Quantitative trait loci influencing low density lipoprotein particle size in African Americans

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Abstract Genomic regions that influence LDL particle size in African Americans are not known. We performed family-based linkage analyses to identify genomic regions that influence LDL particle size and also exert pleiotropic effects on two closely related lipid traits, high density lipoprotein cholesterol (HDL-C) and triglycerides, in African Americans. Subjects (n = 1,318, 63.0 ± 9.5 years, 70% women, 79% hypertensive) were ascertained through sibships with two or more individuals diagnosed with essential hypertension before age 60. LDL particle size was measured by polyacrylamide gel electrophoresis, and triglyceride levels were log-transformed to reduce skewness. Genotypes were measured at 366 microsatellite marker loci distributed across the 22 autosomes. Univariate and bivariate linkage analyses were performed using a variance components approach. LDL particle size was highly heritable (h2 = 0.78) and significantly (P < 0.0001) genetically correlated with HDL-C (ρG = 0.32) and log triglycerides (ρG = −0.43). Significant evidence of linkage for LDL particle size was present on chromosome 19 [85.3 centimorgan (cM), log of the odds (LOD) = 3.07, P = 0.0001], and suggestive evidence of linkage was present on chromosome 12 [90.8 cM, LOD = 2.02, P = 0.0011]. Bivariate linkage analyses revealed tentative evidence for a region with pleiotropic effects on LDL particle size and HDL-C on chromosome 4 (52.9 cM, LOD = 2.06, P = 0.0069). These genomic regions may contain genes that influence interindividual variation in LDL particle size and potentially coronary heart disease susceptibility in African Americans.—Kullo, I. J., K. Ding, E. Boerwinkle, S. T. Turner, and M. de Andrade. Quantitative trait loci influencing low density lipoprotein particle size in African Americans. J. Lipid Res. 2006. 47: 1457–1462.

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Low-density lipoprotein particles vary in size, and smaller LDL particles are considered to be more atherogenic than larger particles (1–4). Together with decreased high density lipoprotein cholesterol (HDL-C) and increased triglyceride levels, small LDL particle size constitutes the syndrome of atherogenic dyslipidemia, which is associated with a significant increase in the risk for coronary heart disease (5, 6). Several studies have investigated the genetic basis of LDL particle size [reviewed by Bosse, Perusse, and Vohl (7)]. Most of the studies have been limited to non-Hispanic whites, and genomic regions that influence interindividual variation in LDL particle size in African Americans are unknown. African Americans have lower levels of triglycerides and higher levels of HDL-C than do non-Hispanic whites (8), and Haffner et al. (9) reported that LDL particle size may also vary with ethnicity. Thus, the genetic determinants of LDL particle size in African Americans cannot be extrapolated from studies in other ethnic groups and will need further delineation.

Because of the well-recognized correlation between LDL particle size, HDL-C, and triglycerides, it is likely that genes with pleiotropic effects on these lipid traits exist. We (10) and others (11) have demonstrated that shared genetic effects (pleiotropy) account for a significant proportion of the phenotypic correlations between LDL particle size, HDL-C, and triglycerides. Therefore, in addition to univariate linkage analyses to identify genetic regions that influence LDL particle size, we performed bivariate linkage analyses in African American sibships to identify additional regions that may exert pleiotropic effects on pairwise combinations of LDL particle size, HDL-C, and triglycerides. Such studies have the potential to yield new insights into the genetic basis of the interindividual variation of LDL particle size and the susceptibility to coronary heart disease in African Americans (12).

METHODS

Sample

Subjects included African Americans from Jackson, Mississippi, participating in the Genetic Epidemiology Network of Arteriopathy (GENOA) study, a multicenter, community-based study of hypertensive sibships that aims to identify genes
influencing blood pressure levels and the development of target organ damage as a result of hypertension (13). Recruitment into the initial phase of the GENOA study (September 1995 to June 2001) has been described previously (14). Between December 2000 and October 2004, 1,350 of the original GENOA-Jackson participants returned for a second study visit to undergo measurement of risk factors and traits, including LDL particle size and assessment of target organ damage resulting from hypertension. Genotypic (microsatellite markers) and phenotypic (LDL particle size) data were available for 1,318 Jackson participants in phase II. The study was approved by the Institutional Review Board of the University of Mississippi (Jackson). Written informed consent was obtained from each participant.

Height was measured by stadiometer, weight by electronic balance, and body mass index (BMI) was calculated as kg/m². Resting systolic and diastolic blood pressure levels were measured in the right arm with a random-zero sphygmomanometer (Hawksley and Sons, West Sussex, UK). Participants were considered diabetic if they reported using insulin or oral hypoglycemic agents or if they reported a physician diagnosis of diabetes. Those who were hypertensive, and 18.3% were on lipid-lowering medications. Information about the use of lipid-lowering medications was obtained from participants at the time of the study.

Measurement of lipid variables
Blood samples were obtained by venipuncture after an overnight fast. Standard enzymatic methods were used to measure total cholesterol, HDL-C, and triglycerides (15). LDL particle size was measured by polyacrylamide gel electrophoresis as described previously (16, 17). The mean LDL particle size was then determined by averaging weighted diameters for each fraction. Two controls (mean particle diameters of 264 and 254 Å) were analyzed with every 10 study samples. Interassay coefficients of variation were 0.77% (SD = 2.0 Å) and 1.46% (SD = 3.7 Å), respectively.

Genotyping
DNA was extracted from 10 ml of EDTA-anticoagulated blood drawn from all study participants according to standard procedures. Microsatellite markers (CHL/C/Weber screening set 9.0, n = 396) were genotyped using standard PCR-based methods by the Mammalian Genotyping Center of the Marshfield Medical Research Foundation. Marker order and genetic map distances were those provided by the Marshfield Medical Research Foundation. Marker order and genetic map distances were those provided by the Marshfield Medical Research Foundation (research.marshfieldclinic.org genomics/). Inconsistencies of the genotypes with pedigree structure were identified by the Lange and Goradia algorithm (18) as implemented in the PedCheck software (19). Instances that could not be resolved as genotyping errors were considered as missing data.

Statistical analyses
Before genetic linkage analyses, we assessed whether the assumption of normality in the distribution of each lipid trait was violated (20). Triglyceride levels were positively skewed and were therefore log-transformed. LDL particle size, HDL-C, and log triglycerides were adjusted for age, sex, BMI, diabetes, history of smoking, and statin use in the genetic analyses. Genetic and environmental correlations between adjusted lipid traits were estimated by variance decomposition using maximum likelihood methods (21), and the phenotypic correlations between traits were calculated based on genetic and environmental correlations (22). The heritability \( h^2 \) of each trait was calculated as the proportion of the total phenotypic variance attributable to additive genetic effects.

Univariate and bivariate linkage analyses were performed using the S-Plus library Multic, which employs a multivariate variance components approach that is an extension of the univariate approach described by Amos (23) and de Andrade et al. (24). Multipoint identity-by-descent sharing among pairs of relatives was calculated using the SIMWALK2 software program (25). This program estimates multipoint identity-by-descent probabilities using an alternative Markov chain Monte Carlo algorithm to efficiently accommodate large sibships and provides estimates in agreement with deterministic methods.

To test for genetic linkage, a likelihood ratio test (LRT) was used in which the LRT is defined as \( 2 \times 1 \log \) likelihood under the null hypothesis) - \( \log \) likelihood under the alternative hypothesis). Under the null hypothesis, the linked gene parameter(s) are restricted to equal zero (\( \sigma = 0 \) for all \( e \)). For the bivariate linkage analysis, the distribution of the bivariate test that the linked-gene components and covariance are zero is a mixture of \( X_1^2 \), \( X_2^2 \), and \( X_1 X_2 \), as described by Self and Liang (26).

All log of the odds (LOD) scores for the multipoint linkage analyses were calculated from the LRT values as \( LRT/(2 \times \ln(10)) \). For the univariate linkage analyses of LDL particle size, HDL-C, and log triglycerides, we considered multipoint LOD scores of \( \geq 3.00 \) as statistically significant evidence of linkage, scores of \( \geq 2.00 \) as suggestive evidence of linkage, and scores of \( \geq 1.30 \) as tentative evidence of linkage (27). These multipoint LOD score thresholds correspond to genome-wide \( P \) values of \( \leq 0.0001, \leq 0.001, \) and \( \leq 0.007 \), respectively (27). Bivariate linkage analyses were performed for each pairwise combination of the traits. To achieve levels of statistical significance comparable to the univariate linkage thresholds, we considered bivariate LOD scores of \( \geq 4.00 \) as statistically significant evidence of linkage, scores of \( \geq 2.87 \) as suggestive evidence of linkage, and scores of \( \geq 2.06 \) as tentative evidence of linkage. These higher bivariate thresholds were calculated using asymptotic values of a mixture of \( X_1^2 \), \( X_2^2 \), and \( X_1 X_2 \) distribution. We considered a region to have possible pleiotropic effects if the bivariate LOD score was at least 2.66 and the \( P \) value was less than either of the univariate maxima.

RESULTS
The study sample of 1,318 subjects belonged to 674 sibships and included 1,133 sibpairs; there were 312 sibships of size 1, 201 sibships of size 2, and 161 sibships of size 3 or greater. Seventy percent of the subjects were women, 71% were hypertensive, and 18.3% were on lipid-lowering medications (Table 1).

**TABLE 1.** Descriptive characteristics of the subjects (n = 1,318)

| Characteristic | Mean ± SD or (%) | Range |
|---------------|------------------|-------|
| Age (years)   | 63.0 ± 9.5       | 26.4–91.6 |
| Women (%)     | 927 (70.3)       |       |
| BMI (kg/m²)   | 31.5 ± 6.6       | 16.4–60.3 |
| Hypertension  | 1049 (79.0)      |       |
| History of smoking (%) | 534 (40.5) |       |
| LDL particle size (Å) | 268.8 ± 4.9 | 251–285 |
| HDL-C (mg/dl) | 57.4 ± 18.0      | 21.7–175.7 |
| Triglycerides (mg/dl) | 119.0 ± 69.1 | 28.5–813.5 |
| Log triglycerides | 4.66 ± 0.46 | 3.35–6.70 |
| Statin use    | 241 (18.3)       |       |

BMI, body mass index; HDL-C, high density lipoprotein cholesterol. Values shown are means ± SD for quantitative traits or percentages for categorical traits.
Heritability and genetic correlations

LRT results indicated significant heritability ($P < 0.001$) for each of the three lipid traits: LDL particle size, HDL-C, and triglycerides (Table 2). After adjustment for age, sex, BMI, diabetes, history of smoking, and statin use, more than three-quarters of the residual variance in LDL particle size, and more than one-third of the residual variance in log triglycerides was attributable to additive genetic effects (Table 2).

Genetic correlations between the three lipid traits were significantly different from zero ($P < 0.0001$) based on LRT results (Table 2). The genetic correlations between LDL particle size and log triglycerides ($\rho_G = -0.43$) and between HDL-C and log triglycerides ($\rho_G = -0.57$) were negative, whereas the genetic correlation between LDL particle size and HDL-C was positive ($\rho_G = 0.32$).

Linkage analyses

In univariate linkage analyses, there was suggestive evidence of linkage for LDL particle size near D12S1064 on chromosome 12q21 [90.8 centimorgan (cM), LOD = 2.02, $P = 0.0011$] (Table 3, Fig. 1A). Significant evidence of linkage for LDL particle size was observed near D19S589 on chromosome 19q13 (85.3 cM, LOD = 2.02, $P = 0.0006$) (Fig. 1B). Univariate linkage analyses of HDL-C demonstrated tentative evidence of linkage on chromosome 7q35 (159.1 cM, LOD = 1.32, $P = 0.0068$) and 10q21 (81.5 cM, LOD = 1.48, $P = 0.0046$). For log triglycerides, there was tentative evidence of linkage on chromosome 4q21 (104.3 cM, LOD = 1.64, $P = 0.0030$) (Table 3).

Bivariate linkage analyses identified a region near D4S2632 on chromosome 4p15 that may have pleiotropic effects on LDL particle size and HDL-C (52.9 cM, bivariate LOD = 2.06, $P = 0.0069$) (Table 3, Fig. 2A, B). There was suggestive evidence of pleiotropic effects on the pairwise combination of HDL-C and log triglycerides on two chromosomes: chromosome 4q15 (75.9 cM, bivariate LOD = 3.17, $P = 0.0006$) (Fig. 2A, B) and chromosome 16 (91.0 cM, bivariate LOD = 2.29, $P = 0.0042$) (Fig. 2C, D).

**TABLE 2.** Heritabilities (on the diagonal), phenotypic correlations (above the diagonal), and genetic correlations (below the diagonal) of the three lipid traits

| Trait          | LDL Particle Size | HDL-C | Log Triglycerides |
|----------------|-------------------|-------|-------------------|
| LDL particle size | 0.78              | 0.23  | -0.46             |
| HDL-C           | 0.32              | 0.65  | -0.39             |
| Log triglycerides| -0.43             | -0.57 | 0.40              |

Traits were adjusted for age, sex, body mass index, diabetes, smoking status, and statin use. The estimates of heritability and genetic correlations were significant ($P < 0.0001$).

**Discussion**

This study is the first to report heritability and linkage analyses for LDL particle size in African Americans. Numerous analyses have been performed to assess the heritability of LDL particle size in either twin (28, 29) or family studies (30–33). These studies, comprising mostly non-Hispanic whites or Hispanics, found that 30–60% of the variance in LDL particle size was attributable to genetic factors. We found LDL particle size to be significantly heritable in African Americans: 78% of the variance in LDL particle size could be attributed to additive genetic effects.

Although linkage scans for genetic loci affecting LDL particle size have been performed in several previous studies (Table 4), none of these included African Americans. In this study of African American sibships ascertained on the basis of hypertension, we found significant evidence of linkage (LOD = 3.07) on chromosome 19q13 (LOD-1 interval: 73.3–96.7 cM) (Fig. 1B). Allayee et al. (34) found tentative evidence for linkage for peak LDL particle size in this region of chromosome 19q13 (78.1 cM, LOD = 1.6) in Dutch Caucasian families. These results

**TABLE 3.** Maximum multipoint LOD scores (and positions in cM) and P values for the univariate and bivariate linkage analyses LDL particle size, HDL-C, and log triglycerides

| Chromosome | LDL Size     | HDL-C       | Log Triglycerides | LDL Size and HDL-C | LDL Size and Log Triglycerides | HDL-C and Log Triglycerides |
|------------|--------------|-------------|-------------------|---------------------|-------------------------------|-----------------------------|
| 4          | 0.52 (176.10)| 0.68 (65.93)| 0.25 (167.55)     | 2.06 (52.94)        | 0.72 (206.98)                 | 3.17 (75.90)                |
| 7          | 0.0608       | 0.0383      | 0.1399            | 0.0069              | 0.1237                        | 0.0006                      |
| 8          | 0.97 (64.52) | 1.32 (159.06)| 1.16 (121.54)    | 1.18 (155.10)       | 1.33 (122.39)                 | 1.55 (120.70)               |
| 9          | 0.0171       | 0.0068      | 0.0104            | 0.0455              | 0.0334                        | 0.0296                      |
| 10         | 0.059 (94.08)| 1.12 (158.37)| 1.64 (104.26)   | 0.85 (161.86)       | 1.33 (102.56)                 | 1.87 (109.34)               |
| 11         | 0.0515       | 0.0116      | 0.003             | 0.091               | 0.0326                        | 0.0105                      |
| 12         | 0.48 (28.31) | 1.48 (81.53)| 0.16 (59.03)     | 1.26 (13.82)        | 0.48 (120.97)                 | 1.61 (82.30)                |
| 13         | 0.0696       | 0.0046      | 0.1936            | 0.0388              | 0.2064                        | 0.0182                      |
| 14         | 2.02 (90.80) | 0.62 (48.70)| 0.64 (19.68)     | 2.07 (90.80)        | 2.09 (89.11)                  | 1.10 (51.22)                |
| 15         | 0.0011       | 0.0457      | 0.0434            | 0.0068              | 0.0064                        | 0.0541                      |
| 16         | 0.06 (100.39)| 1.15 (95.56)| 0.15 (10.56)     | 0.82 (95.28)        | 0.09 (10.36)                  | 2.29 (91.02)                |
| 17         | 0.2974       | 0.0107      | 0.2011            | 0.0986              | 0.4883                        | 0.0042                      |
| 18         | 3.07 (85.26) | 0.06 (23.96)| 0.21 (9.84)      | 2.97 (85.26)        | 3.06 (84.46)                  | 0.29 (9.84)                 |
| 19         | 0.0001       | 0.2942      | 0.1639            | 0.001               | 0.0008                        | 0.3026                      |

cm, centimorgan; LOD, log of the odds. Variables were adjusted for age, sex, BMI, diabetes, smoking, and statin use. Positions are distances from $p$ terminus in cm. The following LOD scores are highlighted in boldface: $\geq 1.3$ in univariate linkage analyses, and $\geq 2.06$ in bivariate linkage analyses with the $P$ value lower than for either of the univariate maxima. Data from chromosomes without any LOD scores of $\geq 1.3$ in univariate or $\geq 2.06$ in bivariate linkage analyses are not shown.
suggest the presence of a quantitative trait locus on chromosome 19q13 that influences LDL particle size. The linkage peak for LDL particle size on chromosome 12q21 (LOD = 2.02) (Fig. 1A) appears to be novel and has not been reported previously. Univariate linkage analyses for HDL-C and log triglycerides yielded only weak linkage signals (LOD < 2.0).

Bivariate linkage analyses may provide greater statistical power to identify genetic loci with effects too small to be detected in single-trait analyses (35). Using such an approach, we previously found a locus with pleiotropic effects on LDL particle size and HDL-C on chromosome 1 (LOD = 4.48, 4 cM) in non-Hispanic whites participating in the GENOA study (17). In the present study, bivariate analysis of pairwise combinations of the three lipid traits revealed three genomic loci that may have pleiotropic effects on these traits (Fig. 2B, D). In the loci identified, the univariate LOD scores were not suggestive of linkage to any of the individual traits, but the bivariate analyses yielded a higher LOD score with a lower P-value than for any of the univariate maxima. Given that common metabolic pathways influence these traits, a gene with pleiotropic effects on the traits, rather than tightly linked genes, is likely to be responsible for the linkage signal of the bivariate phenotype.

An overlap of the bivariate LDL particle size-HDL-C and HDL-C-log triglyceride linkage signals was noted in the chromosome 4q13 region, raising the possibility that the region may have a pleiotropic effect on all three traits. We performed trivariate linkage analyses to assess whether a quantitative trait locus in the region influenced the three lipid traits. A significant increase in the LOD score was not noted, suggesting the presence of two separate loci in-

![Fig. 1. Results of univariate multipoint variance component linkage analyses for LDL particle size on the chromosome 12 (A) and chromosome 19 (B). Markers adjacent to the log of the odds-1 (LOD-1) interval are shown along the top of each plot. cM, centimorgan.](image)

![Fig. 2. Results of univariate (A, C) and bivariate (B, D) multipoint variance component linkage analyses for the three lipid traits on chromosome 4 (A, B) and chromosome 16 (C, D). Markers adjacent to the LOD-1 interval are shown along the top of each plot. HDL-C, high density lipoprotein cholesterol; TG, triglycerides.](image)
fluencing the LDL particle size-HDL-C and the HDL-C-log triglyceride traits (analyses not shown).

We attempted to identify potential positional candidate genes for the lipid traits in the LOD-1 regions of the linkage signals (i.e., LOD ≥ 1.3 in univariate and LOD ≥ 2.06 in bivariate linkage analyses). Of the genes suggested by previous linkage or association studies to influence LDL particle size, an apolipoprotein gene cluster (APOE/C1/C4/C2) was noted to be adjacent to the linkage peak on chromosome 19q13. Two important genes involved in lipid metabolism, CETP (cholesteryl ester transfer protein; chromosome 16q21) and LCAT (lecithin-cholesterol acyl-transferase; chromosome 16q22), were present under the HDL-C-log triglyceride bivariate signal on chromosome 16q22. We did not find any obvious candidate genes under the remaining linkage signals.

We also performed a functional network analysis to identify the interaction of known candidate genes for LDL particle size with genes under the linkage signals, using the Ingenuity® Pathway Analysis tool (www.ingenuity.com) (see supplementary figure). Ingenuity® Pathway Analysis is a knowledge-based discovery tool and the largest curated database of previously published findings on mammalian biology (36). Three genes, CLEC11A (C-type lectin domain family 11, member A), KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog), and KITLG (KIT ligand), under the linkage signals on chromosome 19q13, chromosome 4p15, and chromosome 12q21, respectively, interact with the LDL receptor gene (LDLR) shown previously to be a positional candidate gene for LDL particle size (37). In this network, CLEC11A increases the phosphorylation of KIT (38), there is a protein-protein interaction between KIT and KITLG (39), and in turn, KITLG can increase the expression of LDLR (40). These interactions, by affecting LDLR, may influence LDL particle size, although this needs confirmation in additional studies.

In conclusion, our findings indicate the presence of a quantitative trait locus on chromosome 19 that influences LDL particle size in African American sibships ascertained based on hypertension. In addition, there is suggestive evidence for a locus on chromosome 12 that influences this trait and a locus on chromosome 4 that may have pleiotropic effects on LDL particle size and HDL-C. Linkage analysis of LDL particle size and correlated lipid traits is a step toward identifying genetic variants that influence coronary heart disease susceptibility in African Americans.14

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