Apolipoprotein A-V Genetic Variation and Plasma Lipoprotein Response to Fibrates

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The field of pharmacogenetics has begun to reveal solid evidence for the relationship between interindividual variability in response to drug treatment and one’s genetic background. In the lipoprotein field, response to statin treatment and the severity of adverse events from statin treatment has been linked to genetic variation. Now, new evidence of a relationship between apolipoprotein A-V genetic variation and plasma lipoprotein response to fibrates has been found.

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The field of pharmacogenetics promises to explain interindividual variability in response to both beneficial and adverse effects of medications. In theory, interindividual differences in drug response could be the result of functional polymorphisms in the human genome that encode differences in: (1) genes that act within pathophysiological pathways underlying the disease whose natural history is being targeted by the drug; (2) pharmacokinetic activity of drug transporters or of processing or metabolizing enzymes; and (3) pharmacodynamics of gene products expressed as carriers or receptors for drug molecules. In the lipoprotein field, inhibitors of 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) (HMG-CoA) reductase (“statins”) have been studied pharmacogenetically, with genotypes of many common DNA polymorphisms associated with variation in plasma low-density lipoprotein (LDL) cholesterol responses (reviewed by Kajimami et al³). The associated genes typically encode proteins that are involved in cholesterol biosynthesis, such as HMG-CoA reductase, in plasma LDL metabolism, such as the LDL receptor, apolipoprotein (apo) E and B, and in drug metabolism, such as certain cytochrome P450 enzymes. Furthermore, the severity of adverse events from statin treatment, such as myopathy, could be determined in part by interindividual variation in genes involved in ubiquitination.⁴ Similarly, plasma LDL cholesterol response to the cholesterol absorption inhibitor ezetimibe has been associated with variation in Niemann-Pick C like protein 1 (NPC1L1), the presumed target of ezetimibe (reviewed by Huff et al⁵). In contrast, genetic differences in the response to fibric acid derivatives, or fibrates, have been less comprehensively evaluated.

Fibrates, such as gemfibrozil, fenofibrate, and bezafibrate, are helpful in correcting the dyslipidemia seen in patients who have moderate to severe hypertriglyceridemia, often with depressed high-density-lipoprotein (HDL) cholesterol. However, the evidence that fibrates effectively reduce vascular disease end points is less convincing than that for statins. Fibrates reduce plasma concentrations of triglyceride by up to 50% and raise plasma HDL cholesterol by up to 20%, with variable effects on LDL cholesterol. Fibrates might exert their wide range of metabolic effects through their mimicry of the structure and functions of free fatty acids. Like fatty acids, fibrates bind to specific transcription factors, primarily peroxisome proliferator-activated receptor (PPAR)-alpha, a member of the nuclear hormone receptor superfamily that is expressed in liver, kidney, heart, and skeletal muscle. On migration from cytoplasm to nucleus, ligand-activated PPARs heterodimerize with the retinoic acid X receptor, RXR, and the heterodimer is recognized by specific PPAR response elements (PPREs) in the regulatory regions of target genes, including those whose products are involved in metabolism of triglyceride-rich lipoproteins, such as lipoprotein lipase (LPL) and apo C-III, as well as apo A-I and A-II, as well as the ABCA1 transporter and the SR-B1 receptor. Indeed, single nucleotide polymorphisms (SNPs) in the PPAR gene encoding PPAR-alpha and the APOC3 gene encoding apo C-III have been shown to be associated with interindividual differences in the plasma lipoprotein response to fibrates. The APOA5 gene, encoding apo A-V, also has a functional PPRE and human primary hepatocytes treated with fenofibrate displayed a strong induction of APOA5 mRNA, suggesting that APOA5 is a PPAR-alpha target gene that might mediate triglyceride response to fibrates. Now, a new pharmacogenetic study by Lai and colleagues in the current issue of Arteriosclerosis, Thrombosis and Vascular Biology implicates genetic variation in APOA5 as a determinant of plasma lipoprotein response to fibrates.

Apo A-V was first identified in 2001 using a bioinformatic comparison of conserved genomic sequences between mouse and human. The physiological role of apo A-V was solidified by such evidence as hypertriglyceridemia observed in knock-out mice, as hypertriglyceridemic phenotypes of probands with rare loss-of-function mutations in APOA5, and as associations of SNP genotypes or haplotypes with plasma triglyceride concentrations. Apo A-V plays an important role in hydrolysis of triglyceride-rich lipoproteins, perhaps by enhancing LPL activity. However, somewhat paradoxically, its plasma concentrations—which are relatively low compared with other apolipoproteins—are ele-
A, Proposed mechanism for wild-type apolipoprotein (apo) A-V S19 variant (AV-S19) as an activator of intravascular triglyceride (TG) hydrolysis by lipoprotein lipase (LPL) (modified from Merkel and Heeren\textsuperscript{30}). High-density lipoprotein (HDL) provides apo A-V to TG-rich lipoproteins, such as very low–density lipoprotein (VLDL). Apo A-V may target VLDL to endothelial proteoglycans and LPL. After hydrolysis, apo A-V can be reused by other VLDL particles while remnants of lipolysis (Rem) are released into the circulation. B, Proposed mechanism of baseline metabolism for carriers of the apo A-V W19 variant. The defective signal peptide or receptor ligand function associated with apo A-V W19 may reduce the efficiency of VLDL targeting and delay or attenuate lipolysis. Resultant turnover rates of apo A-V and VLDL might be lower, with increased plasma TG concentration under certain circumstances. C, Proposed situation in apo A-V W19 carriers under fenofibrate treatment. Fenofibrate mediates: (1) increased expression of apo A-V through PPARA-RXR dimer binding, and (2) a reduction of VLDL and increase in HDL via some independent mechanism that enhances TG/cholesterol exchange between lipoprotein particles, leading to a reduction of plasma TG. In this context, the apo A-V W19 variant might be able to function as efficiently as the apo A-V S19 variant, perhaps explaining the greater improvement in lipoprotein profile of A-V W19 carriers on fenofibrate.
vated in patients with hypertriglyceridemia.25–27 Thus, although apo A-V must be important in human triglyceride metabolism, aspects of its pathophysiological mechanistic roles still need to be better understood.

Lai and colleagues evaluated the association of 2 well-studied SNPs in the APOA5 gene—namely the −1131C>T promoter SNP and the 56C>G (trivial name p.S19W) nonsynonymous SNP—with plasma lipoprotein responses in 791 men and women from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study who were treated with fenofibrate for 3 weeks.18 The study subjects were not representative of patients who would typically receive fenofibrate treatment—their mean plasma triglyceride concentration was relatively normal, and a 3-week follow-up is earlier than the time point at which most lipidologists would request a repeat lipoprotein profile. However, as a relatively healthy group, these study subjects presented fewer confounding metabolic variables: in one sense they might have provided a “cleaner” or “purer” study substrate on which to detect differential associations with plasma triglycerides, albeit across a very narrow quantitative range. The main findings included enhanced favorable changes in plasma triglycerides and HDL cholesterol among carriers of the APOA5 56G (W19) allele. In the fasting state, APOA5 56G carriers had a significant decrease in plasma triglyceride concentration and increase in HDL cholesterol in response to fenofibrate compared with noncarriers. During the postprandial nonfenofibrate study phase, 56G carriers had higher plasma triglyceride and lower HDL cholesterol than noncarriers at all time points. After fenofibrate treatment, these genotype-specific differences in postprandial response were lost. Parallel favorable shifts in lipoprotein particle size were seen in response to fenofibrate among 56G carriers. In contrast, APOA5 −1131T>C genotype was not associated with differential response to fenofibrate, indicating that the association was specific for 56G>C, an observation that is not surprising considering that the −1131T>C and 56C>G SNPs are not in linkage disequilibrium and are present within distinct haplotypes of the APOA5 gene.19,21–23

The APOA5 56C>G (p.S19W) nonsynonymous SNP changes the primary amino acid sequence of the signal peptide from serine to tryptophan at codon 19, possibly affecting cleavage of the signal peptide or lipid affinity or some other function. HepG2 cells transfected with the tryptophan-containing construct (56G) had significantly decreased secretion compared with the serine-containing (56C) construct.28 Yet, interestingly, in vivo, human studies report APOA5 56G carriers having both higher plasma triglyceride and apo A-V.29 In this study, APOA5 56G carriers had higher fasting plasma triglyceride and very low—density lipoprotein (VLDL), a finding that replicates other studies.22,23 But if the apo A-V W19 protein isoform has compromised function, why did 56G carriers in the GOLDN study respond better to fenofibrate than noncarriers? As elevated plasma triglyceride concentrations have been shown to positively correlate with apo A-V concentrations in 56G carriers, the response would not be explained by fenofibrate-induced APOA5 mRNA expression. Instead, Lai and colleagues suggest that fenofibrate, by an unknown mechanism, independently reduces triglyceride concentrations by mediating the exchange of triglycerides/cholesterol between HDL and VLDL particles. Thus, under the condition of fenofibrate-mediated reduction of triglyceride levels, both variants would function as effectively, and similar levels of triglyceride and HDL cholesterol would be observed for carriers and noncarriers, as shown in the study (Figure).

The APOA5 association with fenofibrate response in the GOLDN study has a few implications. First, the study is consistent with a growing body of evidence that among numerous SNPs at the APOA5 locus, 56G>C (p.S19W) is unique because it: (1) has proven dysfunction in vitro28; (2) is relatively common in several populations; and (3) is the defining polymorphism of a unique APOA5 haplotype that appears to be consistently associated with moderately elevated plasma triglyceride concentrations. It would be important to determine whether this SNP shows a consistent association with severely elevated plasma triglycerides, such as those observed in patients with hyperlipoproteinemia type 5, or with the response to these individuals to treatments such as fibrates. Nonetheless, the results of the GOLDN study suggest that fibrates should be on the list of lipid-lowering medications for which a genetic basis for interindividual differences in plasma lipoprotein response is likely. Finally, interindividual genetic differences could be added to the factors that underlie the observed inconsistencies among clinical trials of fibrates with respect to cardiovascular outcomes.7–10 Future pharmacogenomic studies with larger sized samples might help to clarify which individuals are most likely to benefit from fibrate therapy.

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None.

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