

Brief Report

Meta-Analysis of Genome-Wide Linkage Studies of Quantitative Lipid Traits in Families Ascertained for Type 2 Diabetes

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Dyslipidemia is a major risk factor for coronary heart disease, which is the predominant cause of mortality in individuals with type 2 diabetes. To date, nine linkage studies for quantitative lipid traits have been performed in families ascertained for type 2 diabetes, individually yielding linkage results that were largely nonoverlapping. Discrepancies in linkage findings are not uncommon and are typically due to limited sample size and heterogeneity. To address these issues and increase the power to detect linkage, we performed a meta-analysis of all published genome scans for quantitative lipid traits conducted in families ascertained for type 2 diabetes. Statistically significant evidence (i.e., $P < 0.00043$) for linkage was observed for total cholesterol on 7q32.3-q36.3 (152.43–182 cM; $P = 0.00004$), 19p13.3-p12 (6.57–38.05 cM; $P = 0.00026$), 19p12-q13.13 (38.05–69.53 cM; $P = 0.00001$), and 19q13.13-q13.43 (69.53–101.1 cM; $P = 0.00033$), as well as LDL on 19p13.3-p12 ($P = 0.00041$). Suggestive evidence (i.e., $P < 0.00860$) for linkage was also observed for LDL on 19p12-q13.13, triglycerides on 7p11-q21.11 (63.72–93.29 cM), triglyceride/HDL on 7p11-q21.11 and 19p12-q13.13, and LDL/HDL on 16q11.2-q24.3 (65.2–130.4 cM) and 19p12-q13.13.

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AADM, Africa-America Diabetes Mellitus; AFDS, Amish Family Diabetes Study; CHD, coronary heart disease; GENNID, Genetics of NIDDM; GSMA, Genome Scan Meta-Analysis; HKFDS, Hong Kong Family Diabetes Study; LOD, logarithm of odds; SAFADS, San Antonio Family Diabetes Study.

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Linkage for lipid traits has been previously observed on both chromosomes 7 and 19 in several unrelated studies and, together with the results of this meta-analysis, provide compelling evidence that these regions harbor important determinants of lipid levels in individuals with type 2 diabetes. *Diabetes* 56:890–896, 2007

Coronary heart disease (CHD) is the leading cause of death in individuals with type 2 diabetes (1). The high prevalence of CHD among these individuals is largely due to dyslipidemia, which is influenced by both environmental and genetic factors (2). Over 90 genome scans have been performed to identify loci for lipid levels, including nine linkage studies of quantitative lipid traits performed in ethnically diverse populations of families ascertained for type 2 diabetes (3–10). Common chromosomal regions have been identified in some of these studies; for example, linkage on chromosome 19 was observed for triglyceride levels in families with Northern-European ancestry (6) and total cholesterol levels in Pima Indians from Arizona and African Americans from the Genetics of NIDDM (GENNID) Study (3,5). Similarly, linkage on chromosome 3 was observed for LDL cholesterol levels in an Old Order Amish population (10) and for triglyceride/HDL levels in Caucasian families from the GENNID Study (3). However, most of the regions observed in these genome scans have not been overlapping, including linkage on 15q and 9p for plasma triglycerides and HDL cholesterol, respectively, in Mexican-American families (7,8); chromosome 7 for HDL cholesterol in Africans (9); chromosome 6 for triglycerides in a Chinese population from Hong Kong (4); and chromosome 11 for triglyceride/HDL cholesterol in Hispanics from the GENNID Study (3). While some of these analyses yielded logarithm of odds (LOD) >3.0 , the majority of LOD scores reported in these studies were well below the threshold normally considered statistically significant.

While disparities in linkage findings for lipid traits in families ascertained for type 2 diabetes and lack of statistically significant evidence for linkage can result from both locus heterogeneity and utilization of different study designs, in most cases, they are most commonly attributable to inadequately sized study samples. In the nine genome scans for lipid traits conducted in families with type 2 diabetes, sample sizes ranged from 240 to 998 individuals, and most of these studies had low power to detect statisti-

cally significant evidence for linkage. The goal of this study, therefore, was to overcome many of the limitations associated with detecting statistically significant evidence of linkage for a complex trait and augment the power to detect statistically significant evidence of linkage for lipid traits in families with type 2 diabetes. To this end, we combined LOD scores from each of the nine genome scans using a meta-analysis approach. This study is the first meta-analysis of linkage results for quantitative lipid traits measured in families ascertained for type 2 diabetes and represents the largest genetic linkage study of lipid traits conducted to date in a population with diabetes.

RESEARCH DESIGN AND METHODS

Characteristics of participants from the nine populations used in the present study are shown in Table 1. Linkage results for quantitative lipid traits (triglycerides, total cholesterol, LDL, HDL, triglyceride/HDL, and LDL/HDL) were used from the following populations with families ascertained for type 2 diabetes: 59 African-American families, 153 Caucasian families, and 115 Hispanic families from the GENNID Study (3); 179 Chinese nuclear families from the Hong Kong Family Diabetes Study (HKFDS) (4); 292 (998 siblings), 201 (590 siblings), and 188 (548 siblings) Pima Indian families for total cholesterol, HDL cholesterol, and triglycerides, respectively, from the Gila River Indian Community in Arizona (5); 415 individuals from 27 families as part of the San Antonio Family Diabetes Study (SAFADS) (7,8); 19 families (379 individuals) with Northern-European ancestry (6); 295 sibling pairs from the Africa-America Diabetes Mellitus (AADM) Study (9); and 28 Old Order Amish pedigrees collected as part of the Amish Family Diabetes Study (AFDS) (10). Extensive details of the study populations and methods used in each study have been previously described (3–10).

Statistical analysis. The Genome Scan Meta-Analysis (GSMA) program (11,12) was used to assess evidence for linkage utilizing results from analyses of triglycerides, LDL, total cholesterol, HDL, LDL/HDL, and triglyceride/HDL. Bins were created using Marshfield map distances. Of the nine genome scans, only two used marker maps with Marshfield map distances; for the remaining studies, distances were converted to Marshfield map distances by inserting the marker names in the Marshfield database (<http://research.marshfieldclinic.org/genetics/>). In total, 116 bins of ~30 cM (range 26.2–32.9) spanning the genome were created. Following this, the maximum LOD score for a bin in each study was identified and were used to assign ranks to each bin in each separate study. Ranks were then summed across studies and used to estimate the probability of observing a bins summed rank by chance, i.e., the proportion of replicates with summed rank equal to or greater than that observed when combining the results of all studies (11). We have described this method in detail elsewhere (13).

Because sample sizes varied considerably among the studies evaluated here, both unweighted and weighted GSMA analyses were performed. The data were weighted according to the number of individuals genotyped in the respective study populations, such that $weight = [\sqrt{N}(\text{genotyped individuals})]/[\text{mean of } \sqrt{N}(\text{genotyped individuals}) \text{ over all studies}]$ where $n = 612, 415, 572, 897, 819, 582, 240, 379,$ and 998 (or 548 or 590 depending on the trait being analyzed) for the AFDS, SAFADS, AADM, HKFDS, GENNID (Caucasians), GENNID (Hispanics), GENNID (African Americans), Caucasians with Northern-European ancestry, and Pima Indian studies, respectively (3–10).

Statistically significant evidence for linkage, equivalent to Lander and Kruglyak's (14) definition of one false positive per 20 meta-analyses, was assessed using a Bonferroni correction ($0.05/116$), giving $P < 0.00043$, whereas suggestive evidence for linkage, defined as one false positive per meta-analysis, corresponded to $P < 0.00860$. We, however, did not correct for the six lipid traits because they were correlated.

RESULTS

Nine genome scans for lipid traits have been performed in families ascertained for type 2 diabetes. Characteristics of the participants from each study are shown in Table 1. These populations were drawn from diverse ethnic backgrounds including American-Indian, Old Order Amish, African, African-American, and Chinese study samples, as well as two groups of unrelated Caucasian and Hispanic individuals. We performed a meta-analysis for the following quantitative lipid traits: LDL (seven studies), HDL (nine studies), triglycerides (nine studies), total cholesterol

TABLE 1
Characteristics of participants from the studies used in the GSMA

Study	AFDS		SAFADS		AADM		HKFDS		GENNID		Northern-European ancestry		Pima Indians	
	Old Order Amish	Mexican Americans	African Americans	Chinese	African Americans	Hispanics	African Americans	Hispanics	Caucasian	American Indian	Caucasian	Hispanics	American Indian	Hispanics
<i>n</i>	612	415	572	897	819	582	240	379	998					
Male (%)	44.6	41.2	42.1	40.6	43.6	32.9	36.3	45.6	44.2					
Female (%)	55.4	58.8	57.9	59.4	56.4	67.1	63.7	54.4	55.8					
With diabetes (%)	10.6	26.4	100	38.2	45	54	45	24	61.0					
Age (years)	47.1 ± 15.3	43.3 ± 17.3	53.1 ± 10.8	42 ± 15	54.3 ± 15.8	51.1 ± 15.4	50.4 ± 15.6	45.5 ± 16.7	41.4 ± 12.3					
Study design	Extended pedigrees	Extended pedigrees	Sib-pairs	Nuclear families	Nuclear families	Nuclear families	Nuclear families	Extended pedigrees	Sib-pairs					
Program used	SOLAR	SOLAR	Merlin	Merlin	GH	GH	GH	SOLAR	SAS					
MaxLOD*	2.47 (3)	3.88 (15)	4.34 (7)	2.58 (6)	3.36 (3)	2.26 (19)	2.54 (11)	2.56 (19)	3.89 (19)					
MaxLOD trait	LDL	TG	HDL	TG	TG/HDL	TC	TG/HDL	TG	TC					

Data are means ± SD unless otherwise indicated. *Highest LOD score observed; the chromosome number is given in parenthesis. TC, total cholesterol; TG, triglyceride.

TABLE 2
LOD scores and *P* values meeting criteria for significant or suggestive evidence for linkage (i.e., $P < 0.00043$ or $P < 0.00860$, respectively)

Cytogenetic location	cM location (Mb in parenthesis)	Trait	AFDS	SAFADS	AADM	HKFDS	GENNID Caucasian	GENNID African American	GENNID Hispanic	Northern-European ancestry	Pima Indian	GSMA (LOD)*	GSMA (<i>P</i>)†
7q32.3-q36.3	152.43–182(130.1–158.2)	TC	1.19	—‡	0.86	1.53	1.30	0.43	0.92	0.09	0.55	3.38	0.00004§
19p13.3-p12	6.57–38.05(1–19.8)	TC	1.15	—	1.08	0.67	0.51	1.58	0.91	0	3.89	2.62	0.00026§
19p12-q13.13	38.05–69.53(19.8–43.3)	TC	1.54	—	1.43	0.73	0.63	2.26	1.16	0.11	3.11	3.95	0.00001§
19q13.13-q13.43	69.53–101.1(43.3–63.8)	TC	0.13	—	1.04	0.62	0.53	1.94	1.18	0.30	1.50	2.52	0.00033§
19p13.3-p12	6.57–38.05(1–19.8)	LDL	2.15	—	0.92	0.85	1.23	1.14	0.61	0	—	2.43	0.00041§
19p12-q13.13	38.05–69.53(19.8–43.3)	LDL	2.24	—	2.54	0.71	0.43	1.41	0.34	0	—	1.58	0.00354
19q13.13-q13.43	69.53–101.1(43.3–63.8)	LDL	0.16	—	1.55	0.49	0.75	1.60	0.90	0	—	1.26	0.00812
7p11-q21.11	63.72–93.29(53.9–86.2)	TG	0.61	1.85	0.04	0.61	0.50	0.52	0.86	1.25	0.01	1.89	0.00161
7p11-q21.11	63.72–93.29(53.9–86.2)	TG/HDL	—	—	—	0.60	0.57	0.57	1.21	1.00	—	2.10	0.00094
19p12-q13.13	38.05–69.53(19.8–43.3)	TG/HDL	—	—	—	0.83	0.48	0.40	1.17	1.56	—	1.87	0.00168
16q11.2–16q21	65.2–97.8(40.7–65.2)	LDL/HDL	—	—	—	0.87	1.15	0.18	0.70	0.03	—	1.50	0.00436
16q21-q24.3	97.8–130.4(65.2–88.8)	LDL/HDL	—	—	—	0.82	0.68	0.22	1.26	0.02	—	1.46	0.00477
19p12-q13.13	38.05–69.53(19.8–43.3)	LDL/HDL	—	—	—	0.83	0.97	0.68	2.08	0	—	1.49	0.00437

*LOD score for weighted analysis. †*P* value for weighted analysis. ‡Results were not available. §Significant evidence (Bonferroni correction: $P < 0.00043$). ||Suggestive evidence (Bonferroni correction: $P < 0.00860$). The cytogenetic location, LOD scores for individual studies, GSMA LOD scores, and GSMA *P* values are given for the 13 regions identified. No differences between weighted and unweighted analyses were found, and results for weighted analyses are shown here. TC, total cholesterol; TG, triglyceride.

(eight studies), triglyceride/HDL (five studies), and LDL/HDL (five studies). The number of studies included in the meta-analyses varied according to the availability of trait data from the original genome scans for a given population (Table 1).

We observed statistically significant evidence (i.e., $P < 0.00043$) for linkage in four bins for total cholesterol on 7q32.3-q36.3 (152.43–182 cM), 19p13.3-p12 (6.57–38.05 cM), 19p12-q13.13 (38.05–69.53 cM), and 19q13.13-q13.43 (69.53–101.1 cM), as well as one bin for LDL on 19p13.3-p12 (Table 2). To evaluate the distribution of *P* values across the genome, summed ranks were plotted against the bin number for total cholesterol and LDL, which were the only traits showing statistically significant evidence for linkage (Figs. 1 and 2, respectively). In addition, eight regions also showed suggestive evidence (i.e., $P < 0.00860$) of linkage for different traits: 19p12-q13.13 and 19q13.13-q13.43 for LDL, 7p11-q21.11 (63.72–93.29 cM) and 19p12-q13.13 for triglyceride/HDL, 7p11-q21.11 for triglycerides, and 16q11.2–16q21 (65.2–97.8), 16q21-q24.3 (97.8–130.4 cM), and 19p12-q13.13 for LDL/HDL. However, in the analysis of HDL, no bins met the criteria for statistically significant or suggestive evidence for linkage, as described in RESEARCH DESIGN AND METHODS.

DISCUSSION

In this study, we report the results from the first meta-analysis of linkage data undertaken to date to identify loci underlying quantitative lipid traits in families ascertained for type 2 diabetes. We have found statistically significant evidence of linkage for total cholesterol on 7q32.3-q36.3 and chromosome 19 and for LDL on 19p13.3-p12. Suggestive evidence for linkage was also observed on 19p12-q13.13 and 19q13.13-q13.43 for LDL, 7p11-q21.11 for triglycerides, 7p11-q21.11 and 19p12-q13.13 for triglyceride/HDL, and 16q11.2–16q21, 16q21-q24.3, and 19p12-q13.13 for LDL/HDL. These results demonstrate that combining data from unrelated studies conducted in families ascertained for type 2 diabetes can successfully address important limitations commonly associated with linkage analysis, such as relatively modest sample size, and increase the power to detect statistically significant evidence for linkage.

The strongest evidence of linkage for lipid traits identified in this study was found on chromosomes 7 and 19. Linkage for lipid traits has been previously observed in both of these regions in several studies. For example, linkage on chromosome 7 for triglyceride/HDL (15) was found in randomly ascertained families and for triglyceride levels in two unrelated studies of families ascertained for obesity and one study of families ascertained for type 2 diabetes (7,16,17). A statistically significant *P* value identified in this meta-analysis, combined with multiple observations of linkage in unrelated studies, supports the presence of a gene(s) in this region with important effects on triglyceride levels. It is worth noting that only nominal evidence for linkage was observed for this locus in the individual studies, indicating that meta-analysis may be a powerful tool for identifying susceptibility loci for complex traits such as lipid levels.

While the 7q32.3-q36.3 locus is a strong candidate for genetic control of triglyceride levels, the most consistent and compelling evidence of linkage for lipid traits was observed on chromosome 19. Linkage for various lipid traits to chromosome 19 has been observed in several

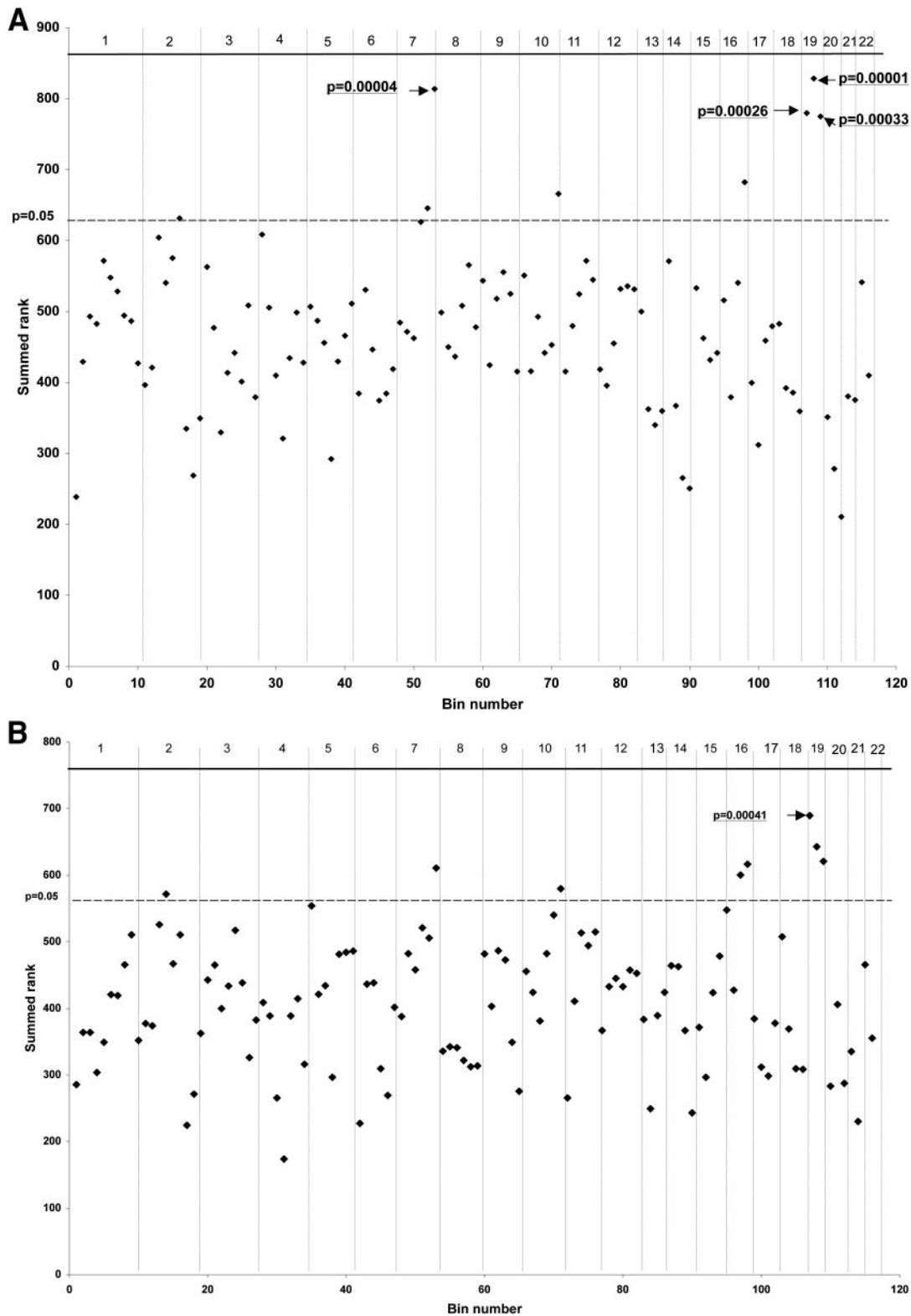
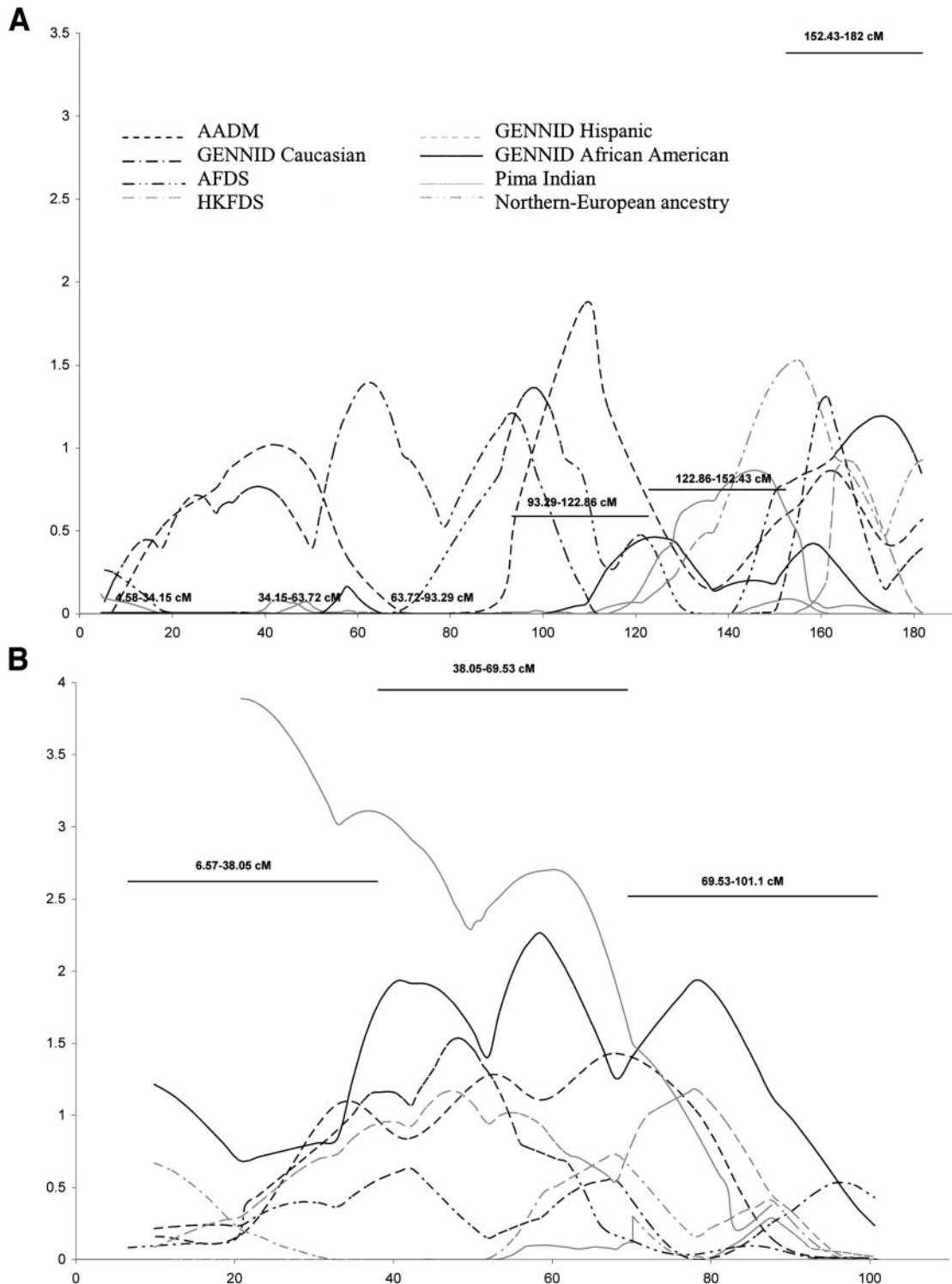


FIG. 1. Summed ranks in relation to bin number in the analysis of lipid traits. Summed ranks are plotted against the GSMA bin number. There are a total of 116 bins. Vertical lines divide the bins according to chromosome. **A:** Total cholesterol levels: three bins on chromosome 19 and one bin on chromosome 7 showed significant evidence as indicated. **B:** LDL levels: one bin on chromosome 19 showing significant evidence for linkage.

studies including total cholesterol in Pima Indians (5) and African Americans (3), triglycerides in non-Hispanic Caucasians (6), and LDL in Old Order Amish (10) and Africans (9); notably, these five studies involved families ascertained for type 2 diabetes. In addition, linkage to chromo-

some 19 was also observed for LDL cholesterol in randomly ascertained American Indians (18) and Caucasians (19) and a combination of randomly and obesity-ascertained families (20), as well as for LDL particle size, in randomly ascertained Mexican-American families (21)



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FIG. 2. LOD score plots for chromosome 7 (A) and chromosome 19 (B). Horizontal lines indicate the LOD score of the meta-analysis for a given bin that extends 29.57 cM for chromosome 7 and 31.48 cM for chromosome 19, with cM interval for each bin given above the line.

and African Americans ascertained for hypertension (22). Together, these findings are consistent with chromosome 19 being an important locus for regulation of lipid levels among individuals from diverse ethnic backgrounds. Further, the identification of this locus in five of the nine published genome scans conducted in families ascertained for type 2 diabetes supports the idea that studies of such populations, in whom effects of genetic variants affecting

lipid levels may occur earlier or more severely, may facilitate the discovery of genes with critical roles in lipid metabolism in individuals with diabetes and in the general population.

The identification of chromosome 19 both in a single bin identified for multiple traits (total cholesterol, LDL, triglyceride/HDL, and LDL/HDL) and across multiple bins (total cholesterol) suggests possible pleiotropic effects of a gene

in this region and/or multiple genes affecting a single trait. This effect is not unique to our study, as multiple peaks have also been observed in other studies. Heijmans et al. (23) identified peaks on each arm of chromosome 19, and a broad linkage peak extending from the p to the q arm was observed in an African-American population (3). There are many genes located in this region that encode proteins with direct effects on lipid metabolism, including hormone-sensitive lipase (*LIPE* at 19q13.1-q13.2), apolipoprotein E (*APOE* at 19q13.2), and LDL receptor (*LDLR* at 19p13.2). It is therefore possible that variants in multiple genes within this region interact with one another to exert effects of varying magnitude on lipid levels. In addition, the low proportion of variance of cholesterol levels explained by these genes, e.g., the *APOE* locus contributed as low as 10% of the variance in one study (13), might suggest the role of genes on other chromosomes, including cholesteryl ester transfer protein (*CETP*) and apolipoprotein B (*APOB*).

While we have found statistically significant evidence for linkage for different quantitative lipid traits using meta-analysis, we recognize that utilization of ethnically diverse populations may yield results that are difficult to interpret, in light of potential effects of locus heterogeneity. However, low heterogeneity was observed for total cholesterol in bins corresponding to 7q32.3-q36.3, 19p13.3-p12, 19p12-q13.13, and 19q13.13-q13.43 (results not shown). The fact that common regions of linkage were identified in this analysis, despite differences in ethnicity in the study samples, is consistent with common genetic influences across the different populations.

In summary, we observed statistically significant evidence for linkage for total and LDL cholesterol on chromosome 19 and for total cholesterol on chromosome 7 in a meta-analysis of genome scan results from families ascertained for type 2 diabetes. These findings, combined with previous reports of linkage on chromosomes 7 and 19, provide compelling evidence that these regions harbor genes with important effects on lipid levels.

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