For example, whereas the angiotensin-converting enzyme gene (*ACE*) insertion/deletion (I/D) polymorphism has previously been studied for its association with lipid, angiographic, and clinical endpoint variability in response to fluvastatin and pravastatin, Potaczek et al. [42] have recently investigated its role in atorvastatin-mediated changes (in conjunction with an ACE inhibitor) of fibrinolytic markers, thrombin-antithrombin complexes, C-reactive protein, and adhesion molecules. In this study, the magnitude in reduction in D-dimer concentrations was smaller in D/D homozygotes compared with I carriers ($P = 0.03$); however, CRP was lowered to a greater extent in the D/D group. These results should be interpreted with caution because there were only seven individuals with the D/D genotype and 19 I carriers. Nonetheless, this small study highlights the move to investigate the role of diverse gene polymorphisms and nonlipid biomarkers of drug response thought to be important in CVD pathogenesis. The same group has published findings relative to the *IL6* gene, which encodes the multifunctional proinflammatory cytokine interleukin-6 (IL-6), showing no genotype effect on statin response gauged by inflammatory markers [43,44]. Interestingly, the studied IL-6 polymorphism (–174G>C) had previously been correlated with variability in fluvastatin-mediated changes in lipoprotein(a) and pravastatin-mediated changes in lipids and first fatal/nonfatal events [7].

In addition to *ACE* and *IL6*, other inflammation-related genes have been studied, including those that encode IL-1 β , tumor necrosis factor- α , CD14, paraoxonase 1 (PON1), and myeloid IgA Fc receptor [7,45]. Furthermore, non-LDL-related phenotypes of interest in

newer statin pharmacogenetic studies include antiplatelet activity [46], antioxidant effect [47], and HDL and triglyceride response [48–50]. *PON1* is a good example of the expansion of statin pharmacogenetics to include novel phenotypes. PON1 is an HDL-associated esterase thought to be cardioprotective in part by inhibiting oxidative modification of LDL cholesterol, a major first step in atherosclerosis initiation. Earlier studies investigated the role of two nonsynonymous SNPs, Leu55>Met and Glu192>Arg, on pravastatin-induced changes in apoAI and HDL and demonstrated a positive association with both SNPs [51]. Association studies were expanded to investigate the Glu192>Arg polymorphism as a co-variate of angiographically determined coronary disease and cardiovascular events in fluvastatin-treated patients with neutral findings [52]. In the latest, and arguably most novel, iteration of *PON1*-statin pharmacogenetics, Sardo et al. [53] investigated whether the previously mentioned SNPs, in addition to a T-107>C promoter SNP, were associated with atorvastatin antioxidant effects in a study of 205 patients with hypercholesterolemia; antioxidant response phenotype was defined as change in ex vivo LDL oxidizability, PON1 activity, and/or LDL vitamin E content in response to 3 months of 10 mg/d of atorvastatin. Although there were differences in both baseline and post-treatment PON1 activity levels by T-107>C genotypes, the antioxidant effects of atorvastatin were similar across all groups. Of particular note, the study employed a placebo group to demonstrate robustness of any drug effect, a rare feature of pharmacogenetic studies and a clear advantage of prospectively designed evaluations. Although there were no significant findings in genotype-associated variations in drug response, this study highlights the move toward investigation of novel intermediate phenotypes in a prospective fashion with rigorous design criteria.

One of the most innovative examples of prospective statin pharmacogenetic studies can be found in investigations of endothelial nitric oxide synthase (eNOS) gene (*NOS3*) polymorphisms. The inflammatory-atherosclerotic cycle is partly triggered and perpetuated by endothelial dysfunction and reduced production of endothelium-derived nitric oxide (NO). Statins have been shown to positively impact NO synthesis putatively through enhanced expression of eNOS, the enzyme that is responsible for conversion of L-arginine to L-citrulline and formation of NO in the endothelium. Because many of the proposed mechanisms of statin benefit on improving endothelial function are mediated through enhanced eNOS activity, it stands to reason that *NOS3* polymorphisms may amplify or attenuate statin-mediated improvement in endothelial function, including reduction in mediators of inflammation.

Two recent papers have investigated the role of the functional *NOS3* T-786>C promoter polymorphism on statin-mediated changes in blood nitrite and inflammatory marker concentrations [54,55]. Both investigations employed the same study sample and showed similar findings in that the benefits of atorvastatin in increasing whole blood nitrite levels (a surrogate for antioxidant activity) and lowering concentrations of inflammatory cytokines (CD40L, VCAM-1, P-selectin, and MMP-9) were limited to individuals with the –786CC genotype. This is consistent with what would be predicted from the functional data in that the –786C allele has been associated with diminished eNOS expression. As such, it would be expected that eNOS-mediated benefits of statins (ie, antioxidant and anti-inflammatory effects) would be greatest in those with the –786CC genotype.

In addition to the obvious clinical implications of these findings, particularly in primary/primordial prevention, the design of this study should be considered as a prototypical study for future pharmacogenetic studies. Specifically, a broad patient population was prescreened and prospectively enrolled in the study based on *NOS3* genotype. Prescreening and enrollment based on genotype is a strategy that has not been frequently utilized in pharmacogenetic studies to date, and mirrors the prospective approach that will likely be needed if future pharmacogenetic studies are to undertake genotype-guided therapy. Enrollment based on genotype will enable investigators to have balanced genotype groups for study comparisons. Furthermore, attempts can be made to enroll equal numbers of individuals from various racial groups between genotype strata. This could circumvent the problem of genetic association studies where there is often an overabundance of people with one genotype; furthermore, this enrollment approach will theoretically address the issues of confounding due to population stratification and cryptic genetic substructure between racial groups. The use of a placebo and limitation of enrollment to wild-type homozygotes and variant homozygotes is also a powerful tool in demonstrating drug-by-genotype effect and should be considered in future studies. A framework for such a genotype-enriched population is presented in Figure 1.

Next Steps in Research

In addition to prospective studies where enrollment is based on genotype, in vitro pharmacogenetic studies could provide either hypothesis generation or validation of statin pharmacogenetic associations observed in vivo. For example, Roncal et al. [56] investigated whether a polymorphism in the plasminogen activator inhibitor-1 (*PAI-1*) gene was associated with variable pravastatin inhibition of IL-1–stimulated PAI-1 expression in human umbilical vein endothelial cells (HUVECs). HUVECs with any of the three *PAI-1* 4G/5G promoter polymorphism genotypes (ie, 4G/4G, 4G/5G, and 5G/5G) were cultured in the presence of pravastatin and IL-1, and attenuation of IL-1–stimulated expression and release of PAI-1 was measured. IL-1–induced expression and secretion of PAI-1 were modified by pravastatin at various time points in a genotype-dependent fashion, with 4G/4G cells exhibiting the greatest response. This functional in vitro approach has been performed previously in cancer pharmacogenetics, is new in CVD pharmacogenetics, and clearly enriches statin pharmacogenetics by providing an additional supportive line of evidence for genotype-mediated drug responses.

Integrating functional in vitro pharmacogenetics into statin clinical studies is an important step in creating a body of evidence translatable to clinical practice. In addition, genotyping technology and bioinformatics capability continue to evolve, allowing for more sophisticated analyses of genetic variation on a genomic level. Methodologic approaches to statin pharmacogenetics have been largely limited to candidate SNP studies. However, in the near future statin pharmacogenetic studies are likely to include tag SNP, putative functional SNP, whole genome, and perhaps family-based linkage analyses. Each approach has its strengths and weaknesses, but undoubtedly will help refine the contribution of genetic variability to drug response [57•].

In addition to larger-scale studies (in terms of number of typed variants), analysis and modeling approaches will be important in classifying the role of genetic variation in statin efficacy and toxicity. Ruano et al. [58•] used sensitivity analysis principles analogous to those found in game theory, resource allocation, and pharmacoeconomics to determine if polymorphisms in 10 candidate genes related to vascular function were associated with CK activity (as a surrogate for statin-induced muscle injury) in statin-treated patients. It was found that the *NOS3* and angiotensin II type 1 receptor genes (*AGTR1*) were robustly associated with muscle activity in patients treated with atorvastatin or simvastatin. As data on genetic variation and its contribution to statin responses emerge, a centralized repository of curated data, literature, and putative pathways of drug response are required. Such a database is typified by the National Institutes of Health (NIH)-funded Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB). This Internet-based tool is available in the public domain (<http://www.pharmgkb.org>) and serves to facilitate pharmacogenetics research by housing genotype and phenotype data for myriad conditions, including dyslipidemia. Figure 2 represents an idealized, integrative approach to statin pharmacogenetics that includes in vitro/in silico functional analyses, prospective study design, and bioinformatics considerations.

Conclusions

Pharmacogenetics is an important tool in making individualized therapy a tenable goal. Statin pharmacogenetics, in particular, is a rapidly evolving area of research. Novel approaches to pharmacogenetics have extended statin pharmacogenetic observations to new phenotypes and candidate genes. With the growing appreciation for statin pleiotropy, future pharmacogenetic studies are likely to focus not only on lipids, but on inflammatory and other intermediate endpoints. In order to advance the field, an integrative strategy of patient-oriented, in vitro, and in silico studies will ideally be performed with data available in highly functional databases. Regardless of whether or not genotype will be used to routinely guide statin treatment, the ultimate value added by statin pharmacogenetics is likely to include improvement of our understanding of cardiovascular pharmacology and the molecular basis of disease.

Acknowledgments

This work was supported in part by American Heart Association Florida/Puerto Rico SDG Grant 0435278B and NIH grant GM74492.

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Figure 1.

Schematic of prospective genotype-stratified pharmacogenetic study. Informed consent, initial eligibility determination, and samples for genotyping are obtained at the prescreening visit. Subjects with needed genotypes are asked to return to meet biochemistry inclusion criteria. In this scenario, wild-type homozygous (A/A) and variant homozygous subjects (B/B) will be enrolled to maximize likelihood of seeing genotype effects. If eligible, participants are given statins, and protein biomarkers are measured and compared by genotype groups at the end of study. An alternative iteration (*dashed lines*) includes a parallel placebo arm or employs a crossover design within genotype groups.

Figure 2.

Integrative approach to statin pharmacogenetics. Any of a number of methodologic approaches can be taken to identify genetic associations with drug response, including candidate single nucleotide polymorphism (canSNP), haplotype tag SNP (tSNP), putative functional SNP (pfSNP), family linkage, or whole genome analyses (WGA). Furthermore, putative causal SNPs or haplotypes can be identified or validated by in silico and in vitro analyses. Replication studies for any positive associations should be performed, and both test and replication datasets should be deposited in a publicly available, curated database such as the Pharmacogenetics and Pharmacogenomics Knowledge Base (<http://www.pharmgkb.org>). The described interplay requires increasingly sophisticated bioinformatics tools.