Meta-analysis of genome-wide linkage studies for quantitative lipid traits in African Americans

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Genetic influences on lipid traits have been suggested by numerous studies. In addition to heritability studies, over 50 genome scans have been performed to identify regions of linkage for quantitative lipid levels. Five of these scans have been performed in African Americans (four univariate and one bivariate linkage analysis), but with results that have been largely inconclusive. Linkage analyses are often limited by both sample size and heterogeneity, which may lead to nominal LOD scores or lack of evidence for linkage; the use of meta-analysis to combine linkage results from populations with similar ethnic backgrounds may help overcome some of these limitations. Thus, we performed a meta-analysis using data from four genome scans conducted in African American families to identify chromosomal regions showing evidence of linkage for total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL). Significant evidence (i.e. \( P < 0.00042 \)) for linkage was found for LDL on chromosome 1q32.1–q41 (\( P_{\text{weighted}} = 0.00014 \) and \( P_{\text{unweighted}} = 0.00007 \)) and 1q41–q44 (\( P_{\text{weighted}} = 0.00017 \) and \( P_{\text{unweighted}} = 0.00014 \)). We found suggestive evidence (i.e. \( P < 0.00847 \)) for TG on 16p12.1–q11.2 and for HDL on 4p15.1–p11. We also assessed heterogeneity between studies and found significant evidence for low heterogeneity for both regions on chromosome 1q (\( P = 0.0300 \) and \( P = 0.0279 \), respectively) for LDL and chromosome 16 (\( P = 0.0429 \)) for TG. Statistically significant evidence for linkage and low heterogeneity on chromosome 1q therefore suggest that this region may harbor a gene underlying the inheritance of LDL in African Americans.

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in the USA with a total economic burden of approximately $142 billion (1). Major risk factors for CHD include hypertension (2,3) and abnormal levels of circulating lipids (4). Diet, exercise, tobacco use and alcohol consumption are among the most common, modifiable environmental agents affecting lipid levels (1,5–7); however, genetic factors are also well-recognized determinants of dyslipidemia. Twin (8,9) and pedigree (9,10) studies have found that lipid levels show significant evidence of heritability in the general population and genetic variants underlying numerous monogenic lipid-related disorders have been identified (11). Taken together, these findings suggest that lipid levels may be influenced by genetic factors. Identification of such

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factors may lead to improved treatment and prevention strategies for dyslipidemia and CHD.

To date, over 50 genetic linkage studies have been performed in the analysis of quantitative lipid traits with results showing evidence for linkage on every chromosome (12). Of these linkage studies, five have been performed in African American populations with different results across studies (13–17). Two studies utilized data from the Hypertension Genetic Epidemiology Network (HyperGEN) study (13,17), including one which identified the highest LOD score on chromosome 20 for triglycerides (TG) (LOD = 2.77) (13) and another which involved bivariate analysis of TG and low density lipoprotein cholesterol (LDL) where the highest LOD scores were found on chromosomes 6 and 21 (LOD = 2.0 in both regions) (17). The maximum LOD score observed in the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) study was found on chromosome 1q for LDL (14), whereas a fourth study found evidence for linkage on chromosomes 13 and 16 for TG in individuals ascertained for obesity (15). More recently, we have observed suggestive evidence of linkage for total cholesterol (TC) on chromosome 19 in African American families from the Genetics of NIDDM (GENNID) study (16).

Much of the disparity in linkage findings can be attributed to locus heterogeneity, utilization of different study designs, dissimilar methods of ascertainment and statistical analyses and, oftentimes, a small sample size. Combining results from independent studies may help provide a more powerful method of testing linkage, especially when a locus contributes a weak effect in each study, possibly due to small sample size.

To increase the power to detect linkage for lipid traits where individual studies may have weak effects and to compensate for the effects of heterogeneity, we did a meta-analysis of genome scans performed in African Americans. Additionally, owing to possible presence of heterogeneity as evidenced by different results across the African American genome scans, tests were performed to identify specific chromosomal regions showing significant evidence of low or high heterogeneity. To our knowledge, this is the first meta-analysis of linkage results for quantitative lipid traits measured in African Americans.

RESULTS

Table 1 describes the characteristics of the participants from each study used in the meta-analysis. Five genome scans for lipid traits have been performed in African American families; however, one of these (17), a bivariate analysis, overlapped in study population with a previous report (13), thus only data from the original study (13) were used in the meta-analysis. A genome scan meta-analysis (GSMA) (18,19) was performed for the quantitative lipid traits LDL (three studies), high density lipoprotein cholesterol (HDL) (two studies), TG (four studies) and TC (two studies). Table 2 describes the results obtained in the GSMA showing chromosomal regions, P-values and LOD scores for regions with significant or suggestive evidence for linkage. Significant evidence of linkage for LDL was observed in two bins (1q32.1–q41 and 1q41–q44) for both unweighted data and data weighted according to the number of individuals genotyped in each study population. The results for LDL are shown graphically in Figure 1 with summed ranks plotted against the bin number. In addition, two regions showed evidence for suggestive linkage: chromosome 16 for TG and chromosome 4 for HDL. Several regions had both Pord ≤ 0.05 and Psumrnk ≤ 0.05: 3p26.3–p23 and 6p25.3–p22.2 for HDL (weighted), 1p21.1–q11, 3p12.3–q12.3 and 4p15.1–q11 for TG (weighted) and 12q23.3–q24.3 for TG (unweighted). No bins met the criteria of significance (as described in Materials and Methods) in the analysis of TC.

Significant/suggestive P-values were observed for regions with the highest LOD score in only two of the four individual studies: in the obesity-ascertained study, the highest LOD score (LOD = 3.66) was observed for TG on chromosome 16 with a GSMA Psumrnk (weighted) = 0.00245 and in the HERITAGE study, the highest LOD score of 2.1 was observed for LDL on chromosome 1 with a Psumrnk (weighted) = 0.00014 (Table 2). In contrast, in the HyperGEN study, the highest LOD score was observed for TG on chromosome 20 and the Psumrnk (weighted) = 0.08541 and in the GENNID study, the highest LOD score was observed for TC on chromosome 19 and the Psumrnk (weighted) = 0.34300.

We next evaluated evidence for heterogeneity between study groups for the 118 bins defined in the GSMA (see Materials and Methods). Tests for both high (P ≥ 0.95) and low (P ≤ 0.05) heterogeneity were performed using the program HEGESMA (20,21). Three of the regions showing evidence for linkage in the GSMA also showed significant evidence of low heterogeneity (P ≤ 0.05) (i.e. bins 1q32.1–q41 and 1q41–q44 for LDL and 16p12.1–q11.2 for TG) (Table 3). However, the region identified for HDL (bin 4p15.1–p11) did not show significant evidence of low heterogeneity (Phet_unweighted = 0.2200 and Phet_weighted = 0.2270). In contrast, several bins not identified in the GSMA showed significant evidence of low heterogeneity in the HEGESMA analysis: i.e. chromosome 16 for LDL, chromosomes 6 and 9 for HDL and chromosomes 1, 2, 10, 11 and 19 for TG (Table 3). It is worth noting that bins showing significant evidence of low heterogeneity may be affected by the rank assigned. Upon adjustment for rank, the number of bins showing significant evidence of low heterogeneity was reduced from 12 to four bins: one bin each for LDL (10p12.1–q11.2) and HDL (6p22.2–p21.2) and two bins for TG (1q41–q44 and 2q12.1–q21.3) still showed significant evidence of low heterogeneity (Table 3). In the test for high heterogeneity (P ≥ 0.95), significant evidence was observed in eight bins for HDL, 11 bins for LDL, 10 bins for TG and eight bins for TC. However, none of these bins showed significant evidence of high heterogeneity upon adjustment for rank (data not shown). No bins identified in the GSMA showing evidence for linkage had significant evidence of high heterogeneity.

DISCUSSION

To date, only four univariate genome scans have been performed in the analysis of quantitative lipid traits in African Americans, and all have yielded different results. Here, we
Table 1. Characteristics of participants from the studies used in the GMSA

<table>
<thead>
<tr>
<th>Study population</th>
<th>HyperGEN (13)</th>
<th>HERITAGE (14)</th>
<th>GENNID (16)</th>
<th>Obesity ascertained (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1027</td>
<td>277</td>
<td>240</td>
<td>276</td>
</tr>
<tr>
<td>LDLa mean (mg/dl)</td>
<td>121.1 ± 36.7</td>
<td>111.2 ± 30.0</td>
<td>125.0 ± 36.0</td>
<td>—</td>
</tr>
<tr>
<td>TG mean (mg/dl)</td>
<td>98.2 ± 51.8</td>
<td>91.2 ± 53.1</td>
<td>93.0 ± 51.2</td>
<td>140.9 ± 78.9</td>
</tr>
<tr>
<td>TC mean (mg/dl)</td>
<td>196.3 ± 39.8</td>
<td>—</td>
<td>191.6 ± 38.9</td>
<td>—</td>
</tr>
<tr>
<td>HDL mean (mg/dl)</td>
<td>52.4 ± 14.9</td>
<td>—</td>
<td>46.1 ± 11.6</td>
<td>—</td>
</tr>
<tr>
<td>Study design</td>
<td>Sib-pairs</td>
<td>Sib-pairs</td>
<td>Nuclear families</td>
<td>Nuclear families</td>
</tr>
<tr>
<td>(program used)</td>
<td>(GENEHUNTER)e (39)</td>
<td>(SEGPATH)f (40)</td>
<td>(GENEHUNTER)e (39)</td>
<td>(MERLIN_regress)g (41)</td>
</tr>
<tr>
<td>Number of markers</td>
<td>391</td>
<td>654</td>
<td>371</td>
<td>382</td>
</tr>
</tbody>
</table>

Lipid levels given are prior to transformation and adjustment for covariates. References for the studies and programs used are given in parentheses.

aNumber of participants in the study.

bConcentration ± SD.

cmg/dl, milligrams per deciliter.

dResults were not available.

eGENEHUNTER: Variance components and identity-by-descent (IBD) probabilities are estimated for sib-pairs/nuclear families.

fSEGPATH: Variance components method is an extension of a path-analysis model of family member resemblance.

gMERLIN_regress: In this method, IBD is regressed onto the squared differences and sums of trait values for relative pairs.

<table>
<thead>
<tr>
<th>Chromosomal location</th>
<th>Bin number</th>
<th>Trait</th>
<th>HyperGEN</th>
<th>HERITAGE</th>
<th>GENNID</th>
<th>Obesity-ascertained</th>
<th>GSMA (Psumrnk)</th>
<th>GSMA (Psumrnk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q32.1–q41</td>
<td>9</td>
<td>LDL</td>
<td>1.11</td>
<td>2.07</td>
<td>1.45</td>
<td>—</td>
<td>0.00007d</td>
<td>0.00014d</td>
</tr>
<tr>
<td>4p14–q44</td>
<td>10</td>
<td>LDL</td>
<td>1.12</td>
<td>1.53</td>
<td>1.12</td>
<td>—</td>
<td>0.00004d</td>
<td>0.00017d</td>
</tr>
<tr>
<td>16p12.1–q11.2</td>
<td>98</td>
<td>TG</td>
<td>0.68</td>
<td>0.30</td>
<td>0.52</td>
<td>3.66</td>
<td>0.00092e</td>
<td>0.00247e</td>
</tr>
<tr>
<td>4p15.1–p11</td>
<td>29</td>
<td>HDL</td>
<td>1.57</td>
<td>—</td>
<td>0.53</td>
<td>—</td>
<td>0.01357</td>
<td>0.00807y</td>
</tr>
</tbody>
</table>

The cytogenetic location, LOD scores for individual studies and GSMA Psumrnk are given for the four regions identified. Results for unweighted and weighted analyses are shown.

Psumrnk for unweighted analysis.

Psumrnk for weighted analysis.

Results were not available.

Significant evidence (Bonferroni correction: Psumrnk < 0.00042).

Suggestive evidence (Bonferroni correction: Psumrnk < 0.00847).

report results from the first meta-analysis for quantitative lipid traits conducted in African Americans. Significant results were observed on chromosome 1q (1q32.1–q41: Pweighted = 0.00014; Punweighted = 0.00007) and 4p14–q44: Pweighted = 0.00017; Punweighted = 0.00014) in a region showing only modest LOD scores in the three individual studies used in the analysis of LDL levels (LOD = 1.11, 2.07 and 1.45 for the HyperGEN, HERITAGE and GENNID studies, respectively) (13,14,16). In addition to nominal evidence in all three African American studies used in the meta-analysis, this region has also been identified for LDL (LOD = 2.5) in a combined sample of randomly and obesity-ascertained Caucasian families (22). The HERITAGE study, used in the current meta-analysis, also identified this region for the phenotype LDL–apolipoproteinB (LOD = 3.29) (14).

Suggestive evidence for linkage in the GSMA was observed for TG on chromosome 16. This region overlaps a locus identified for TG (analyzed as a qualitative trait) in Dutch and Finnish families (23). Additional studies have found evidence for linkage for various quantitative lipid traits, including LDL particle size, HDL, TG/HDL and a bivariate analysis of TC and TG on 16q (24–27), suggesting possible pleiotropic effects of a gene in this region. Suggestive evidence was also observed on chromosome 4p15.1–p11 for HDL. Two studies have shown evidence for linkage on chromosome 4p: in the analysis of LDL peak particle diameter as part of the Quebec Family Study (28) and TG levels in families ascertained for familial combined hyperlipidemia (29).

There are several genes mapping to the region with significant evidence for linkage on chromosome 1q that could be considered potential candidates for lipid metabolism. Here, we describe two potential candidate genes. One candidate is the HSD11B1 (11-beta-hydroxysteroid dehydrogenase, Type 1) gene, which has been implicated in lipid and lipoprotein metabolism. Mice overexpressing HSD11B1 develop hyperlipidemia (30), whereas HSD11B1 knockout mice exhibit increased lipid catabolism (31). Another candidate is the LBR (lamin B Receptor) gene, which belongs to the sterol reductase family and may play a role in cholesterol biosynthesis (32). LBR is homologous to the delta-7 sterol reductase gene, which functions in sterol metabolism (33).
scans were on different chromosomes (13–16), suggesting the possibility that heterogeneity might be present. To test for the presence of heterogeneity, P-values were estimated to detect either high ($P_{\text{het}}/C_{21} > 0.95$) or low ($P_{\text{het}}/C_{20} < 0.05$) heterogeneity. Several regions showed significant evidence for high heterogeneity. However, as described in Materials and Methods, the rank of the bin may affect the result. Therefore, for bins showing significance, we repeated the analysis after adjustment for rank. No bins showed significant evidence for high heterogeneity upon adjustment for rank. These results suggest that a gene underlying the inheritance of lipid traits may be present in the same region across all studies. However, it is important to note that failure to reject the null hypothesis may be due to low power, because only four studies were used in this analysis.

Tests for low heterogeneity resulted in several regions showing significance. Importantly, regions identified in the GSMA analysis, i.e. the two regions on chromosome 1q for LDL and one bin on chromosome 16 for TG, showed significantly low P-values ($P_{\text{het}} < 0.05$). However, results were not significant upon adjustment for rank. In contrast, significant evidence of low heterogeneity was not observed on chromosome 4 for HDL, both prior to and upon adjustment for rank. However, it would still be important to analyze this region further because suggestive evidence for linkage was observed in the GSMA, although higher priority should be given to the regions identified on chromosomes 1 and 16.

Taken together, the results from tests for high and low heterogeneity suggest the presence of either modest heterogeneity or low heterogeneity between the populations used in the meta-analysis.

Regarding adjustment for rank, the authors of HEGESMA (20) note that in the analysis of ranks only ±2 from the bin of interest (see Materials and Methods), the null distribution may not be normally distributed. Furthermore, when average ranks are very high, a large number of permutations and computational power may be necessary to accurately assess the P-value of these bins (20,21). Therefore, significance prior to adjustment for rank cannot be discounted, as observed for chromosomes 1 and 16 for LDL and TG, respectively.

We recognize that there are several factors to consider concerning the individual studies used in the meta-analysis. First, different ascertainment schemes were used for each of the studies which might result in discrepant results. However, despite different ascertainment schemes, common regions of linkage were identified, as evidenced by the chromosome 1q linkage, which would suggest common genetic influences across the different populations. Another factor to consider is the different sample sizes for each study. The results presented in Tables 2 and 3 show only small differences in the results for weighted and unweighted analyses, suggesting a small role of sample size in the results of the meta-analysis.

**Figure 1.** Summed ranks in relation to bin number in the analysis of LDL. Summed ranks are plotted against the GSMA bin number. There are a total of 118 bins. Vertical lines divide the bins according to chromosome. Two bins on chromosome 1 showed significant evidence as indicated.
In summary, significant evidence for linkage and low heterogeneity for LDL was observed on chromosome 1q in African Americans. These results show that meta-analysis is a useful tool when individual effects are weak, specifically because only nominal evidence for linkage to 1q was observed in each of the individual linkage studies. Together, these findings suggest that 1q may be an important locus for control of LDL levels in African Americans.

MATERIALS AND METHODS

Study participants

To date, five variance components genome scans have been performed for quantitative lipid traits in African Americans, two of which utilized data from the same population (13,17). Characteristics of participants from the four populations used in the present study are given in Table 1. Details of the study populations and methods used in each study have been previously described (13–17,34–38).

Briefly, the Genetics of NIDDM (GENNID) study was initiated to establish a repository of families ascertainment by the presence of at least two siblings with type 2 diabetes. Lipid levels were measured in Caucasian, African American, Hispanic and Japanese American families from 13 study centers (35). For the current study, linkage results for the lipid traits TG, TC, LDL and HDL measured in 240 individuals (79 males and 161 females) from 59 African American families with 276 individuals. The families were ascertained by the presence of an obese proband with BMI $\geq 40$ kg/m$^2$ and at least one sibling with BMI $\geq 30$ kg/m$^2$. Covariate-adjusted lipid levels were subject to linkage analysis using the program MERLIN_regress (41).

Statistical analysis

The GSMA program (18,19) was used to assess evidence for linkage utilizing results from analyses of TG, LDL, TC and HDL. Two studies used marker maps with Marshfield map distances. For the two studies that did not, distances were converted to Marshfield map distances by inserting the marker names in the Marshfield database (http://research.marshfield-clinic.org/genetics/). These were then used to create 118 bins of $\sim 30$ cM across the genome (ranging from 26.1 to 33 cM). The highest LOD score for a bin in each study was identified and using these, ranks were given to each bin separately in each study, with the highest LOD score having the highest rank (i.e. 118, corresponding to the number of bins). The ranks were then summed across studies and used to estimate two $P$-values (Pord and Psqmrnk) when combining the results of all studies. Psqmrnk is the probability of observing
a bin’s summed rank by chance, i.e. the proportion of replicates with summed rank equal to or greater than that observed. \( P_{ord} \) is the probability of observing a given bin’s summed rank in that particular bin (across all replicates) by chance, i.e. the proportion of replicates for a given bin number with summed rank equal to or greater than that observed in the region with the same bin number (19). 100 000 permutations were used for this purpose.

Both unweighted and weighted GSMA analyses were performed. The data were weighted according to the number of individuals genotyped in the respective study populations, as recommended by the authors of GSMA [weight = \( \sqrt{N} \) (genotyped individuals)/\( \sqrt{N} \) (genotyped individuals) over all studies] where \( N = 1027, 277, 240 \) and \( 276 \) for the HyperGEN, HERITAGE, GENNID and obesity-ascertained studies, respectively (13–16).

Significance of the \( P \)-values estimated in the analysis was assessed in three ways (19): (i) using a Bonferroni correction, 0.05/118 (giving \( P_{sumrnk} < 0.00042 \)) was used to assess significant evidence [equivalent to Lander and Kruglyak’s (42) definition of one false positive per 20 meta-analyses], (ii) suggestive evidence (one false positive per meta-analysis) giving \( P_{sumrnk} < 0.00847 \) and (iii) both \( P_{sumrnk} \leq 0.05 \) and \( P_{ord} \leq 0.05 \).

A test for heterogeneity was performed using the program Heterogeneity and Genome Search Meta-Analysis (HEGESMA) (20,21). This program utilizes the ranks and weights assigned to each study as implemented in GSMA. The extent of heterogeneity was estimated by the \( \chi^2 \) statistic \( \chi^2 = \sum w_i (R_i - \bar{R})^2 \) (21,43). In this equation, the sum is over all studies, \( w_i \) is the weight for study \( i \), \( R_i \) the rank for study \( i \) and \( \bar{R} \) the mean rank across all studies. Both weighted and unweighted analyses were performed. The ranks for each study were randomly permuted from which \( \chi^2 \) was estimated. 10 000 permutations were performed, and a null distribution of \( \chi^2 \) was used to estimate significance levels for observing heterogeneity. \( P \leq 0.05 \) and \( P \geq 0.95 \) were used to assess significant evidence of low and high heterogeneity, respectively (20,21). In addition, \( P \)-values for bins with significant evidence of low/high heterogeneity were further analyzed to test whether the specific bin rank affected heterogeneity. For this, only the null distribution of \( \chi^2 \) for bins \( \pm 2 \) the bin of interest was used to test for significance as implemented in HEGESMA.

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