Human Scavenger Receptor Class B Type I Variants, Lipid Traits, and Cardiovascular Disease

Kasey C. Vickers, PhD; Annabelle Rodriguez, MD

Over the years, pioneering work from Monty Krieger’s laboratory has solidified the role of scavenger receptor class B type I (SR-BI) as a physiologically relevant lipoprotein receptor, especially in mouse models.1,2 It is safe to conclude that the complete absence of SR-BI in mice is associated with significant increases in circulating high-density lipoprotein cholesterol (HDL-C) fractions of abnormal composition and size; however, the effect of SR-BI-deficiency on circulating apoB cholesterol levels has not been extensively studied in mice or humans. This is an important point of emphasis given that, in comparison with mice, cholesterol transport in humans primarily resides in the apoB fractions.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN (K.C.V.); and Department of Cell Biology, Center for Vascular Biology, University of Connecticut Health Center, Farmington (A.R.).

Correspondence to Annabelle Rodriguez, MD, Center for Vascular Biology, University of Connecticut Health Center, 263 Farmington Ave, Farmington. E-mail rodriguezoquendo@uchc.edu

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The study by Acton et al11 was one of the earliest studies to examine the associations of various SCARB1 single nucleotide polymorphisms (SNPs) with complex lipid traits. In this study, the investigators sequenced the SCARB1 gene in 489 healthy men and women from Zaragoza, Spain, and concentrated analyses on variants with MAF>0.1%. This yielded 2 exonic SNPs (rs4238001 and rs5888) and 1 intronic variant (intron 5) for association studies with plasma lipid traits and anthropometric measurements. Results suggested that men homozygous for the rs4238001 SNP (a missense variant in exon 1 that causes a glycine to serine amino acid change at position 2) had significantly lower low-density lipoprotein cholesterol and triglyceride levels and higher HDL-C levels when compared with men homozygous for the major allele. No significant associations of rs4238001 with lipid levels were found in women. In contrast, although Niemsiri et al10 identified the rs4238001 SNP among common variants in their resequencing study, they did not observe any significant associations of this SNP with lipid traits in men or women. It should be noted that Niemsiri et al10 did report an MAF for this SNP at 0.082, whereas Acton et al11 observed this variant at an MAF of 0.117, which suggests the possibility of differences in the underlying population structure of the 2 study groups. Alternatively, differences in gene–gene and gene–environment effects might also explain the different outcomes for this specific SNP with lipid traits.

Of the 44 variants identified in the resequencing project, Niemsiri et al10 report that 4 common variants were nominally associated with higher plasma apoB levels and 3 were associated with HDL-C levels (not all of these 3 intronic SNPs showed the same direction of effect); however, only 3 apoB-associated SNPs survived false discovery rate corrections. All of the 3 significant variants associated with apoB were intronic with rs2343394 (intron 2) and rs2278986 (intron 3) being in strong linkage disequilibrium. We have previously shown that subjects with hyperalphalipoproteinemia (defined as HDL-C levels, ≥60 mg/dL) who were carriers of the minor allele for rs2278986 had significantly less SR-BI protein when
compared with carriers of the reference allele. Interrogation of the HaploReg database (http://www.broadinstitute.org/mammals/haploreg) identified several regulatory motifs that were predicted to alter transcription factor (TF) binding at the rs2278986 site (CTCF, MZF1, NRSF, PTF1-β, PAX4, CREB1, Smad, UFIH3β, VDR, ZID, and Zifp281). This is another example, of many, that suggests that intronic SNPs can exert functional phenotypic effects and are likely because of enhancer/repressor function.

A major goal of the study by Niemsiri et al. was to resequence the SCARB1 gene to identify rare low-frequency SNPs (MAF, <1%) that might be significantly associated with complex lipid traits. The known rare missense variant in exon 3 (rs5891) was found to be significantly associated with higher apoB levels (β = 5.8; P = 0.012), and 2 novel rare variants were associated with lower triglyceride and higher apoB levels. We previously showed that rs5891 was associated with higher HDL-C levels in younger women of the Old Order Amish. It needs to be stressed that although the direction of effect is different across study populations, it does not necessarily imply that the particular SNP is nonfunctional but more so that results need to be interpreted in the context of population structure or gene–environment context.

In the study by Niemsiri et al., all 3 of the common SNPs significantly associated with HDL-C levels were intronic. For example, rs11057844 resides within the first intron of SCARB1 and it was associated with a negative β effect, whereas the other SNPs (rs701106 and rs838880) were associated with a positive β effect. Most interestingly, an interrogation of the Encyclopedia of DNA Elements database (http://www.genome.ucsc.edu) revealed that TFs max, c-myc, and BAF155 have been shown to bind to the rs11057844 SNP with a high GC percentage, which suggests that this locus might be methylated. In contrast, bioinformatics from Encyclopedia of DNA Elements revealed only 1 TF binding to rs701106 and none directly binding to rs838880 (although TF binding was observed at SNPs nearby in linkage disequilibrium with rs838880). We previously showed that the SCARB1 intronic SNP, rs10846744 (located in intron 1 but not in linkage disequilibrium with rs11057844), was significantly associated with subclinical atherosclerosis and incident cardiovascular disease in participants of the Multi-Ethnic Study of Atherosclerosis. It is important to note that rs10846744 was significantly associated with atherosclerotic disease but not with lipid traits (total cholesterol, low-density lipoprotein cholesterol, triglyceride, and HDL-C levels), and the association was not influenced by other traditional risk factors, such as age, sex, hypertension, smoking, diabetes mellitus, or obesity. Our results are in agreement with the study by Niemsiri et al., in which although the rs11057844, rs701106, and rs838880 SNPs are significantly associated with HDL-C, the β effects are modest and are not consistent in the direction of effect. This does not imply that neither of these SNPs could exert functional effects; in fact, one is worthy of further exploration (rs11057844) given the number of TFs found to bind to this locus.

With regards to rare variants identified by resequencing that were associated with HDL-C levels, the exon 5 variant (rs201977189, β = 0.29; P = 0.028) and 2 intronic variants (intron 6, β = 0.40; P = 0.033 and intron 7, β = 0.37; P = 0.047) were significantly associated with higher HDL-C levels. The association of these rare SNPs with higher HDL-C levels might suggest SR-BI functional deficiency, particularly for the rs201977189 SNP harbored in exon 5. Niemsiri et al. did not examine the effects of either common or rare variants on SR-BI protein expression; however, results by Vergeer et al. suggested a lack of correlation between circulating HDL-C levels and the rare P297S SCARB1 variant on SR-BI macrophage protein levels. These investigators found that the rare P297S variant was associated with significantly higher HDL-C and higher macrophage SR-BI protein levels in carriers but without a significant association with atherosclerosis.

Conclusions

On the basis of the work by Niemsiri et al., we conclude that further exploration of the functional relationships between SR-BI and apoB levels is certainly warranted. For the past 20 years, SR-BI has mainly been studied through the lens of HDL-cholesterol ester uptake; however, as already noted, SR-BI has many biological functions. On the basis of findings from the study by Niemsiri et al., we found that a deeper look at SR-BI’s functional association with non-HDL lipoproteins and oxidized lipids is needed, and this is particularly important in the context of the role of apoE. Moreover, hepatic SR-BI likely accounts for the majority of low-density lipoprotein cholesterol ester selective core uptake, as determined by evidence from hepatocytes isolated from SR-BI-deficient mice.

Given the high prevalence of hypercholesterolemia, especially low-density lipoprotein cholesterol, it is certainly possible that common and rare variants in the SCARB1 locus exert major effects on genetic causes of familial hypercholesterolemia.

Disclosures

Dr Rodriguez holds inventorship rights for SCARB1 molecular diagnostic testing, and she is the founder of Lipid Genomics. Dr Vickers is a consultant for Procter & Gamble.

References


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