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A genome wide quantitative trait linkage analysis for serum lipids in type 2 diabetes in an African population

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Abstract

Lipid abnormalities are strongly linked with coronary heart disease and are common in type 2 diabetes. However, little is known about the genetic determinants of serum lipids in African populations. An autosomal genome scan was performed for linkage to five plasma lipid phenotypes (total cholesterol, triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and VLDL-cholesterol (VLDL-C)) in the Africa–America Diabetes Mellitus (AADM) study. Two hundred and ninety-five affected sibling pairs with type 2 diabetes mellitus enrolled from Ghana and Nigeria were genotyped for 390 microsatellite markers with an average inter-marker distance of 9 cM. Multipoint variance components linkage analysis showed that HDL-C had a LOD score of 4.34 near marker D7S3061 and 3.00 near marker D7S513. Some clustering of linkage evidence to several lipid phenotypes was observed on chromosomes 5 (LDL-C, total cholesterol, VLDL-C), chromosome 7 (HDL-C, TG) and chromosome 19 (total cholesterol, LDL-C, TG). Principal component analysis of the five phenotypes yielded two factors, one (TG, HDL-C and VLDL) of which was linked to QTLs on chromosomes 2, 5 and 7, while the other (total cholesterol and LDL-C) was linked to a different set of QTLs on chromosomes 2, 5 and 18. Several of these regions have been reported to be linked to lipids in other studies. Follow up investigations are warranted in view of the central role serum lipids play in the aetiopathogenesis of cardiovascular disease.

Keywords: Genome scan; Lipids; Cholesterol; Type 2 diabetes; Africa

1. Introduction

Serum lipids play a major role in the pathogenesis of coronary heart disease. It is now well established that the risk of CHD is positively correlated with serums levels of total cholesterol, triglycerides (TG) and LDL-cholesterol (LDL-C) and is inversely correlated with HDL-cholesterol (HDL-C) levels [1–6]. More subtle abnormalities, such as particle size, have also been shown to be risk factors for CHD. For example, LDL particle size has been shown to be associated with the risk of CHD, with small LDL particles being con-

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sidered a component of an atherogenic lipoprotein phenotype [7,8]. Due to the important role played by dyslipidaemia in CHD, the Third Adult Treatment Panel Guidelines of the US National Cholesterol Education Program (ATP III) recommended a full fasting lipoprotein profile to include total cholesterol, LDL-C, HDL-C and triglyceride levels as the initial lipid measurement in all individuals for CHD risk assessment [9]. Lipid abnormalities are known to be more common among individuals with type 2 diabetes mellitus (T2DM) and their relatives [10–12]. These lipid abnormalities, including high triglyceride and low HDL-C, predate the onset of glucose intolerance [13] and further increase the risk of CHD in this population subgroup. Therefore, detection and control of dyslipidaemia in this specific group can reduce myocardial infarction, coronary deaths and overall mortality in T2DM [14].

Several intermediate measures of lipid metabolism (including total cholesterol, TG, HDL-C and LDL-C) have been shown to have a significant genetic component with estimates of heritability ranging between 30% and 80% [15–17]. While numerous candidate genes have been tested for linkage and/or association to these traits, most of the known candidate genes explain very little of the variation in these lipid measures. Increasingly, genome scans are being used to investigate the issue further since it is likely that several (or many) genes of small effect influence serum lipid levels. Because genome scans make no a priori assumptions about the number and location of these genes, there is a greater likelihood that they will shed more light on the genomic regions influencing the variation of these lipid measures.

Various epidemiological studies conducted over the last three decades suggest that the serum lipid profiles of many populations in sub Saharan Africa differ substantially from what is known of other geographical populations. For example, studies in Nigeria, Ghana, Zimbabwe and other countries in the region show lower levels of total cholesterol, triglycerides and LDL-C with higher levels of HDL-C when compared with populations of Europe and North America [18–21]. However, little is known about the genetic determinants of serum lipid levels in African populations. The few candidate gene studies that have been conducted showed that polymorphisms influencing lipid levels do exist in African populations. For example, a recent study found that several apoD polymorphisms, some unique to African populations, were associated with various lipid measures [22]. However, to our knowledge, no genome scan has been done for quantitative trait loci (QTL) linked to serum lipids in African population. In the present study, we report the findings of a genome scan for lipids conducted in the Africa–America Diabetes (AADM) Mellitus Study. We investigate linkage to five serum lipid measures: total cholesterol, triglycerides, HDC-C, LDL-C and VLDL-C. In addition, we construct composite phenotypes using principal components analysis and use these as traits in a second set of linkage analyses. We decided on this strategy because it is the strategy most likely to detect genomic regions that are linked to each phenotype, while at the same time identifying regions that are linked to two or more phenotypes (i.e. genomic regions with pleiotropic effects). Finally, we compare the areas of suggestive or significant linkage found in this study, which have been reported in other geographic populations.

2. Subjects and methods

The participants in this study were all enrolled from the Africa–America Diabetes Study, which has been described more fully elsewhere [23]. The protocol was approved by the institutional review board (IRB) of each participating institution and written informed consent was obtained from each participant.

2.1. Enrollment procedures

The design of the AADM study is that of an affected sib pair (ASP) study with both siblings having T2DM. Briefly, participants were enrolled from three centers in Nigeria (Enugu, Ibadan and Lagos) and two centers in Ghana (Kumasi and Accra). Eligible probands were required to: be older than 25 years at the time of diagnosis of type 2 diabetes, have at least one full sibling with T2DM, not have classical features of type 1 diabetes (i.e., insulin dependence, repeated episodes of ketoacidosis), have no cases of type 1 diabetes in first degree relatives and have no more than one parent who is a known diabetic patient. The diagnosis of diabetes was based on the America Diabetes Association (1999) criteria [24]. A clinic examination was conducted that included a medical history, anthropometric measurements and blood sampling. Weight was measured in light clothes on an electronic scale to the nearest 0.1 kg, and height was measured with a stadiometer to the nearest 0.1 cm. The other clinical measurements done have been described elsewhere [23]. Body mass index (BMI) was computed as weight in kg divided by the square of the height in metres. Body composition was estimated using bioelectric impedance analysis (BIA). All BIA measurements were made using a single-frequency (50 kHz) battery-operated bioimpedance analyzer (model BIA 101Q; RJL Systems Inc., Clinton Township, MI, USA). From the measured resistance, impedance was calculated and then total body water, fat-free mass (FFM) and fat mass (FM) were subsequently computed using validated population-specific equations [25]. Percent body fat (PBF) was calculated as (fat mass/weight) $\times$ 100.

2.2. Measurement of serum lipids

Lipid measurements were done on samples obtained from participants after an overnight fast of at least 8 h. Total cholesterol and TG were determined enzymatically on an Abbott Spectrum Multichromatic Analyzer—using methods, which are standardized to in-house Reference Methods and to the Centers for Disease Control Reference Methods. Prepara-

tions of HDL-C assay were obtained by the treatment of whole plasma with dextran sulfate-magnesium (MW 50,000) followed by centrifugation in the microfuge. This precipitates the lipid-rich particles of VLDL and LDL, leaving HDL in the supernate. Supernates were screened for turbidity and filtered, if necessary, to remove particles that can interfere with the accuracy of the assay. LDL-cholesterol was estimated by the Derived Beta Quantification method which utilizes the Friedewald algorithm: LDL = total cholesterol − HDL − TG/5. Performance in assay of total cholesterol and HDL-cholesterol was consistent with an intra-assay coefficient of variation (CV) < 1.5% and <3.0% for triglycerides.

2.3. Genotyping

Genotyping was done at the Center for Inherited Disease Research (CIDR). The CIDR marker set is composed primarily of trinucleotide and tetranucleotide repeats and consists of 392 primer pairs with average spacing of 8.9 cM throughout the genome. There are no gaps in the map larger than 18 cM. The average marker heterozygosity is 0.76. Approximately 10% of the marker loci are different between the current CIDR marker set and the Marshfield Genetics screening set Version 8. Almost all reverse primer sequences have been modified from the Version 8 sequences in order to reduce '+A' artifacts. The resulting PCR products are sized using a capillary sequencing platform. Data for the markers are generated with 218 PCR reactions (41 triplex reactions, 92 duplex reactions and 85 single reactions). Each primer pair has undergone extensive optimization to improve performance and reliability.

For this study, 390 short tandem repeat markers were genotyped for an average sex-equal distance of 9 cM and with no gaps greater than 18 cM. Error rate was 0.1% per genotype. Inconsistency rate was 0.11%. Extensive quality checks were carried out to verify consistency of marker genotyping and stated pedigree relationships. First, we used the 390 markers to check pedigree errors by means of the RELTEST program in statistical analysis for genetic epidemiology (SAGE) Release 4.0, which uses a likelihood method to check the degree of biological relatedness for each sib-pair and classifies the biology relationship for each sib pair. Then, PEDCHECK [26] was used to check for Mendelian inconsistencies. The errors identified in PEDCHECK were assumed to have occurred in the genotyping process and the associated markers were set to missing among the appropriate pedigree members. Hardy–Weinberg equilibrium at each locus was assessed by the X^2-test.

2.4. Data analysis

Descriptive statistics were calculated using Stata Version 8 (Stata Corp, College Station, TX). Because of the sensitivity of the variance components method to assumptions of normality, we first examined the distribution of the values of each trait. Of the five traits studied, only total cholesterol was normally distributed. The other four were not and were transformed to normality before analysis as follows: TG (square root transformation), HDL-C (log-transformation), LDL-C (log-transformation) and VLDL (inverse square root transformation). Analysis of variance of the transformed variables was carried out with age, sex, BMI, PBF, waist circumference and waist–hip ratio (WHR) in order to identify significant covariates. The effect of significant covariates was removed by regression. The standardized residuals of the regression models that included the significant covariates for each trait were then used in the linkage analyses. Trait-specific values that fell beyond four S.D. from the mean of the trait were considered as outliers and excluded from further analysis. This led to the exclusion of the following numbers for each trait: total cholesterol (3), TG (2), HDL-C (1), LDL-C (2) and VLDL-C (2).

Linkage analysis was done using the multipoint variance components linkage analysis approach [27–29] as implemented in the MERLIN program [30]. In variance components linkage analysis, the variance of a trait is decomposed into locus-specific effects determined by the identity-by-descent (IBD) relationships (additive QTL variance), the residual additive genetic effects (additive polygenic variance) and individual specific random environmental effects (random environmental variance). The null hypothesis is that the additive QTL variance equals zero (no linkage) and this was tested by comparing the likelihood of the restricted model with that of a model, in which the additive QTL variance is estimated. The difference between the two log likelihoods produces a logarithm of odds (LOD) score. Twice the difference between the two log likelihoods of these models yields a test statistic that is asymptotically distributed as a 50:50 mixture of a X^2 variable and a point mass at zero. One unit LOD support intervals were obtained by identifying the peaks of the maximum LOD score on the plot of the multipoint results, dropping down one LOD unit and finding the chromosomal region defined by the shoulders of the curve [31]. Firstly, each phenotype was analyzed for evidence of linkage to a QTL. Then, the principal component factor analysis (PCFA) technique was used to extract the underlying factors of the five traits. PCFA is a data-reduction technique that reduces a number of correlated variables into fewer uncorrelated factors and has been applied to linkage analysis for correlated traits [17]. The technique was used as follows: (1) principal components analysis was used to reduce the original variables to linear combinations (components) that account for the maximum amount of total variance in the original variables; the number of significant components was determined based on eigenvalues which represent the amount of variance attributable to each factor. (2) Factors with eigenvalues $\geq$1.0 were extracted using varimax rotation to produce interpretable scores (3) Factor loadings, which are the correlations between each variable and the factor in question, were used to interpret the factors as well as characterize the factor structure. Two factors were extracted, together accounting for

81% of the variance of the traits. The scores of each factor were then used in a separate set of linkage analyses. A LOD score > 3.3 was taken as evidence of significant linkage and a LOD score >1.9, but <3.3 as evidence of suggestive linkage [32]. The Marshfield age- and sex-averaged maps were used in the linkage analyses.

To estimate the probability of obtaining false positive evidence of linkage, we conducted gene-dropping simulations using MERLIN [30]. Marker data were simulated under the null hypothesis of no linkage or association to observed phenotypes, while retaining the same pedigree structures, maps, marker allele frequencies and missing data patterns. We simulated 1000 replicates for each of the traits and then conducted the same linkage analyses described above on each of the replicates. The probability of obtaining a false positive result was defined as the proportion of replicates for which we obtained a specified LOD score or higher.

3. Results

Two hundred and ninety-five siblings pairs were studied. Characteristics of this study sample are shown in Table 1. The mean age was about 53 years and did not differ between men and women. Women had greater adiposity than men did, as evidenced by a greater mean BMI, FM and PBF. One-quarter of the women had a BMI $\geq 30\,kg^2$ in contrast to only 11% of the men. More than one-half of the participants had hypertension (Table 1).

The descriptive statistics, covariates and sib–sib correlations of the five lipid phenotypes are shown in Table 2. All the traits with the exception of HDL-C showed low (<0.3), but significant correlations with the measures of adiposity (data not shown). Again, all the traits with the exception of HDL-C had age and at least one measure of adiposity as significant covariates on multiple linear regression modeling. However, the significant covariates accounted for only a small proportion of the variance and model r^2 did not exceed 10% for any trait. Sib–sib trait correlations ranged between 0.27 (for TG and VLDL-C) and 0.36 for LDL-C and heritability exceeded 50% for all traits, indicating a significant genetic component to the variance of each trait. The heritability estimates were 71% for total cholesterol, 52% for TG, 56% for HDL-C, 72% for LDL-C and 54% for VLDL-C.

Significant linkage of HDL-C was found to a QTL on chromosome 7 at 128 cM from p-ter (LOD 4.34), near marker D7S3061 (Table 3). This was the only LOD score in the study that exceeded the Lander–Kruglyak criterion for significant linkage of a LOD of at least 3.3. However, several other QTL met the criteria for suggestive linkage as shown in Table 4,

Table 1
Characteristics of study sample

Characteristic	Men	Women	All
Number	241	331	572
Age	53.6 (10.4)	52.8 (11.0)	53.1 (10.8)
Weight (kg)	71.8 (12.9)	69.6 (15.5)	70.5 (14.3)
Body mass index (kg/m^2)*	24.8 (4.0)	27.5 (5.6)	26.3 (5.2)
Waist circumference (cm)	90.8 (11.3)	92.4 (10.4)	91.7 (10.8)
Waist–hip ratio*	0.93 (0.07)	0.90 (0.07)	0.91 (0.07)
Fat mass (kg)*	15.8 (8.3)	25.3 (11.3)	21.2 (11.2)
Fat-free mass (kg)*	56.1 (7.0)	44.4 (6.0)	49.3 (8.7)
Fat mass (%)	20.9 (8.1)	34.9 (9.1)	29.0 (11.1)
Hypertensive[a] (%)	50.6	58.6	55.2
Obese (BMI $\geq 30\,kg/m^2$) (%)	10.8	25.8	19.4

All figures are mean (S.D.) unless otherwise indicated.
[a] Hypertension defined as blood pressure ≥140/90 mmHg or on anti-treatment.
* Significant male–female differences at $p < 0.001$.

Table 2
Summary statistics, significant covariates and sib–sib correlations of serum lipids measured

Lipid fraction	Men, median (IQ range)	Women, median (IQ range)	Significant covariates[a]	r^2 (%) for model with covariates[a]	Sib–sib correlation[b]
Total cholesterol	173 (152, 202)	197 (194, 228)	Age, percent fat mass	10.4	0.35
Triglycerides	76 (53, 101)	82 (60, 110)	Age, percent fat mass, waist–hip ratio	5.2	0.27
HDL-cholesterol	41 (34, 51)	44 (37, 54)	None	–	0.29
LDL-cholesterol	114 (91, 143)	129 (104, 156)	Age, percent fat mass	9.7	0.36
VLDL-cholesterol	16 (11, 22)	17(12, 22)	Age, percent fat mass, waist–hip ratio, waist circumference	8.4	0.27

Medians and interquartile (IQ) ranges used to describe the data since most of the traits were not normally distributed.
[a] Trait used in model is the transformed variable.
[b] Covariate-adjusted transformed variable used.

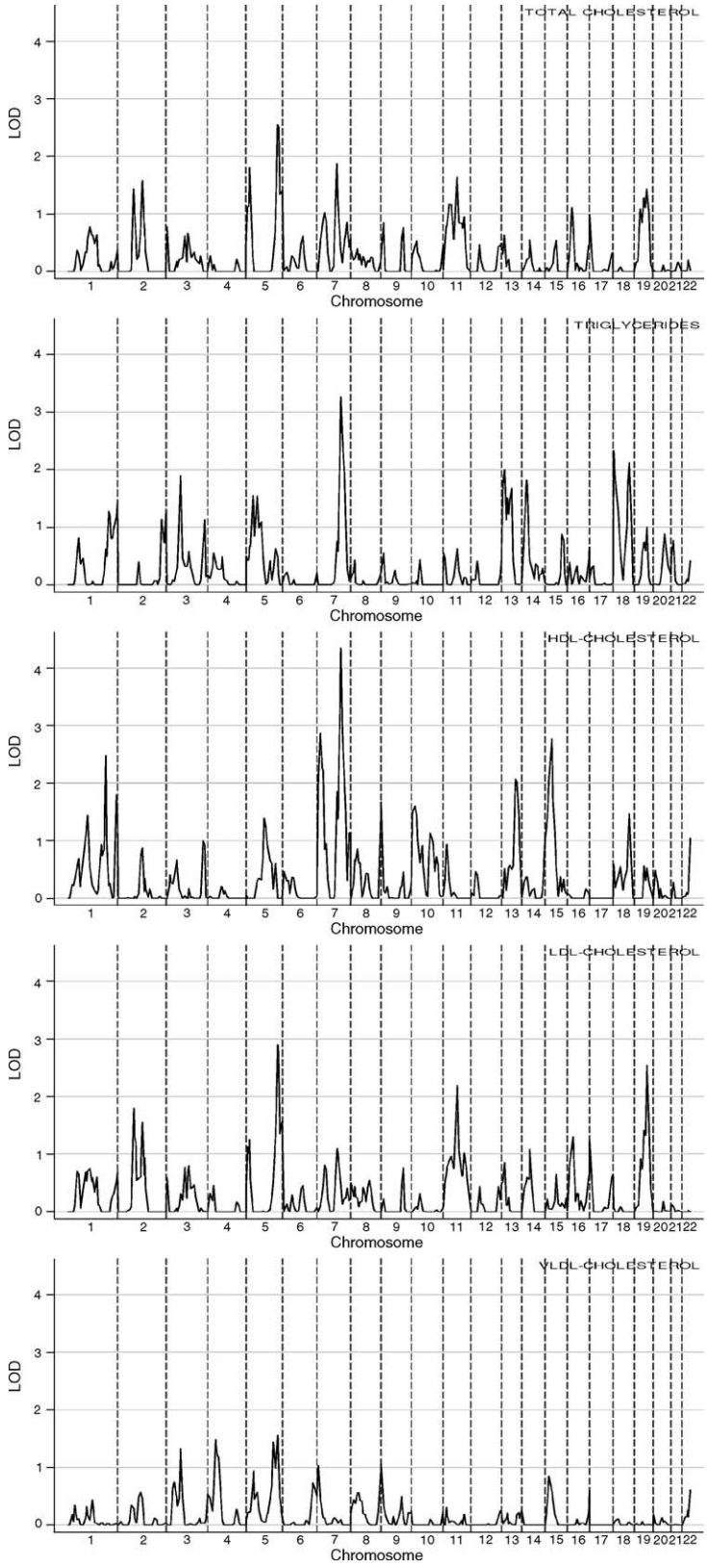

Fig. 1. Figure showing LOD scores on all autosomes for the five lipid phenotypes studied.

Table 3
Genomic regions showing significant or suggestive linkage with the lipid phenotypes studied

Cytogenetic region	Location (cM)	Phenotype	LOD Score	Nearest marker	1-LOD unit support interval (cM)	LOD score for the other traits at the same location if > 1
Significant linkage						
7q31	128 at 7	HDL-C	4.34	D7S3061	122–135	TG 3.26
Suggestive linkage						
1q25	212 at 1	HDL-C	2.48	D1S1660	206–215	
3p14	79 at 3	TG	1.89	D3S1766	69–86	VLDL-C1.33
5q33	169 at 5	LDL-C	3.01	D5S1471	163–179	Cholesterol 2.55
7p21	21.5 M at 7	HDL-C	3.0	D7S513	7–34	VLDL-C1.56
11q13	76 at 11	LDL-C	2.19	D11S2371	63–84	Cholesterol 1.64
13q11	15.5 at 13	TG	2.02	D13S217	9–60	
15q11.2	32 at 15	HDL-C	2.90	D15S1012	17–41	
18p11.32	4 at 18	TG	2.34	D18S818	3–27	
18q21	89 at 18	TG	2.12	D18S862	76–99	HDL-C 1.47
19q13.1	69.5 at19	LDL-C	2.57	D19S178	61–78	Cholesterol 1.43 TG 1.00

Table 4
The lipid factors identified by PCA in this study and the genomic regions showing suggestive linkage with the factors

Factor (% variance explained)	Traits loading highly on factor	Heritability (%)	Location (cM)	LOD Score	Nearest marker	1-LOD unit support interval (cM)
Factor 1 (48.3)	TG, HDL-C, VLDL	43.7	261 at 2	2.05	D2S125	235–261
			38.5 at 5	2.00	D5S2848	26–83
			128 at 7	1.98	D7S3061	119–147
			7.5 at 18	2.66	D18S976	3–26
Factor 2 (32.8)	Cholesterol, LDL-C	68.9	136 at 2	2.08	D2S1328	128–148
			169.5 at 5	2.21	D5S1471	162–181

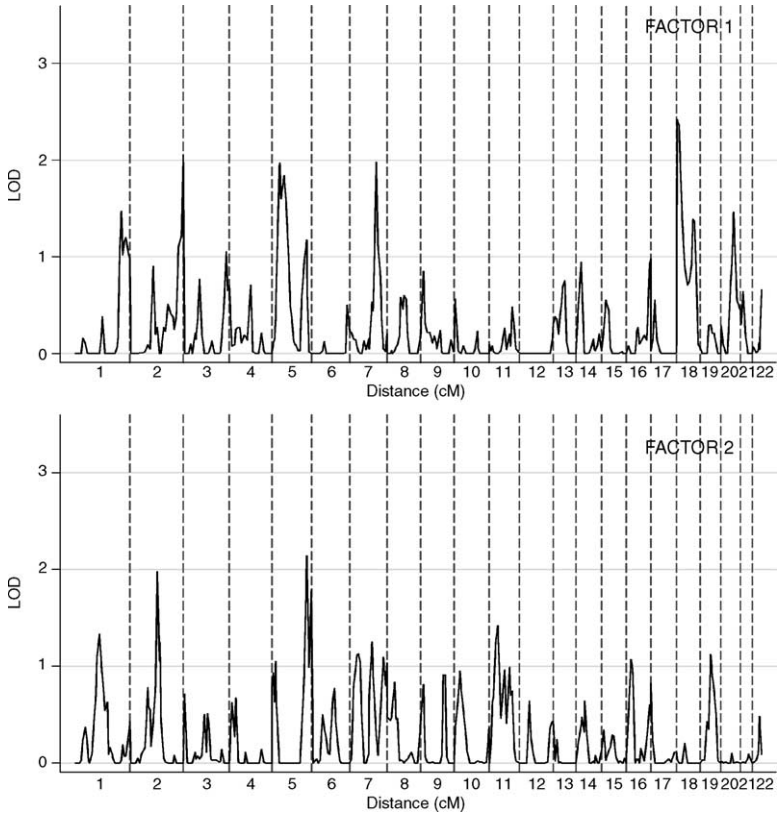

Fig. 2. Figure showing LOD scores on all autosomes for the two composite lipid factors.

with three of them (location 128 cM on chromosome 7 for TG, location 169 cM on chromosome 5 for LDL-C and location 21.5 cM on chromosome 7 for HDL-C) reaching a LOD of at least 3.0. Significant or suggestive linkage was found for two of the five traits at the same locus for a QTL on chromosome 7 (at 128 cM) and chromosome 5 (at 169 cM). LOD scores on all the chromosomes for all five phenotypes are shown in (Fig. 1).

The two lipid factors extracted showed maximum LOD scores of between 2 and 2.2 to QTLs on chromosomes 2 and 5 (Fig. 2). The QTL on chromosome 7 (at 128 cM) that showed suggestive evidence of linkage with HDL-C and TG also showed a LOD score of 2.05 with factor 1 (Fig. 2). Lipid factor 2's highest LOD score was at 7.5 cM on chromosome 18, which is 3.5 cM away from the QTL found for TG on the same chromosome during single trait linkage analyses.

Based on the simulations conducted, the genome wide empirical probability of obtaining a LOD score of 4 or higher for total cholesterol, TG, HDL-C, LDL-C and VLDL-C was 0.002, 0.026, 0.044, 0.021 and 0.001, respectively; while the probability of obtaining a LOD score of 3 or higher was 0.074, 0.219, 0.275, 0.123 and 0.003, respectively.

4. Discussion

Serum lipid abnormalities have major public health significance, being some of the most potent risk factors for CHD and occurring in association with T2DM and the metabolic syndrome. For these reasons, delineating their environmental and genetic determinants has been a major focus of several teams of investigators over several decades. The geographic population studied is of particular interest because serum lipid profiles of many populations in sub Saharan Africa differ substantially from what is known of other geographical populations (as noted above) and this difference is paralleled by a lower incidence of coronary heart disease and type 2 diabetes, among other chronic diseases [33,34]. The availability of better and more affordable genotyping tools has enabled the study of the genetic determinants move into an era, where candidate gene polymorphisms and genome scans with anonymous markers are typed in samples in several populations. In the present study, we conducted a genome scan for serum lipids in T2DM in an African population. Our examination of covariates show that age and obesity are significant covariates of most of the studied serum lipid levels, although in no case do they account for more than 10% of the variance of the trait. We used two complementary approaches in evaluating linkage evidence. Firstly, we examined single phenotypes for evidence of linkage. Secondly, since it is likely that these lipid phenotypes are correlated and may (at least in part) be under the control of the same genes, we constructed multivariate or composite phenotypes using principal component factor analysis. The latter approach is being increasingly used to investigate correlated phenotypes and/or to detect pleiotropic QTLs, for example, to investigate insulin resistant syndrome-related phenotypes [17].

Significant or suggestive linkage signals were found for at least one of the studied lipid phenotypes on several chromosomes, including chromosomes 1, 3, 5, 7, 11, 13, 15, 18 and 19. The strongest linkage signal in this study was on chromosome 7q31 (at 128 cM from p-ter) near marker D7S3061 where HDL-C had a LOD score of 4.34 and TG had a LOD score of 3.26. This is very close to a linkage signal (LOD = 3.2) for a "lipid factor" (comprising HDL and ln TG) in Mexican–Americans [17]. In addition, two other studies found evidence of linkage of the same region—one in Pima Indians [35] to a lipid factor in the first study, the other in Mexican–Americans [16] to TG (LOD = 2.1) and HDL (LOD = 1.7). This suggests that this region is likely to harbor genes that influence HDL-C and TG levels. While several known candidate genes exist in this region, such as the paraoxonase (PON1) and plasminogen activator inhibitor (PAH) genes, the possibility of the existence of novel candidate genes in this region cannot be excluded. The finding of a genomic region showing significant linkage to both TG and HDL-C as a principal component factor, but not to individual phenotypes is consistent with earlier findings that suggest that the two traits are influenced by both shared and unshared genes [36].

The QTL on chromosome 1 (at 1q25 near marker D1S1660) linked to HDL-C in this study is very close to a QTL for the same phenotype reported from the HyperGEN study with a LOD score of 2.13 in whites and to the QTL linked to the "lipid factor" (comprising HDL and ln TG) with a LOD score of 1.9 among Mexican–Americans [17]. Finally, Duggirala et al. [16] found a QTL on chromosome 15 (between markers GABRB3 and D15S165) linked to log TG at a location very close to the one linked to HDL-C on chromosome 15q in the present study. Thus, the present study found linkage signals very close to those reported for multiple lipids phenotypes in several other major studies. Two of the linkage regions in this study are novel—the 5q33 region (peak at 169 cM from p-ter) and the 7p21 region (peak 21.5 cM from p-ter). Interestingly, the interleukin-6 (*IL-6*) gene is located in the 7p21 region. IL-6 polymorphisms have been shown to be associated with lipid abnormalities in healthy subjects in at least one study [41]. No candidate genes involved in lipid metabolism are known to map to 5q33 region at the present time.

The composite phenotype constructs obtained by principal component factor analysis showed linkage to fewer regions than on univariate linkage analysis with each of the five phenotypes. Some of these regions were similar to those obtained on univariate linkage analysis (e.g. the QTLs on chromosomes 5 and 7), while the ones on chromosome 2 were not significantly linked to any single phenotype. This suggests, as in other studies, that analysis of composite or multivariate phenotypes may detect genomic regions with significant linkage in situations where single phenotype analysis may fail to do so. In a recent study [37], the use of a

TG-total cholesterol factor identified two loci with suggestive evidence of linkage that the individual traits did not, suggesting that principal component factor analysis can help dissect the genetic basis of tightly correlated traits. However, this does not mean that the analysis of single traits is unnecessary since it has been shown that the fact that two traits are correlated does not mean that their LOD scores are and a LOD peak at a given location does not necessarily imply that a correlated trait has a LOD peak at the same location [38]. It should be noted that the maximum LOD scores of the composite phenotypes were lower than those obtained with univariate phenotype linkage analysis. This may reflect several factors, including: the pleiotropic effect of the QTLs may be very small, the sample size of the study may be too small to detect pleiotropic effects with confidence and the composite phenotype may have more complex characteristics than can be described using this method of linkage analysis.

One potential limitation of this study is that all participants have T2DM and if loci that influence lipid levels in diabetic persons are different from those in nondiabetic individuals, the findings may be applicable only to participants with diabetes since serum lipid levels are altered in diabetes. However, there is good evidence that familial determinants of cholesterol, TG and HDL are the same in both diabetic and nondiabetic individuals [39] and that the genetic predisposition to TG affects both diabetic and nondiabetic individuals similarly [40]. Even in the absence of such evidence, there are still good reasons for identifying genetic loci linked to lipids in T2DM since the disease condition adversely affects their lipid profiles thereby leading to a much higher risk of CHD than the general population. Another potential limitation is that the QTLs found in this study may be linked to diabetes rather than to serum lipid levels per se. However, most other studies have not found this to be so. In the genome scan for T2DM in the AADM study [42], the regions that showed the strongest evidence for linkage (on chromosomes 12, 19 and 20) were very different from those identified in this set of linkage analyses for serum lipids.

In conclusion, we have conducted a genome wide scan for QTLs that are linked to serum lipid phenotypes in a sample of affected siblings with T2DM from an under-studied population in sub Saharan Africa. Using a multipoint variance components linkage analysis method, we sought for evidence of linkage of the selected traits using 390 markers distributed across the genome. The strongest linkage evidence was to a QTL on chromosome 7q, which was linked to both HDL-C (LOD = 4.34) and TG (LOD = 3.26). Weaker evidence of linkage was found to other QTLs on chromosomes 1, 3, 5, 7, 11, 13, 15, 18 and 19. Composite phenotypes constructed using the principal components factor analysis technique yielded QTLs on chromosomes 2 and 5, which were not detected during univariate linkage analysis. Several of the linkage signals have previously been reported in other populations. The findings of the present study add to the accumulating evidence of the genetic determinants of serum lipids, which play major roles in the etiology and pathogenesis of CHD. Finally, this study provides valuable data from a population in an under-studied geographical region: sub Saharan Africa.

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