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Genetic variants associated with VLDL, LDL and HDL particle size differ with race/ethnicity

Alexis C. Frazier-Wood[a,b,c], **Ani Manichaikul**[d,e], **Stella Aslibekyan**[a], **Ingrid B. Borecki**[f], **David C. Goff, MD**[g,h,i], **Paul N. Hopkins**[j], **Chao-Qiang Lai**[k], **Jose M. Ordovas**[k,l,m], **Wendy S. Post**[n,o], **Stephen S. Rich**[e], **Michèle M. Sale**[d,p,q], **David Siscovick**[r], **Robert J. Straka**[s], **Hemant K. Tiwari**[b], **Michael Y. Tsai**[t], **Jerome I. Rotter**[u], and **Donna K. Arnett**[a]

[a]Department of Epidemiology, University of Alabama at Birmingham, Birmingham AL, United States

[b]Section on Statistical Genetics, University of Alabama at Birmingham, AL, United States

[c]Division of Epidemiology, Genetics and Environmental Sciences, University of Texas School of Public Health, Houston, TX, United States

[d]Center for Public Health Genomics, Division of Biostatistics and Epidemiology, University of Virginia, Charlottesville, VA, United States

[e]Department of Public Health Sciences, Division of Biostatistics and Epidemiology, University of Virginia, Charlottesville, VA, United States

[f]Department of Genetics, Washington University School of Medicine, St. Louis, MO, US

[g]Department of Epidemiology & Prevention, Wake Forest University, Winston-Salem, NC, United States

[h]Department of Internal Medicine, Wake Forest University, Winston-Salem, NC, United States

[i]Department of Social Sciences and Health Policy, Wake Forest University, Winston-Salem, NC, United States

[j]Department of Internal Medicine, University of Utah, Salt Lake City, UT, United States

[k]Nutrition and Genomics Laboratory, Jean Mayer-US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, United States

[l]The Department of Epidemiology and Population Genetics. Centro Nacional Investigación Cardiovasculares (CNIC) Madrid, Spain

[m]IMDEA Food, Madrid, Spain

[n]Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States

[o]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

[p]Center for Public Health Genomics, University of Virginia, Charlottesville, Virginia

[q]Department of Medicine, University of Virginia, Charlottesville, Virginia

[1]*Corresponding author*: Alexis Frazier-Wood, PhD; Division of Epidemiology, Genetics and Environmental Sciences, University of Texas School of Public Health, Houston, TX, United States; (713)-500-9814; LekkiWood@Gmail.com.

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[r]Cardiovascular Health Research Unit, University of Washington, Seattle, WA, United States

[s]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN

[t]Department of Laboratory Medicine and Pathology, University of Minnesota, MN

[u]David Geffen School of Medicine, UCLA, Los Angeles, CA, Unites States

Abstract

Background—Specific constellations of lipoprotein particle features, reflected as differences in mean lipoprotein particle diameters, are associated with risk of insulin resistance (IR) and cardiovascular disease (CVD). The associations of lipid profiles with disease risk differ by race/ethnicity, the reason for this is not clear. We aimed to examine whether there were additional genetic differences between racial / ethnic groups on lipoprotein profile.

Methods and results—Genotypes were assessed using the Affymetrix 6.0 array in 817 related Caucasian participants of the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN). Association analysis was conducted on fasting mean particle diameters using linear models, adjusted for age, sex and study center as fixed effects, and pedigree as a random effect. Replication of associations reaching $P<1.97 * 10^{-05}$ (the level at which we achieved at least 80% power to replicate SNP-phenotype associations) was conducted in the Caucasian population of the Multi-Ethnic Study of Atherosclerosis (MESA; N=2430). Variants which replicated across both Caucasian populations were subsequently tested for association in the African-American (N=1594), Chinese (N=758) and Hispanic (N=1422) populations of MESA. Variants in the *APOB* gene region were significantly associated with mean VLDL diameter in GOLDN, and in the Caucasian and Hispanic populations of MESA, while variation in the hepatic lipase (*LIPC*) gene was associated with mean HDL diameter in both Caucasians populations only.

Conclusions—Our findings suggest the genetic underpinnings of mean lipoprotein diameter differ by race/ethnicity. As lipoprotein diameters are modifiable, this may lead new strategies to modify lipoprotein profiles during the reduction of IR that are sensitive to race / ethnicity.

Keywords

Lipoprotein size; race / ethnicity; ApoB; Hepatic Lipase; NMR

Background

Different constellations of lipoprotein subfraction concentrations, reflected in the heterogeneity in lipoprotein fraction size, are now considered a biomarker of metabolic dysfunction, such as CVD and IR (Festa et al., 2005; Garvey et al., 2003; Goff Jr., D'Agostino Jr., Haffner, & Otvos, 2005; Gray et al., 1997). Lipoprotein subfraction distribution and the associated average diameter for a fraction are modifiable through diet and exercise, making them a potential target for interventions aimed at reducing IR and CVD (Beard, Barnard, Robbins, Ordovas, & Schaefer, 1996; Lemieux et al., 2002; Melenovsky et al., 2002; Wood et al., 2006). The associations between lipoprotein size and disease risk, and the possibility that lipoprotein size may become a clinical intervention target, have increased efforts to understand the etiology of lipoprotein size heterogeneity.

Both candidate gene and genome-wide association (GWAS) approaches have been used to identify genetic risk factors for shifts in subfraction distribution, (Austin et al., 1998; Couture et al., 2000; Freeman, 2003; Nishina, Johnson, Naggert, & Krauss, 1992; Okumura et al., 2003; Osgood, 2003; Rotter et al., 1996; Ruel et al., 2002; Talmud et al., 2000, 2004; Wang, Qiang, Chen, Zhang, & Zhuang, 2002). A recent GWAS identified 15 loci associated

with the mean diameter of VLDL, LDL or HDL, but replication was reported for only 10 loci in two independent samples (Chasman et al., 2009). The single nucleotide polymorphism (SNP) associations with mean particle diameter were identified in Caucasian populations. Generalization beyond Caucasian populations is complicated for several reasons. First, there is evidence that dyslipidemic profiles differ between ethnic groups, with, for example, Caucasians exhibiting higher LDL cholesterol and triglyceride levels than non-Caucasian populations (O'Meara et al., 2004). Second there is evidence that the relationship of dyslipidemia with CVD may differ between ethnic groups. For example, smaller LDL particle size is associated with hypertension, a risk factor for coronary heart disease, in Caucasians but not in African Americans (Kullo, Jan, Bailey, Mosley, & Turner, 2007). Moreover, total- and LDL -cholesterol concentrations are more strongly associated with cardiovascular disease risk in Caucasians than in African Americans (Kral et al., 2001). Third, the identity of individual SNPs associated with disease risk or biomarkers and their allele frequencies may differ across ethnic groups (Aouizerat et al., 2003; Goodarzi et al., 2003; Wung & Aouizerat, 2003).

In this study, we performed genome-wide scans in GOLDN (a Caucasian population), replicating significant findings in the Caucasian population of MESA, to identify genetic variations contributing to variation in lipoprotein diameters, as well as to confirm loci that have previously been identified. Further, we examined any replicated associations in Caucasians in non-Caucasian populations.

Methods

GOLDN Study Population

The original study population consisted of 1,328 men and women from 148 families consisting of a mix of familial relationships including parent-offspring (N=614), siblings (N=667), grandparent-grandchild (N=89), avuncular (N=617), half-sibling (N=22), grand avuncular (N=69), half avuncular (N=23), first cousins (N=268), half grand avuncular (N=12), 1st cousin once removed (N=81), half 1st cousin (N=11), half 1st cousin once removed (N=4) and 2nd cousin (N=1) relationships. All participants were of European descent recruited in Minneapolis, Minnesota, and Salt Lake City, Utah. The primary aim of the GOLDN study was to characterize the role of genetic and dietary factors on an individual's response to both a high-fat meal challenge and fenofibrate intervention. The details of GOLDN have been published elsewhere (Kabagambe et al., 2009). Briefly, the study protocol consisted of an initial screening visit, during which participants were asked to discontinue the use of lipid lowering drugs and over-the-counter medication that could affect lipid levels. Approximately 4 to 8 weeks later participants' blood samples were collected. The final sample consisted only of those willing to undergo the high-fat meal protocol and a subsequent three week fenofibrate trial; N=833, of which 817 individuals remained after the genotype exclusions detailed below). Although phenotype data are taken from the participants before either the high-fat meal or the fenofibrate intervention, the GWAS genotyping was only conducted on those who completed the fenofibrate protocol. The protocol was approved by the Institutional Review Boards at the University of Minnesota, University of Utah, Tufts University/New England Medical Center and the University of Alabama at Birmingham. Written informed consent was obtained from all participants.

MESA Study Population

The MESA study population consisted of 6,814 men and women, ages 45–84 years, who identified themselves as non-Hispanic white, African-American, Hispanic, or Chinese were recruited from six regions in the United States during years 2000 to 2002. The communities included Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York;

Baltimore City and Baltimore County, Maryland; St Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California. MESA was designed to study the prevalence, risk factors, and progression of subclinical cardiovascular disease in a multiethnic cohort. A detailed description of the study design and methods has been published previously (Bild, 2002). All participants were free of clinically apparent cardiovascular disease. All participants gave informed consent and the protocol was approved by the institutional review board of each of the study centers.

Biochemical Measurements

All plasma samples used for this analysis were collected after an 8- (GOLDN) or 12- (MESA) hour fast. All samples were analyzed for lipid profiles once all collections were made in each study. Measurements of VLDL, LDL and HDL diameter were determined by nuclear magnetic resonance (NMR) spectroscopy by LipoScience (LipoScience Inc, North Carolina). NMR detects the signal emitted by lipoprotein methyl-group protons when in the field of a magnet charged at 400MHz. The NMR signal is decoded to obtain estimates of particle numbers for each of several lipoprotein fractions. The weighted average particle diameter for each lipoprotein fraction (VLDL, LDL and HDL) is calculated as the sum of the average lipoprotein particle diameters multiplied by the relative mass percentage, based on the amplitude of the methyl NMR signal and given in nm. NMR groups intermediate-density lipoproteins (IDL) as a subclass of LDL (Jeyarajah, Cromwell, & Otvos, 2006).

Genotyping

In both GOLDN and MESA, a total of 906,600 SNPs were genotyped using the Affymetrix Genome-Wide Human 6.0 array. Genotypes were defined using the Birdseed calling algorithm (Korn et al., 2008).

GOLDN—SNPs that were monomorphic (55,530) or had a call rate <96% (82,462) were removed from the analysis. Additionally, SNPs were excluded from the analysis based on the number of families with Mendelian errors as follows: for minor allele frequency (MAF) ≥ 20%, removed if errors were present in >3 families (1,486 SNPs); for 20%>MAF≥10%, removed if errors were present in >2 families (1,338 SNPs); for 10%>MAF≥5%, removed if errors were present in >1 family (1,767 SNPs); for MAF<5%, removed if any errors were present (9,592 SNPs). In families with remaining errors, SNPs that exhibited Mendelian error were set to missing (31,595 SNPs). Furthermore, 16 participants with call rates <96% were also removed from any subsequent analyses. Subsequently, 748 SNPs failing the Hardy-Weinberg equilibrium (HWE) test at P-value $<10^{-6}$ were excluded from association analyses.

After conducting the quality control measures above, and then excluding SNPs with minor allele frequency (MAF) less than 1%, those that deviate from Hardy-Weinberg Equilibrium proportions (HWE; $P <10^{-6}$), those SNPs missing strand information, and those with discrepancies with the *mlinfo* file, imputation was performed using MACH software (Version 1.0.16). After imputation, a hybrid dataset was created, that included 2,543,887 SNPs, of which 584,029 were initially genotyped in the GOLDN population. Missing typed data were kept as missing in the final genotype data set.

MESA—Sample exclusion criteria included heterozygosity greater than 53% and individual-level genotyping callrate < 95%. Monomorphic SNPs were removed, and there was no filter on HWE or MAF prior to release of the genotypes on dbGaP. IMPUTE version 2.1.0 was used to perform imputation for the MESA SHARe participants (chromosomes 1–22) using HapMap Phase I and II -CEU+YRI+CHB+JPT as the reference panel (release #22 - NCBI Build 36 (dbSNP b126)) (only the CEU reference panel was used for imputation in

Caucasian participants). Relationship inference was performed using KING software (Manichaikul et al., 2010) to identify first- and second- degree relatives, and an unrelated set of individuals was identified for genome-wide association analysis.

Statistical Methods

Population differences—Population differences in age were examined using t-tests. Population differences in gender were examined using a 2-degree of freedom (df) chi-square (X^2) test of freedom. Population differences in mean lipoprotein diameter were examined using regression models with mean lipoprotein diameter as the outcome and population, age and gender as predictors.

GOLDN GWAS—Mean VLDL diameter was log-transformed to approximate a normal distribution. SNP-phenotype associations were tested using mixed linear models. The mean lipoprotein particle diameter was the outcome (for each of the lipoprotein fractions of VLDL, LDL and HDL separately) with each SNP the predictor, and sex, age, and data collection center modeled as fixed effects, and "pedigree" as a random effect. The *lmekin* function in R software (*kinship* package)(Atkinson & Thereau, 2007)) was modeled in the association analysis to correct for the non-independence of the data points (pedigree), which uses a variance component framework to account for the genetic correlation across family members. Population substructure was assessed using principal components generated using EIGENSOFT 3.0 software. As the first 10 principal components did not show a significant association with any outcome (P>.001), they were not included in the mixed models that tested for genotype-phenotype associations. The Bonferroni correction was used to establish genome-wide significance, with the chosen alpha (.05) divided by the total number of SNPs (imputed + genotyped; 2543401) giving rise to a threshold of $P<1.97 \times 10^{-8}$. Quantile-quantile (q-value-q-value) plots were constructed to evaluate deviations from the expected test statistic distribution (Supplementary Figure 1). . Genome-wide Manhattan plots were generated to visualize the results (Supplementary Figure 2).

Replication in Caucasians—The P-value threshold for selecting SNPs from the Caucasian population of GOLDN for replication in the Caucasian population of MESA was chosen at $P<1.97 * 10^{-05}$ (see "Asking for more" 2012). This threshold was validated empirically after the initial GWAS based on power analysis suggesting we would achieve 80% power for replications.

Power analysis—At an alpha level of $P<1.97 * 10^{-05}$, we report 371 significant SNPphenotype associations (Supplementary tables 1–3). For the power analysis only, we used a Bonferroni correction of .05 / 371 which gave rise to the alpha level of P=.00013 needed for 80% power. Using a conservative MAF of .10, and based on an average observed effect size of $\beta = .015$ (Supplementary table 4), using an additive model, we have 84% power to replicate our 371 findings from GOLDN and detect significant SNP-phenotype associations in the Caucasian population (N=2430) of MESA.

Examination of replicated SNPs in non-Caucasian populations—To reduce the likelihood of false positive findings, only associations that replicated in the Caucasian participants of MESA were subsequently examined in a third stage for associations in the non-Caucasian populations.

Examination of SNPs in the MESA populations—All mean particle diameters were log transformed to approximate a normal distribution. To examine genetic associations, linear models were fit in R and controlled for age, sex, principal components of ancestry and data collection center. Within the full MESA cohort, we stratified by race/ethnic group and

eliminated those individuals with top principal components (PCs) of ancestry > 3.5 SD from the mean within any race/ethnic group. Based on our examination of principal components within each race/ethnic group, we used 3 PCs for analysis of Caucasians, 1 PC for African Americans, 3 PCs for Hispanics, and 1 PC for Chinese. A false discovery rate (FDR) correction was used within each ethnic group and q-value values are reported (Benjamini & Hochberg, 1995; Storey & Tibshirani, 2003).

As the sample sizes for the non-Caucasian populations are smaller than those for the Caucasian population in MESA, and MAF may differ by race / ethnicity, we conducted power analysis to examine our power to reject the null hypothesis that SNPs associating with particle diameters in Caucasians also associate with particle diameters in non-Caucasian populations (Supplemental Table 4). Power analysis was conducted using Quanto software v 1.2.4 (Gauderman & Morrison). The observed effects sizes (β) from the SNP-phenotype associations in the Caucasian population of MESA, as well as the observed MAF for each of the non-Caucasian populations of MESA, were used to calculate our power to replicate SNP-phenotype associations. For the Hispanic population we had over 80% power to reject the null hypothesis for all SNP-phenotype associations. For the African-American population, we had over 80% power reject the null hypothesis for all SNP-phenotype associations, except for that of rs10184054 with mean VLDL diameter . In the Chinese population, we have over 80% power to replicate 3 of the SNP-phenotype associations with mean VLDL diameter, but were underpowered to replicate SNP-phenotype associations with mean HDL diameter (power<.40). Therefore, we did not try to replicate SNP associations with mean HDL diameter in the Chinese population.

The software haploview (Barrett, Fry, Maller, & Daly, 2005) was used to visualize linkage disequilibrium (LD) plots for areas of the genome, for all racial/ethnic population, where there were SNPs that were significantly associated with mean lipoprotein diameters in the Caucasian populations of both GOLDN and MESA (Supplemental Figure 3).

Results

Sample characteristics

General characteristics of the GOLDN and MESA study populations are summarized in Table 1. No populations were significantly different in gender, but GOLDN differed from the MESA populations in age (P<.0001; Table 2). For mean VLDL diameter, we saw ethnic differences (P<.0001) between all populations except between GOLDN and the Hispanic participants of MESA (P=.70; Table 2). For mean LDL diameter the two Caucasian populations did not differ (P=.09), nor did the African American population from either Caucasian population (P>.05), however, the Hispanic and Chinese populations were significantly different from all other populations (P<.0001; Table 2).With respect to mean HDL diameter, all populations were significantly different (P<.001; Table 2).

Initial GWAS, conducted on the GOLDN population, gave rise to genomic control parameters lambda of λ=1.0 for mean VLDL diameter, λ=1.1 for mean LDL diameter, and λ=1.2 for mean HDL diameter (Supplementary Figure 1). Given our sample size, λ<1.1 may be expected. Phenotype distribution did not deviate significantly from normal, and pedigree structure was checked using genotypes (allele sharing) as part of GOLDN protocol therefore we could exclude these potential sources of inflation as the cause of the elevated genomic control lambda for mean HDL particle size.”.

For mean VLDL diameter, 6 SNP associations reached genome wide levels of significance in the *ApoB* gene region on Chromosome 2 ($P<1.97*10^{-8}$; Table 3; Supplementary Figure 2). Potential regions of interest, with a number of SNP associations above the threshold for

replication were additionally seen in the budding uninhibited by benzimidazoles 3 homolog (*BUB3)* gene on chromosome 10 and an intergenic region on chromosome 12 (Supplementary Table 1; Supplementary Figure 2). LDL showed no SNP associations at genome wide levels of significance (Supplementary Table 2), but the Manhattan plots showed areas of borderline association in the collagen, type XXVII, alpha 1 (*COL27A1*) gene, and RNA (guanine-7-) methyltransferase (*RNMT*) genes. The only genomewide significant association with mean HDL diameter was a SNP (rs427614) near the potassium voltage-gated channel, KQT-like subfamily, member 4 (*KCNQ4*) gene ($P=3.08*10^{-9}$), and 5 SNPs in the Scinderin (*SCIN*) gene on chromosome 7.

An alpha of $P<1.97*10^{-5}$ was chosen as the criterion for replication in MESA. At this alpha level 89 SNPs were associated with mean VLDL diameter, of which 60 SNPs occur across 14 known loci and 29 are intergenic; 88 SNPs were associated with mean LDL diameter, of which 43 were across 22 known loci, and 45 SNPs were in intergenic regions; and 195 SNPs were associated with mean HDL diameter which represented 114 SNPs across 44 known loci, and 81 intergenic SNPs (Supplemental tables 1–3).

Replication

Of the SNPs meeting the criterion for replication in MESA, 4 replicated SNP associations were seen with mean VLDL diameter, and 3 SNP associations were replicated with mean HDL diameter, in the Caucasian population of MESA with estimated FDR q-value < 0.05; for all significant SNP-phenotype findings, the direction of effect was the same across populations (Table 3). In the Caucasian MESA sample, we replicated associations for four variants in the *APOB* gene with mean VLDL diameter (all $P=.001$; q-value=.01), and three in the hepatic lipase (*LIPC*) gene with mean HDL diameter (all $P<1.97*10^{-5}$; q-value=.007). There were no replicated SNP-phenotype associations with mean LDL diameter across the two samples in Caucasians. The LD structure for the *APOB* gene region, for each racial/ethnic population is displayed in Supplementary Figure 3. *LIPC* variants were not in LD so are not visualized.

The significant SNP-phenotype associations on the *APOB* and *LIPC* genes were examined for associations with mean VLDL and HDL particle diameters respectively in the Hispanic and African American populations; and the significant SNP-phenotype associations on the *APOB* gene was examined for associations with mean VLDL particle diameter in the Chinese population (Table 3). SNPs in *APOB* gene region were significantly associated with mean VLDL diameter in Hispanics (all $P<.001$; q-value=.01), but not in African-Americans nor Chinese populations (all $P>.05$). SNPs in *LIPC* did not show associations with mean HDL diameter in any non-Caucasian populations (all $P>.05$; Table 3).

Discussion

To our knowledge, this is the first study to use genome-wide data to explicitly examine whether genetic variants associating with lipoprotein diameter in Caucasians also associate with those same lipoprotein diameters in non-Caucasian populations. We provide evidence that there is heterogeneity across the racial groups; the variants in the *APOB* gene region that were associated with mean VLDL diameter in Caucasian and Hispanic populations, did not show the same associations in African-American and Chinese populations. In addition, variation across the intronic region of the *LIPC* gene was suggestively associated with mean HDL diameters but only in Caucasians.

In our data, we report four SNPs to be associated with mean VLDL diameter (rs10184054, rs6544366, rs6728178 and rs7557067). These SNPs were not shown to be significant in previous analysis, but 2 SNPs in LD with rs10184054, rs6544366, rs6728178 and rs7557067

have been previously associated with total VLDL concentration, small VLDL concentration and mean VLDL diameter (rs676210) and mean LDL diameter, triglycerides and medium VLDL concentration previously (rs673548; Chasman et al., 2009). This is strong evidence to support the association of SNPs in the *APOB* gene with mean VLDL diameter in Caucasians. We report that SNPs in *APOB* were associated with mean VLDL diameter in the Hispanic but not African-American nor Chinese populations of MESA. MAFs are somewhat lower in these latter two populations; while this suggests that the genetic associations of VLDL diameter may differ across ethnic groups, the genetic background of each race / ethnicity must be considered when interpreting the results.

Our analysis suggested that variants in the *LIPC* locus are associated with mean HDL diameter in Caucasians. The *LIPC* locus was associated with HDL size in the GWAS reported by Chasman and colleagues, but in the same paper, this association did not replicate (Chasman et al., 2009). In our study, variants at this locus did not reach genome-wide levels of significance in GOLDN but met our criterion for discovery and replication, thus providing further, but not conclusive, evidence that variants on the *LIPC* may affect HDL particle diameter in Caucasians.

It is not entirely clear why we found race and ethnicity-specific SNP associations. While the LD structure of genotyped SNPs in the *ApoB* gene region was somewhat different for African-Americans compared to Caucasians and Hispanics, this was not the case for Chinese. Given that lipoprotein diameters are influenced by many genes, future research should examine the entire genome for associations with lipoprotein diameters in non-Caucasian populations. In addition, future research could examine racial and ethnic differences in other lipidemia phenotypes, such as ApoB to ApoE ratio. Non-genetic differences between the populations and geneenvironment interactions should also be considered; given research showing that association between HDL-C and polymorphisms on the *LIPC* gene may be modified by dietary intake (Nettleton, Steffen, Ballantyne, Boerwinkle, & Folsom, 2007).

Our study must be considered in the light of several limitations. Replication of SNPs significantly associated with mean particle diameter in GOLDN, but not in the Caucasian population of MESA, remains an immediate concern. Differences between the two samples must be considered as a possible source of lack of replication; for example 13–18% of MESA participants (dependent on race / ethnicity) were on lipid lowering drugs at the time of data collection, whereas there was a washout period for such in GOLDN. Only mean HDL diameter was significantly different between those Caucasian participants of MESA taking, and those Caucasian participants not taking, lipid lowering drugs (a finding replicated in GOLDN; Frazier-Wood. et al., in press). Although we cannot fully exclude the role that lipid-lowering drugs may have played in mediating the relationship between genetic variation and mean lipoprotein diameter, we highlight that a similar percentage of participants across all populations of MESA were taking a lipid-lowering drugs, lending support to our ethnicity-specific findings. Nonetheless, the results should be interpreted with caution and we are further unable to exclude ethnicity-specific responses to the medications. In addition, although our SNP-phenotype associations are replications of previous findings in Caucasians, giving us confidence in their validity, it is not clear why we failed to replicate several loci that were associated with mean particle diameter in a previous GWAS (Chasman et al., 2009). This may arise from the relatively modest sample size in the initial GWAS, or from baseline differences used in the initial discovery GWAS, such as the mixed-gender population in GOLDN, compared to the female only sample of Chasman and colleagues GWAS (Chasman et al., 2009).

Nonetheless, we provide strong evidence that SNPs in or near *APOB* are associated with VLDL size in Caucasian and Hispanic populations, but perhaps not African-American nor Chinese populations; and variation in the *LIPC* gene is associated with mean HDL diameter in Caucasian populations, but not Hispanic nor African-American populations. The implication is that the differences seen in lipoprotein subclass profiles stratified by race / ethnicity may be at least partially genetically determined. As lipoprotein diameters are modifiable through diet, exercise and pharmacological interventions (Beard et al., 1996; Lemieux et al., 2002; Melenovsky et al., 2002; Wood et al., 2006) how the analysis presented here should inform race- and ethnicity- stratified prediction and treatment of IR warrants further research efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Means (+/− standard deviation), or percentages for demographic characteristics, and fasting lipid traits and lipoprotein diameters for the GOLDN and MESA study participants.

	GOLDN	MESA			
	Caucasian	**Caucasian**	**African-American**	**Hispanic**	**Chinese**
N	817	2430	1594	1422	758
Gender, % male	48	48	46	48	49
Age, years	48.8 (16.2)	62.7(10.2)	62.3(10.1)	61.4(10.3)	62.4(10.4)
Lipid lowering drugs, % taking	0	18	16	13	14
VLDL diameter, nm	51.29 (7.86)	49.10 (8.39)	47.26 (6.72)	50.89 (8.53)	46.39 (7.15)
LDL diameter, nm	20.81 (0.88)	20.81 (0.56)	20.79 (0.51)	20.64 (0.58)	20.61 (0.50)
HDL diameter, nm	8.84 (0.45)	9.25 (0.46)	9.30 (0.48)	9.19 (0.42)	9.29 (0.41)
Triglycerides, mg/dL	138.31 (97.46)	131.96 (78.62)	103.46 (56.60)	156.28 (85.41)	143.32 (86.00)
LDL-cholesterol, mg/dL	122.71 (31.65)	117.09 (30.27)	116.70 (33.50)	119.90 (32.93)	114.86 (28.73)
HDL-cholesterol, mg/dL	46.48 (13.02)	52.42 (15.80)	52.37 (15.20)	47.52 (12.97)	49.31(12.44)

Table 2

P-values for comparisons of demographic and fasting lipoprotein diameter characteristics across populations.

	GOLDN	MESA			
	Caucasian	Caucasian[b]	African-American	Hispanic	Chinese
Age (above) / Gender (below)					
GOLDN Caucasian	-	<.0001	<.0001	<.0001	<.0001
MESA Caucasian[b]	.29	-	.23	.0002	.43
MESA African-American	.04	.16	-	.02	.90
MESA Hispanic	.37	.91	.17	-	.05
MESA Chinese	.61	.69	.17	.78	-
VLDL diameter (above) / LDL diameter (below)					
GOLDN Caucasian	-	<.0001	<.0001	.70	<.0001
MESA Caucasian[b]	.09	-	<.0001	<.0001	<.0001
MESA African-American	.44	.08	-	<.0001	<.0001
MESA Hispanic	<.0001	<.0001	<.0001	-	<.0001
MESA Chinese	<.0001	<.0001	<.0001	<.0001	-
HDL diameter (above)					
GOLDN Caucasian	-	<.0001	<.0001	<.0001	<.0001
MESA Caucasian[b]		-	.001	.0004	<.0001
MESA African-American			-	<.0001	<.0001
MESA Hispanic				-	<.0001
MESA Chinese					-

[a] Tests derived from t-tests for age, a 2-df X^2 test for gender, and a regression model with age and gender as covariates for lipoprotein diameters.

[b] *P*-values for comparisons between MESA Caucasians not on lipid lowering medication vs. GOLDN Caucasian participants: VLDL diameter: *P*<.0001; LDL diameter: *P*<.81; HDL diameter: *P*<.0001;

Table 3

SNPs reaching alpha levels of significance of $P<1.97*10^{-5}$ in GOLDN and q-value (Q)<.05 in Caucasians in MESA in SNP-phenotype associations with VLDL, LDL and HDL diameters

				GOLDN			MESA													
				Caucasians			Caucasians			Hispanics				AA				Chinese		
Marker	**Chr**	**Position**	**CA**[2]	**β**	***P***	***MAF***	**β**	***P***	**Q**	***MAF***	**β**	***P***	**Q**	***MAF***	**β**	***P***	**Q**	***MAF***	**β**	***P***	***MAF***
VLDL diameter / *APOB* gene[1]																					
rs10184054	2	21057374	G(C)	.04	$1.9*10^{-8}$	0.23	.02	.001	.01	0.24	.02	.001	0.1	0.26	.005	0.47	-	0.15	.01	0.15	0.72
rs6544366	2	21057522	T(G)	.04	$1.9*10^{-8}$	0.25	.02	.001	.01	0.23	.02	.001	0.1	0.26	.006	0.39	-	0.15	.01	0.22	0.27
rs6728178	2	21193946	G(A)	.04	$1.9*10^{-8}$	0.23	−.02	.001	.01	0.23	−.02	.001	0.1	0.26	.0002	0.97	-	0.20	−.01	0.14	0.28
rs7557067	2	21208211	G(A)	.04	$1.7*10^{-8}$	0.25	.02	.001	.01	0.24	.02	.001	0.1	0.26	.005	0.49	-	0.15	.01	0.14	0.29
HDL diameter / *LIPC* gene																					
rs261338	15	56522297	G(A)	.13	$1.7*10^{-05}$	0.16	.01	.002	.01	0.17	−.00	.09	-	0.14	−.001	0.65	-	0.22	-	-	0.05
rs473224	15	56524633	T(G)	−.13	$1.2*10^{-05}$	0.15	−.01	$9.8*10^{-05}$	.01	0.17	.004	.13	-	0.10	−.0002	0.94	-	0.13	-	-	0.03
rs488490	15	56524953	C(A)	−.13	$1.3*10^{-05}$	0.15	−.01	.0001	.01	0.17	.004	.13	-	0.10	.0004	0.87	-	0.13	-	-	0.03

[1] SNP within a 50 kb window of the listed gene

[2] CA = Coded allele; non-coded allele in brackets