

Genetic loci for blood lipid levels identified by linkage and association analyses in Caribbean Hispanics[§]

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Abstract To identify genetic loci influencing blood lipid levels in Caribbean Hispanics, we first conducted a genome-wide linkage scan in 1,211 subjects from 100 Dominican families on five lipid quantitative traits: total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), and LDL-C/HDL-C ratio. We then investigated the association between blood lipid levels and 21,361 single nucleotide polymorphisms (SNP) under the 1-logarithm of odds (LOD) unit down regions of linkage peaks in an independent community-based subcohort (N = 814, 42% Dominican) from the Northern Manhattan Study (NOMAS). We found significant linkage evidence for LDL-C/HDL-C on 7p12 (multipoint LOD = 3.91) and for TC on 16q23 (LOD = 3.35). In addition, we identified suggestive linkage evidence of LOD > 2.0 on 15q23 for TG, 16q23 for LDL-C, 19q12 for TC and LDL-C, and 20p12 for LDL-C. In the association analysis of the linkage peaks, we found that seven SNPs near *FLJ45974* were associated with LDL-C/HDL-C with a nominal $P < 3.5 \times 10^{-5}$, in addition to associations ($P < 0.0001$) for other lipid traits with SNPs in or near *CDH13*, *SUMF2*, *TLE3*, *FAH*, *ARNT2*, *TSHZ3*, *ZNF343*, *RPL7AL2*, and *TMC3*.[¶] Further studies are warranted to perform in-depth investigations of functional genetic variants in these regions.—Dong, C., A. Beecham, L. Wang, S. Slifer, C. B. Wright, S. H. Blanton, T. Rundek, and R. L. Sacco. Genetic loci for blood lipid levels identified by linkage and association analyses in Caribbean Hispanics. *J. Lipid Res.* 2011. 52: 1411–1419.

Supplementary key words genetics • heritability • single nucleotide polymorphism

This work was supported by National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) Grants R01 NS-40807 (R.L.S.), R37 NS-29993 (R.L.S.), R01 NS-047655 (T.R.), and K24 NS-062737 (T.R.), and by the Evelyn F. McKnight Brain Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health or other granting agencies.

Manuscript received 21 December 2010 and in revised form 4 May 2011.

Published, JLR Papers in Press, May 10, 2011
DOI 10.1194/jlr.P013672

Cardiovascular disease (CVD) and stroke are the leading causes of death and disability in the United States and around the world (1–4). Atherosclerosis, an underlying pathology of CVD, is characterized by lipid accumulation, inflammatory response, cell death, and fibrosis in arterial walls, and it accounts for 75% of all deaths from CVD (5). Compelling evidence accumulated over decades has demonstrated that abnormalities of blood lipid levels are a major contributor to atherosclerotic CVD (6–12). A substantial body of evidence suggests that blood lipid traits have a significant genetic component, with most studies showing the estimates of heritability around 40–70% for total cholesterol (TC), 30–70% for low-density lipoprotein cholesterol (LDL-C), 30–60% for high-density lipoprotein cholesterol (HDL-C), 20–55% for triglycerides (TG), and 30–50% for LDL-C/HDL-C (5, 13–17). Identification of genetic determinants of blood lipid levels may facilitate discovery of novel targets for drug development.

Recently, a large meta-analysis in more than 100,000 individuals of European descent identified 95 loci associated with lipid traits at a level of genome-wide significance and showed that these loci also had an impact on lipid phenotypes in three non-European populations (18). Although these associations appear robust, they together only explain 10–12% of the total variance or 25–30% of the genetic variance for each lipid trait. Given that there are known ethnic disparities in lipid metabolism, atherosclerosis, and cardiovascular disease (19), more studies from a

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LDL-C/HDL-C, LDL-C-to-HDL-C ratio; IL, interleukin; LD, linkage disequilibrium; LOD, logarithm of odds; MAF, minor allele frequency; NOMAS, Northern Manhattan Study; PCA, principal component analysis; SNP, single nucleotide polymorphism; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

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[§]The online version of this article (available at <http://www.jlr.org>) contains supplementary data in the form of one figure.

variety of racial/ethnic groups will help to advance our understanding of the heritability and genetic variations of these complex traits (20, 21).

In the United States, compared with non-Hispanic whites, Hispanics are the fastest growing and largest minority group, with a higher prevalence of lipid abnormalities (19); however, genetic studies of blood lipids have been sparse in non-Mexican Hispanics. To fill the gap of knowledge in this understudied population, we performed an autosomal genome-wide linkage analysis of blood lipid quantitative traits in 100 multigeneration Caribbean Hispanic families from the Family Study of Stroke Risk and Carotid Atherosclerosis (22), followed by a peak-wide association analysis in an independent prospective community-based subcohort from the Northern Manhattan Study (NOMAS) (23).

MATERIALS AND METHODS

Subjects

This study was based on two independent datasets. The first consisted of 1,211 participants with no history of taking cholesterol-lowering medication from 100 Dominican families for genome-wide linkage analysis. The second included a stroke-free NOMAS subcohort of 814 individuals with no history of taking cholesterol-lowering medication for the association analysis of single nucleotide polymorphisms (SNP) under the 1-logarithm of odds (LOD) unit down regions of linkage peaks. Informed consent was provided by the participants, and the study was approved by the Institutional Review Boards of Columbia University, the University of Miami, the National Bioethics Committee, and the Independent Ethics Committee of Instituto Oncologico Regional del Cibao in the Dominican Republic.

The research design and detailed ascertainment scheme for the family study and NOMAS were described previously (22–24). In brief, for the family study, probands were selected from the Caribbean Hispanic participants in NOMAS based on the following criteria: 1) reporting a sibling with a history of myocardial infarction or stroke; or 2) having two of three quantitative risk phenotypes (maximal carotid plaque thickness, left ventricular mass, or homocysteine level > 75th percentile in the NOMAS cohort). To be eligible for NOMAS, participants 1) had never been diagnosed with a stroke, 2) were at least 40 years of age, and 3) resided for at least three months in a household with a telephone in northern Manhattan. A total of 3,298 community subjects were enrolled in 1993–2001, and 199 unrelated household members were recruited in 2003–2008. In the association analysis of linkage peaks, however, we used a convenient subcohort of NOMAS (n = 814, 42% Dominican subset) independent of the family study, who had blood lipid measurements, no history of cholesterol-lowering medication, and genotype data from a genome-wide association study done primarily to study subclinical brain phenotypes.

Blood lipid phenotypes and covariates

At enrollment, all participants underwent a thorough evaluation, including comprehensive medical history, physical examination, review of medical records, and blood sample collection after an overnight fast. Plasma levels of TC and TG were measured using standardized enzymatic procedures with a Hitachi 705 automated spectrophotometer (Boehringer Mannheim, Mannheim, Germany). HDL-C was quantified after precipitation

of plasma apoB-containing lipoproteins with phosphotungstic acid. LDL-C levels were derived from the Friedewald equation (25). LDL-C/HDL-C was calculated based on measured LDL-C and HDL-C.

Covariates in linkage and association analyses included demographic and lifestyle factors assessed at enrollment. Body mass index (BMI) was calculated as measured body weight (in kilograms) divided by the square of height (in meters), and waist-to-hip ratio (WHR) was calculated as measured waist circumference divided by hip circumference. Cigarette pack-years were calculated as number of years smoked multiplied by number of cigarettes smoked per day, then divided by 20. Alcohol drinking was defined as currently drinking more than one drink per month. Leisure-time physical activity was assessed by a questionnaire, and physical inactivity was defined as no moderate or rigorous exercise in a typical 14-day period (26).

Genotyping

For the linkage study, genome-wide genotyping of 383 autosomal microsatellite markers was carried out by the Center for Inherited Disease Research at an average interval of 10 centimorgans (cM). Family structure was verified or adjusted through comparison of the putative relationship between pairs of individuals with those constructed based on the autosomal genotypes by performing a maximized log-likelihood ratio test using PREST (27). Relationships with $P < 1.0 \times 10^{-6}$ in a consistent manner across the family were considered an error. Mendelian errors were also checked on the final family structure using PEDCHECK (28).

For the NOMAS association study, genotyping of DNA samples was performed using the Affymetrix® Genome-Wide Human SNP Array 6.0 chips according to Affymetrix procedures at the Genotyping Core of the John P. Hussman Institute for Human Genomics at the University of Miami. Quality control was applied to both DNA samples and SNPs. Specifically, samples were removed from further analysis if they had call rates below 95%, relatedness or sex discrepancies, or were outliers beyond six SDs from the mean based on EIGENSTRAT analysis (29). SNPs were excluded if they were not in Hardy-Weinberg equilibrium ($P < 1.0 \times 10^{-6}$), had a genotyping call rate less than 95%, or had a minor allele frequency less than 5% as detected by PLINK (30).

Statistical analyses

In the linkage analysis, the outliers beyond mean ± 4 SD were first removed and log-transformation was then performed on all blood lipid phenotypes to reduce the skewness and kurtosis. Polygenic modeling with SOLAR was conducted to screen for a set of covariates: age, sex, age by sex, age², age² by sex, physical activity, smoking pack years, alcohol drinking, body mass index (BMI) and waist-to-hip ratio (WHR) based on a threshold of $P < 0.1$ for inclusion of any potentially significant covariates. For all traits, skewness and kurtosis were further checked for the residuals in the polygenic models and we did not observe departure from normality after adjustment for covariates. A maximum likelihood approach was then implemented in SOLAR to calculate heritability, proportion of alleles shared identical-by-descent (IBD), and multipoint LOD scores (31, 32). Empirical p-values for LOD scores were computed based on 15,000 replicates in which a fully-informative marker, unlinked to the specific trait, was simulated and used to compute possible LOD scores. Power analysis using SOLAR through simulation showed that with the final family sample (n = 1,211), we have at least 85% power detect a QTL with a heritability of 0.27 at a LOD score of 3 or of 0.23 at a LOD score of 2 for a lipid trait, given that the total genetic heritability for the lipid trait is 0.4.

In the association analysis of linkage peaks, population stratification was controlled for with a principal component analysis (PCA) using EIGENSTRAT. We used a subset of approximately 30K independent ($r^2 \geq 0.25$) SNPs across the entire genome to infer the principal components composing the axes of genetic variation in our NOMAS subcohort (supplemental Fig. 1). Besides the covariates screened in the linkage study analysis, three top principal components of PCA (PCA1, PCA2, and PCA3) were screened using a stepwise selection procedure with SAS 9.2 (SAS Institute Inc., Cary, NC). Any covariates with $P < 0.10$ were kept in the model. Assuming an additive genetic model, multiple linear regression analysis was performed with PLINK to investigate the association between lipid levels and 21,361 SNPs located within the 1-LOD support intervals of the five linkage peaks on 7p12 (5,861), 15p23 (5,932), 16q23 (2,578), 19q12 (2,969), and 20p12 (4,021), after adjusting for the selected covariates. In addition, the analysis was carried out in the Dominican subset to check whether the observed associations in the whole NOMAS subcohort remained similar and significant after controlling for population structure using the three top PCAs as covariates. As many SNPs tested within the five regions are highly correlated due to linkage disequilibrium (LD), the effective number of tests in each region was determined based on the sum of singleton SNPs plus LD blocks identified using Gabriel's method (33). A Bonferroni procedure was then applied to adjust for multiple testing in each region as suggested by Nicodemus et al. (34).

RESULTS

Table 1 summarizes the demographic, lifestyle, and phenotypic characteristics of the study samples. The mean age of subjects was 44.1 ± 17.2 and 63.5 ± 8.4 years, respectively, for the Dominican family sample and community-based NOMAS subcohort. Both samples had more female subjects (60% in the family sample and 58% in the NOMAS subcohort) and a comparable average BMI. With an older age distribution, the NOMAS subcohort had a greater mean of TC, LDL-C, TG, and LDL-C/HDL-C, but a lower average HDL-C compared with the family sample.

Table 2 presents the effects of demographic and lifestyle factors on five blood lipid traits (all were log-transformed) and the adjusted heritability estimates for quantitative lipid traits in Dominican families. Both age and age² were correlated with all lipid traits except HDL-C. Sex was associated with HDL-C, TG, and LDL-C/HDL-C,

but not TC and LDL-C. BMI and WHR were the two covariates associated with all five lipid traits. In addition, cigarette pack-years and alcohol drinking were associated with HDL-C but not other lipid traits. No significant effect of leisure-time physical activity or sex-by-age interaction was found on these lipid traits. The variance explained by all covariates was just 11-20% for each of the five lipid traits. After adjustment for the associated covariates, SOLAR polygenic analyses support that lipid traits are under significant genetic influence, with the estimated heritabilities ranging from 0.41 to 0.57 for these lipid traits ($P \leq 1.2 \times 10^{-15}$).

Figure 1 shows a plot of multipoint LOD scores for each lipid trait based on variance component linkage analysis, and **Table 3** lists the chromosomal regions showing suggestive linkage with a multipoint LOD score > 2.0 (35). The strongest linkage was identified on chromosome 7p12 for LDL-C/HDL-C (LOD = 3.91 at 67 cM, empirical $P = 0.00007$, 1-LOD support interval: 37-60 Mb) and on 16q23 for TC (LOD = 3.35 at 111 cM, $P < 0.00007$, 1-LOD support interval: 79-84 Mb). Suggestive linkage was found for LDL-C (LOD = 2.40 at 111 cM on 16q23, LOD = 2.68 at 52 cM on 19q12, and LOD = 2.16 at 20 cM on 20p12), TC (LOD = 2.12 at 20 on 16q23), and TG (LOD = 2.33 at 76 on 15q23) (Table 3). In addition, weak linkage of a multipoint LOD score > 1.5 was found for LDL-C/HDL-C (LOD = 1.53 at 111 cM on chromosome 5, LOD = 1.81 at 21 cM on chromosome 20), LDL-C (LOD = 1.88 at 138 cM on chromosome 9, LOD = 1.58 at 84 cM on chromosome 14), and TG (LOD = 1.95 at 96 cM on chromosome 14, LOD = 1.77 at 10 cM on chromosome 15) (Fig. 1).

In the association analysis of 21361 SNPs within the 1-LOD unit down regions of the five linkage peaks, LD block analysis yielded an effective number of tests of 1,872 for 7p12; 2,620 for 15q23; 1,390 for 16q23; 1,129 for 19q12; and 1,740 for 20p12. **Table 4** reports the lipid-associated SNPs with a nominal $P < 0.0001$ in the whole NOMAS subcohort and NOMAS Dominican subset. The most significant associations were found with LDL-C/HDL-C on chromosome 15 for rs4932506 ($P = 5.05 \times 10^{-6}$, multiple testing adjusted $P = 0.013$, near hypothetical gene *LOC441732*) and on chromosome 7 for rs7806473 [$P = 9.24 \times 10^{-6}$,

TABLE 1. Characteristics of Study Samples

Characteristic	Dominican Family Sample (n = 1,211)	NOMAS Subcohort	
		All (n = 814)	Dominican Subset (n = 343)
Age (years)	44.1 ± 17.2	63.5 ± 8.4	61.6 ± 7.7
Female	61%	58%	62%
Hispanic	100%	65%	100%
Physical inactivity	55%	43%	52%
More than 1 alcohol drink/month	57%	50%	43%
Cigarette pack-years	3.3 ± 9.0	11.2 ± 21.7	7.7 ± 14.7
Body mass index (kg/m ²)	28.5 ± 5.8	28.0 ± 4.8	28.2 ± 4.4
Waist-to-hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
TC (mg/dl)	183.5 ± 40.5	202.8 ± 38.0	201.9 ± 36.2
LDL-C (mg/dl)	109.5 ± 33.7	129.9 ± 34.3	131.2 ± 32.9
HDL-C (mg/dl)	50.3 ± 13.3	47.0 ± 14.8	43.8 ± 11.9
TG (mg/dl)	119.2 ± 86.7	131.5 ± 81.3	134.9 ± 69.6
LDL-C/HDL-C	2.3 ± 1.0	3.0 ± 1.2	3.2 ± 1.1

Values are means ± standard deviation or percentage.

TABLE 2. Covariates and Adjusted Heritability Estimates for Blood Lipid Traits

Polygenic Model	TC	LDL-C	HDL-C	TG	LDL-C/HDL-C
Covariate screened, <i>P</i> -value					
Sex	0.74	0.15	9.99×10^{-15}	7.96×10^{-6}	2.91×10^{-8}
Age	6.99×10^{-13}	3.45×10^{-8}	0.55	6.62×10^{-12}	2.85×10^{-5}
Age ²	6.34×10^{-9}	2.79×10^{-6}	0.9	1.17×10^{-5}	0.0007
Sex*age	0.93	0.98	0.51	0.71	0.93
Sex*age ²	0.04	0.12	0.78	0.20	0.33
Physical activity	0.72	0.95	0.23	0.87	0.66
Alcohol drinking	0.13	0.27	0.01	0.82	0.8
Cigarette pack-years	0.34	0.15	0.06	0.46	0.11
Body mass index	0.01	0.0008	1.77×10^{-9}	5.01×10^{-9}	2.31×10^{-11}
Waist-to-hip ratio	0.02	0.07	0.04	2.08×10^{-5}	0.007
Proportion of variance due to covariates	0.15	0.11	0.15	0.20	0.15
Trait residual skewness	-0.29	-0.44	-0.19	0.52	-0.20
Trait residual kurtosis	0.65	0.79	0.36	0.63	0.39
Adjusted heritability					
$h^2 \pm SE$	0.41 ± 0.07	0.44 ± 0.06	0.54 ± 0.06	0.56 ± 0.06	0.57 ± 0.06
<i>P</i> -value	1.20×10^{-15}	1.42×10^{-17}	9.27×10^{-26}	1.21×10^{-27}	2.33×10^{-27}

Traits were log-transformed.
 h^2 , heritability; SE, standard error.

multiple testing adjusted $P = 0.017$, an intergenic SNP between *FLJ45974* protein (*FLJ45974*) and solute carrier family 25 member 5 pseudogene 3 (*SLC25A5P3*) genes]. Interestingly, seven other intergenic SNPs between *FLJ45974* and *SLC25A5P3* were also associated with LDL-C/HDL-C with a $P < 8.5 \times 10^{-5}$ in the NOMAS subcohort and

$P < 0.01$ in NOMAS Dominican subset. Additionally, 10 other SNPs associated with any lipid trait in the entire NOMAS subcohort or only Dominican subset are located in or near eight known genes, including sulfatase modifying factor 2 (*SUMF2*), transducin-like enhancer of split 3 (*TLE3*), fumarylacetoacetate hydrolase (*FAH*), aryl-hydro-

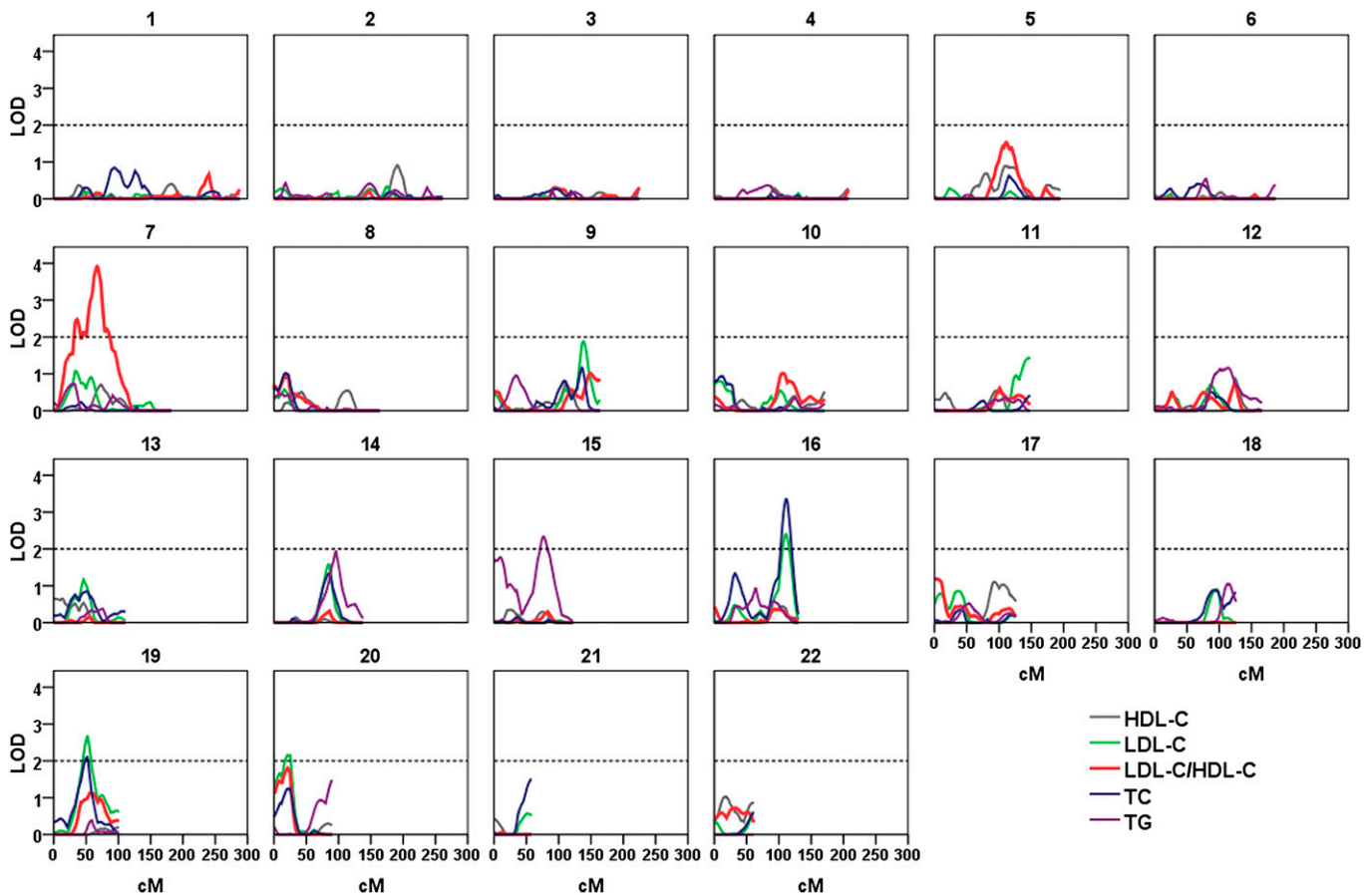


Fig. 1. Results of autosomal genome scan for blood lipid quantitative traits in Caribbean Hispanic families. Multipoint LOD scores are shown in lines for SOLAR variance component analysis. All lipid traits were log-transformed.

TABLE 3. Chromosomal Regions with Multipoint LOD score > 2.0 for Lipid Quantitative Traits

Region	Trait ^a	Nearest Marker	cM	h ² _q	LOD	Empirical P ^b	1-LOD Interval, Mb	References ^c
7p12	LDL-C/HDL-C	D7S1818	67	0.36	3.91	0.00007	37-60	35–39
15q23-24	TG	D15S131/D15S655	76	0.26	2.33	0.0004	65-91	17, 57–61
16q23	TC	D16S3091	111	0.33	3.35	<0.00007	79-84	36, 40–43
	LDL-C	D16S3091	111	0.26	2.40	0.0009	79-84	
19q12	TC	D19S433	52	0.23	2.12	0.001	12-39	5, 13, 16, 52–56
	LDL-C	D19S433	52	0.26	2.68	0.0005	16-39	
20p12	LDL-C	D20S851	21	0.28	2.16	0.001	00-11	54, 62

h²_q, locus-specific heritability; Mb, megabase.

^aTraits were log-transformed.

^bEmpirical P was based on 15,000 replicates for the specific trait.

^cLinkage was reported for lipid traits in previous studies.

carbon receptor nuclear translocator 2 (*ARNT2*), transmembrane channel-like 3 (*TMC3*), cadherin 13 (*CDH13*), teashirt zinc finger homeobox 3 (*TSHZ3*), and zinc finger protein 343 (*ZNF343*); and five are located in or near three hypothetical genes, *LOC10013187*, *LOC100128139*, and ribosomal protein L7a pseudogene 12 (*RPL7AL2*).

In addition, three loci (genes) reported by Teslovich et al. are located within the 1-LOD intervals of the five chromosomal regions showing suggestive linkage in Table 3: Niemann-Pick disease, type C1 gene (*NPC1L1*), c-Maf-inducing protein gene (*CMIP*), and CAP-GLY domain containing linker protein 2 gene (*CLIP2*). Within the three loci, we had genotype data on 2 *NPC1L1* SNPs, 115 *CMIP* SNPs, and 2 *CLIP2* SNPs, but we did not have genotype data on the top SNPs (rs2072183, rs217386, rs2925979, and rs10401969) from these three genes. For the 2 *NPC1L1* SNPs (rs217429 and rs217426), we did not find an association with $P < 0.05$ for any of the lipid traits in either the entire NOMAS subcohort or the NOMAS Dominican subset. For the 2 *CLIP2* SNPs, we observed an association between rs11670882 and TG in the Dominican subset ($P = 0.03$) and between rs2304097 and LDL-C/HDL-C in the whole NOMAS subcohort ($P = 0.02$). Among the 115 *CMIP* SNPs (from 80,041,701 to 80,298,964 bp), 6 SNPs (rs12934986, rs2966120, rs2911278, rs1471152, rs4074144, and rs4889327) were associated with a lipid trait with $P < 0.01$ in the Dominican subset or the entire NOMAS subcohort. The most significant association was found between rs12934986 and HDL-C in the Dominican subset ($P = 0.002$) and the entire NOMAS subcohort ($P = 0.003$).

DISCUSSION

Here we report a comprehensive genetic study of lipid quantitative traits in Caribbean Hispanics by combining a genome-wide linkage scan with peak-wide association. The present study is further complemented by the use of two independent samples: well-characterized Caribbean Hispanic multigeneration families and a community-based prospective cohort mainly composed of Hispanics. This unique resource allows us to search for the genetic loci that influence blood lipid concentrations in a well-characterized minority population in a systematic manner. In our polygenic analysis adjusted for covariates, the heritability estimates ranged from 41–57% for the five quantitative lipid traits in Caribbean families. These estimates are very

comparable to those obtained in most reported family studies from different populations (5, 13–17) and, therefore, provide further evidence that blood lipids are largely under genetic control.

In this report, the largest linkage peak was mapped to chromosome 7p for LDL-C/HDL-C. In this region, there is evidence for both significant linkage with an LOD score of 3.9 and significant association with multiple genetic variants between *FLJ45974* and *SLC25A5P3* in an independent sample, after adjustment for multiple testing. Previously, several studies reported linkage for lipid-related traits in or near this region. For example, a study of 485 pairs of dizygotic Australian twins identified significant linkage in the same region (LOD = 2.9 at 65 cM for log-transformed TG, LOD = 2.6 at 60 cM for log-transformed TG/HDL-C ratio) (36); a meta-analysis of nine populations with families ascertained for type 2 diabetes revealed suggestive linkage for TG (LOD = 1.9) and TG/HDL-C ratio (LOD = 2.1) at 64–93 cM (37); a genome-wide linkage analysis from the Framingham Heart Study found linkage at 52 cM, with a LOD of 2.0 for TG/HDL-C ratio (38); and the San Antonio Family Diabetes Study (SAFADS) of Mexican Americans detected suggestive linkage near this region at 94 cM for log-transformed TG (LOD = 2.1) (39). In our association analysis, the most significantly associated SNPs are located between *FLJ45974* and *SLC25A5P3*, but the function of these two genes is largely unknown. *SLC25A5P3* has been proposed to participate in transport processes, encodes proteins similar to ADP/ATP translocase 2, and is localized in mitochondrion and membrane, whereas the in vivo function of *FLJ45974* is yet unknown. *SUMF2*, a nearby gene with significant SNP association for LDL-C, is one member of the sulfatase-modifying factor family that can catalyze the oxidation of cysteine in the active site of sulfatases into C-alpha-formylglycine, which is necessary for catalytic activities of the sulfatases. It has been shown that *SUMF2* may interact with interleukin (IL)-13 and inhibit IL-13 secretion (40), but its link with lipid metabolism or atherosclerosis is unknown. These genes and others nearby, therefore, are subject to further investigation.

Our second significant linkage peak was observed at 111 cM on 16q23 (LOD = 3.35 for TC, and LOD = 2.40 for LDL-C). This region has been linked to lipid-related traits by scans from different studies, including a Mexican American family study (LOD = 3.7 at 92 cM for HDL-C) (41), a

TABLE 4. Lipid-associated SNPs with $P < 0.0001$ in the NOMAS Subcohort or Dominican Subset

Chr	SNP	BP	Minor/Major Allele (MAF)		Lead Trait ^d	Beta (SE) ^b	P^c	Other Lipid Traits ^{e,d}	Gene Nearby
			All NOMAS Subcohort	NOMAS Dominican Subset					
7	rs4947638	51794849	T/C (0.26)	T/C (0.23)	LDL-C/HDL-C	-0.10 (0.02)	3.27×10^{-5}	HDL-C; LDL-C/HDL-C, HDL-C	LOC100131871
	rs7785376	51923383	G/A (0.17)	G/A (0.14)	HDL-C	0.08 (0.02)	2.25×10^{-5}	LDL-C/HDL-C, TG	LOC100131871
	rs13235686	54095049	G/A (0.12)	G/A (0.13)	LDL-C/HDL-C	0.13 (0.03)	3.34×10^{-5}	LDL-C; LDL-C/HDL-C, LDL-C	FLJ45974/ SIC25A5P3
	rs17560050	54095274	C/A (0.14)	C/A (0.14)	LDL-C/HDL-C	0.12 (0.03)	2.60×10^{-5}	LDL-C; LDL-C/HDL-C, LDL-C	FLJ45974/ SIC25A5P3
	rs17560056	54095333	G/C (0.14)	G/C (0.14)	LDL-C/HDL-C	0.12 (0.03)	2.60×10^{-5}	LDL-C; LDL-C/HDL-C, LDL-C	FLJ45974/ SIC25A5P3
	rs10499728	54098093	A/G (0.14)	A/G (0.14)	LDL-C/HDL-C	0.12 (0.03)	8.45×10^{-5}	LDL-C; LDL-C/HDL-C, LDL-C	FLJ45974/ SIC25A5P3
	rs13233885	54099495	C/T (0.14)	C/T (0.14)	LDL-C/HDL-C	0.12 (0.03)	2.60×10^{-5}	LDL-C; LDL-C/HDL-C, LDL-C	FLJ45974/ SIC25A5P3
	rs7806473	54100065	C/T (0.11)	C/T (0.12)	LDL-C/HDL-C	0.14 (0.03)	9.24×10^{-6}	LDL-C, HDL-C; LDL-C, LDL-C/HDL-C	FLJ45974/ SIC25A5P3
	rs953160	54110101	G/A (0.13)	G/A (0.14)	LDL-C/HDL-C	0.13 (0.03)	2.52×10^{-5}	LDL-C; LDL-C/HDL-C, LDL-C	FLJ45974/ SIC25A5P3
	rs17560210	54110101	C/T (0.14)	C/T (0.15)	LDL-C/HDL-C	0.12 (0.03)	3.42×10^{-5}	LDL-C; LDL-C/HDL-C	FLJ45974/ SIC25A5P3
15	rs13238899	56108112	C/A (0.09)	C/A (0.10)	LDL-C	-0.10 (0.03)	7.02×10^{-5}	LDL-C/HDL-C, TC; LDL-C	SUMF2
	rs17758593	68100336	T/C (0.11)	T/C (0.11)	LDL-C	-0.12 (0.03)	8.13×10^{-5}	TG, LDL-C/HDL-C	TLE3
	rs3858961	78394769	A/G (0.15)	A/G (0.17)	HDL-C	-0.08 (0.02)	6.29×10^{-5}	TC, LDL-C/HDL-C	FAH
	rs4778823	78649800	G/T (0.14)	G/T (0.15)	LDL-C	-0.09 (0.02)	6.35×10^{-5}	TC, LDL-C/HDL-C	ARN2
	rs1482937	79598554	G/C (0.33)	G/C (0.30)	LDL-C	-0.06 (0.02)	4.99×10^{-5}	TC, LDL-C/HDL-C	TMC3
	rs7179520	89972904	G/C (0.18)	G/C (0.16)	LDL-C/HDL-C	-0.11 (0.03)	1.65×10^{-5}	HDL-C	LOC441732
	rs4932506	89976260	A/G (0.14)	A/G (0.11)	LDL-C/HDL-C	-0.14 (0.03)	5.05×10^{-6}	HDL-C	LOC441732
	rs4357934	82148718	G/C (0.32)	G/C (0.32)	TG	0.05 (0.01)	9.13×10^{-5}	LDL-C, LDL-C/HDL-C	CDH13
	rs11645264	82159785	T/C (0.34)	T/C (0.35)	TC	-0.05 (0.01)	9.25×10^{-5}	LDL-C, LDL-C/HDL-C, TC, LDL-C	CDH13
	rs1216119	22501685	T/G (0.29)	T/G (0.27)	LDL-C/HDL-C	-0.12 (0.03)	9.03×10^{-5}	TG, LDL-C, HDL-C, TG	LOC100128139
19	rs7245570	36505242	A/G (0.05)	A/G (0.06)	LDL-C	-0.13 (0.03)	5.23×10^{-5}	TC, LDL-C/HDL-C; LDL-C, TC, LDL-C/HDL-C	TSHZ3
	rs10417470	36896151	C/T (0.48)	T/C (0.47)	LDL-C/HDL-C	0.08 (0.02)	7.27×10^{-5}	HDL-C	TSHZ3
	rs1547063	2427198	G/A (0.35)	G/A (0.35)	TC	0.06 (0.01)	6.15×10^{-5}	LDL-C, LDL-C/HDL-C	ZNF343
20	rs6037842	4366157	G/A (0.10)	G/A (0.12)	LDL-C/HDL-C	0.19 (0.04)	1.61×10^{-5}	LDL-C, HDL-C, TG; HDL-C, LDL-C/HDL-C	RPL7A12

Chr, chromosome; BP, base pair.

^aAll lipid traits were log-transformed. Traits in italics apply only to the Dominican subset; otherwise, traits apply to the entire NOMAS subcohort.

^bRegression coefficient and its standard error (SE) were based on additive genetic effect model after adjustment for significant covariates.

^c P values are bolded if they had a Bonferroni-corrected $P < 0.05$ based on the effective number of tests within the linkage peak.


^dTraits were included if the associated $P < 0.01$ in the entire MONAS subcohort or if $P < 0.02$ in the NOMAS Dominican subset.

Finnish and Dutch family study (LOD = 3.2 at 99 cM for HDL-C) (42), an African American family study (LOD = 2.6 at 100 cM for TG) (43), a French Canadian family study (LOD = 2.6 at 98 cM for HDL-C) (44), and a meta-analysis (LOD = 1.5 at 98-130 cM for LDL-C/HDL-C) (37). In the present study, however, we did not find suggestive linkage for HDL-C. Instead, we observed the connection between 16q23 loci and TC (mainly LDL-C) in both linkage and association analysis in two independent Dominican samples. In the 1-LOD support interval (5 Mb) of this linkage peak, the most significant association was found between TC and SNP rs4357934 in the T-cadherin (*CDH13*) gene ($P = 9.13 \times 10^{-5}$) in a small independent NOMAS Dominican dataset (N = 343). Given the biological function of T-cadherin, this finding is of particular interest. T-cadherin is highly expressed in the cardiovascular and nervous system (45), and it interacts in vascular endothelial and smooth muscle cells with two different ligands, LDL-C and adiponectins, both of which play an important role in cardiovascular physiology (46, 47). Recently, *CHD13* variants were found to be associated with CVD risk, adiponectin concentration, and blood pressure in several large genome-wide association studies (48–52). These features make *CDH13* a promising candidate for further investigation to identify functional variants influencing lipid variations.

In addition to the significant linkage on 7p12 and 16q23, suggestive linkage was found on 15q23 for TG, 19q12 for TC and LDL-C, and 20p12 for LDL-C. Among these three regions, 19q has been linked to lipid quantitative traits with the most consistent linkage evidence in the previous reports, with LOD scores ranging from 1.9 to 5.7 in the region at 50-70 cM among various populations (5, 13, 16, 53–57) (Table 3). Similarly, 15q has previously been implicated in several genome scans of lipid-related traits, with LOD scores from 1.8 to 4.2 in the region at 61-72 cM among various populations (17, 58–62) (Table 3). For 20p12, two studies have shown evidence for linkage in this region: a LOD score of 2.8 for TG at 28 cM in an African sibling sample of the Hypertension Genetic Epidemiology Network (HyperGEN) (63), and 1.6 for LDL-C in French Canadian families (55). In the association analysis of these three linkage peaks, the most significant associations were found between LDL-C/HDL-C and three SNPs (rs7179520 and rs4932506 near hypothetical gene *LOC44173* on 15q, and rs6037842 near *RPL7AL2* on 20p), with a multiple testing adjusted $P < 0.05$. In addition, seven SNPs in or near six genes (*TLE3*, *FAH*, *ARNT2*, *TMC3*, *TSHZ3*, and *ZNF343*) showed an association with a lipid trait with a nominal $P < 0.0001$. *TLE3* may interact with *SIRT1* to suppress the transcriptional activity of nuclear factor- κ B and lead to anti-inflammatory activity (64). *FAH* deficiency is associated with Type 1 hereditary tyrosinemia. While the function of other associated genes in these regions is largely unknown, they may also be candidates for further investigation, given the consistent linkage evidence from independent studies as well as only a small proportion of variance of lipid traits explained by the identified genes.

We also found an association with nominal $P < 0.01$ between lipid traits and six SNPs in *CMIP*, one of the 95 most significant lipid-associated loci reported by Teslovich et al. (18) in the Dominican subset or the whole NOMAS subcohort. The strongest of the six significant associations was found in the Dominican subset between HDL-C and rs12934986, which is 18 kb from the lead SNP rs2925979 observed by Teslovich et al. and replicated in Europeans, Africans, and Asians. As Dominicans have both African and European ancestry, *CMIP* may be a candidate for further investigation.

There are several strengths and weaknesses in this study. The strengths include 1) well-characterized and extended Caribbean Hispanic families with relatively large family size, which minimizes genetic heterogeneity, 2) adjustment for lifestyle factors that were seldom controlled for in previous studies, and 3) follow-up fine mapping in an independent community-based (primarily Caribbean Hispanic) cohort with genomic control. The weaknesses include 1) lack of more accurate lipid phenotypes, such as LDL size and apolipoprotein measures, 2) small sample size of the Dominican dataset in the association analysis, and 3) our findings in this specific population may not be directly generalized to other populations.

In conclusion, we report linkage and association evidence for the presence of genetic variations on 7p, 15q, 16q, 19q, and 20p that influence the blood lipids in the Caribbean Hispanic population. The *CDH13* gene may be of particular interest, given its biological function and association with CVD and other metabolic syndrome-related components. These findings will guide further in-depth investigations of the functional variants of the genes in these regions. 

The authors thank study participants for their collaboration and all staff of the Northern Manhattan Study and Family Study for their energetic efforts in this study.

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