Genome-wide linkage scan reveals multiple susceptibility loci influencing lipid and lipoprotein levels in the Québec Family Study[S]

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Abstract **A genome-wide linkage study was performed to identify chromosomal regions harboring genes influencing lipid and lipoprotein levels. Linkage analyses were conducted for four quantitative lipoprotein/lipid traits, i.e., total cholesterol, triglyceride, HDL-cholesterol (HDL-C), and LDL-C concentrations, in 930 subjects enrolled in the Québec Family Study. A maximum of 534 pairs of siblings from 292 nuclear families were available. Linkage was tested using both allele-sharing and variance-component linkage methods. The strongest evidence of linkage was found on chromosome 12q14.1 at marker D12S334 for HDL-C, with a logarithm of the odds (LOD) score of 4.06. Chromosomal regions harboring quantitative trait loci (QTLs) for LDL-C included 1q43 (LOD = 2.50), 11q23.2 (LOD = 3.22), 15q26.1 (LOD = 3.11), and 19q13.32 (LOD = 3.59). In the case of triglycerides, three markers located on 2p14, 11p13, and 11q24.1 provided suggestive evidence of linkage (LOD > 1.75). Tests for total cholesterol levels yielded significant evidence of linkage at 15q26.1 and 18q22.3 with the allele-sharing linkage method, but the results were nonsignificant with the variance-component method.[JLR] In conclusion, this genome scan provides evidence for several QTLs influencing lipid and lipoprotein levels. Promising candidate genes were located in the vicinity of the genomic regions showing evidence of linkage.**—Bossé, Y., Y. C. Chagnon, J-P. Després, T. Rice, D. C. Rao, C. Bouchard, L. Pérusse, and M-C. Vohl. **Genome-wide linkage scan reveals multiple susceptibility loci influencing lipid and lipoprotein levels in the Québec Family Study. *J. Lipid Res.* 2004.** 45: **419–426.**

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Studies investigating the genetics of blood lipids and lipoproteins have clearly established that genetic factors contribute to these phenotypes (1, 2). Until recently, the molecular bases of blood lipids have been mainly investigated using a candidate gene approach. Although genes accountable for several monogenic dyslipidemias have been identified (3), those underlying the variation in the population at large remain to be found. These results have motivated several investigators to use the genome-scan approach to identify chromosomal regions harboring genes controlling lipoprotein/lipid levels. Such an approach has the ability to find quantitative trait loci (QTLs) without being dependent on an understanding of the physiology governing the traits. Genome scans can generate useful leads and hypotheses whose usefulness is greatly enhanced when the findings are replicated in independent samples (4).

To date, the results of full genome scans for lipoprotein/lipid traits have produced a number of significant findings. For total cholesterol, the results from the Pima Indian community have provided evidence of linkage on chromosome 19p (5). The 1q region was also suggested to contain a locus influencing cholesterol level in obese families (6). A cholesterol-lowering gene was mapped as well on 13q from an extended Israeli family and replicated by the same investigators with a healthy white twin cohort (7). Loci controlling LDL-cholesterol (LDL-C) were re-

Abbreviations: apoA-I, apolipoprotein A-I; BMI, body mass index; FCHL, familial combined hyperlipidemia; IBD, identical by descent; LOD, logarithm of the odds; QTL, quantitative trait locus.

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[S] The online version of this article (available at http://www.jlr.org) contains one additional table.

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ported on 19q in the Hutterites community (8) and on 11p in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study (9). For HDL-C, several major loci were mapped, including 5q in the NHLBI Family Heart Study (10), 8q in Finnish families (11), 9p in Mexican Americans (12), and 6q in the Framingham Study (13). However, the most promising location for an HDL-C locus is on 16q22-q23, from linkages in both Mexican Americans (14) and combined Dutch and Finnish families (15). Data from the Finnish families have also suggested a low HDL-C locus within this region (11). Finally, a putative locus for familial low HDL-C has also been identified near the apolipoprotein A-I (apoA-I)/apoC-III/apoA-IV gene cluster on 11q23 (16). The search for loci influencing triglyceride levels has been similarly fruitful. Genome-wide evidence of linkage has been reported on 2q in Hutterites (17), 10p in Finnish families (18), 15q in a second set of Mexican Americans ascertained for type 2 diabetes (19), and 19q in white Utah families (20).

Based on these observations, it is clear that lipid and lipoprotein traits are influenced by several loci. However, additional genome scans are required to strengthen previous observations and identify the most promising regions underlying the genetic components of these phenotypes. Thus, the purpose of this study was to identify the genomic regions influencing total cholesterol, LDL-C, HDL-C, and triglyceride levels in a cohort of French-Canadian families.

METHODS

Subjects

The Québec Family Study (QFS) is an ongoing investigation of French-Canadian families studying the genetics of obesity and its comorbidities (21). There are four phases in the QFS, and the forth phase is currently in progress. The first phase includes the data collection that took place from 1979 to 1981 on families randomly ascertained. In phase 2, a sample of families from phase 1 were remeasured and additional families, ascertained through obese proband, were recruited and incorporated into the cohort. In the third phase, members of the phase 2 cohort were remeasured and the children of the adult offspring were recruited when they reached 10 years of age. DNA analyses are available for subjects in phase 2 and later. In the current study, the subjects were participants from phase 2 and phase 3 to maximize the number of subjects available for transversal analysis. Serum lipid and lipoprotein concentrations were available for 930 members of 292 nuclear families. This sample represents a half-and-half mixture of random sampling and ascertainment through obese probands. The characteristics of the subjects in the four sex-by-generation groups (fathers, mothers, sons, and daughters) are reported in **Table 1**. All subjects were free of familial lipid disorders requiring lipid-lowering drugs. The Institutional Review Board of Laval University approved all procedures, and all subjects gave written informed consent.

Phenotypes

Blood samples were collected in the morning from an antecubital vein after a 12 h overnight fast. The plasma was separated immediately after blood collection by centrifugation at 3,000 rpm for 10 min for the measurement of plasma lipoprotein/lipid levels. Cholesterol (22) and triglyceride (23) concentrations were determined enzymatically using a Technicon RA-500 automated analyzer (Bayer, Tarrytown, NY). HDL fraction was obtained after precipitation of LDL in the infranatant (>1.006 g/ml) with heparin and $MnCl_2$ (24). The cholesterol content of the infranatant fraction was measured before and after the precipitation step for the measurement of HDL-C and for the calculation of LDL-C. Body mass index (BMI) was determined by weight (kg)/height (m^2).

Genotyping

A total of 443 markers spanning the 22 autosomal chromosomes with an average intermarker distance of 7.2 centimorgans (cM) were genotyped as described previously (25). These markers included 337 microsatellite markers (dinucleotide, trinucleotide, and tetranucleotide repeats) and 106 polymorphisms in 65 candidate genes. The results were stored in a local dBase IV database, GENEMARK, which inspects results for Mendelian inheritance incompatibilities within nuclear families and extended pedigrees. The OMIM gene map (http://www.ncbi.nlm.nih.gov/htbin-post/Omim/getmap) and the bioinformatic site from the University of California, Santa Cruz (http://genome.ucsc.edu/) were used to identify candidate genes.

Linkage analyses

The triglyceride and cholesterol variables were $\log_{10}$ transformed to normalize their distribution before adjustment for covariates. Lipid and lipoprotein traits were adjusted for the effects of age, including squared and cubic terms to allow for nonlinearity, as well as for gender and BMI. The adjustments were performed using a stepwise multiple regression procedure retaining only significant terms ($P < 0.05$). Separate regression models were used for each of six age-by-sex (<30, 30–50, and ≥50 years in male and female) groups. Regression parameters were estimated after exclusion of outliers (±3 SD), and residuals were computed for all subjects. Residual scores were then standardized to a mean of 0 and an SD of 1 before genetic analyses. Subjects whose values were greater than 4 SD from the mean and were separated by more than 1 SD from the nearest internal score were excluded from the analysis because they were considered to be sparse outliers (four subjects for total cholesterol, one for triglyceride, two for LDL-C, and three for HDL-C). Adjustments of the phenotypes were performed using SAS (version 8.02).

We conducted quantitative trait linkage analyses using two different methods. We used the new Haseman-Elston regression-based method (26), which models the trait covariance between sibpairs, instead of the squared sibpair trait difference used in the original method. It regresses the mean-corrected sibpair product on the number of alleles shared identical by descent (IBD). Singlepoint and multipoint estimates of alleles shared IBD were generated using GENIBD software, and linkage was tested using SIBPAL2 software from the S.A.G.E. 4.0 statistical package (27). The maximum number of sibpairs was 534. In the alternative method, the phenotypic covariance among members of a family is assumed to result from the additive effects of linkage attributable to a QTL, a residual familial component attributable to polygenes, and an individual-specific random environmental component. Hypothesis testing was performed by the likelihood ratio test, which tests the null hypothesis that the additive genetic variance attributable to the QTL (σ_q) equals zero ($\sigma_q = 0$) by comparing the likelihood of this restricted model with that of a model in which σ_q is estimated ($\sigma_q \neq 0$). The difference in minus twice the log likelihoods is approximately distributed as a 50:50 mixture of a χ^2 and a point-mass distribution at zero. The logarithm of the odds (LOD) score was computed as $\chi^2/(2 \log_e 10)$. These analyses were performed using the quanti-

TABLE 1. Characteristics of genomic-scan participants by gender and generation groups

	Fathers (n = 194)	Mothers (n = 261)	Sons (n = 213)	Daughters (n = 262)
Age (years)	55.5 ± 10.1	54.8 ± 12.5	26.7 ± 9.7	27.9 ± 10.6
BMI (kg/m^2)	28.4 ± 5.8	28.7 ± 8.0	26.4 ± 7.2	26.8 ± 8.8
Cholesterol (mmol/l)	5.42 ± 0.85	5.44 ± 1.08	4.47 ± 0.91	4.48 ± 0.80
LDL-C (mmol/l)	3.49 ± 0.78	3.35 ± 0.95	2.77 ± 0.78	2.64 ± 0.70
HDL-C (mmol/l)	1.07 ± 0.27	1.37 ± 0.35	1.11 ± 0.25	1.28 ± 0.30
Triglyceride (mmol/l)	1.96 ± 1.12	1.62 ± 0.81	1.31 ± 0.69	1.23 ± 0.56

Values are means ± SD. BMI, body mass index; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol.

tative transmission disequilibrium test computer program (28). We used a LOD score of ⩾3.00 ($P \leqslant 0.0001$) to indicate adequate evidence of linkage and a LOD threshold of ⩾1.75 ($P \leqslant 0.0023$) as suggestive (29).

RESULTS

Before the genome-scan analysis, total cholesterol, triglyceride, LDL-C, and HDL-C levels were adjusted in a stepwise manner for the effects of age, age^2, age^3, gender, and BMI. These covariates accounted for 0–15.3%, 5.7–30.2%, 0–10.6%, and 6.6–32.2% of the total phenotypic variation in total cholesterol, triglyceride, LDL-C, and HDL-C, respectively, depending on the age-by-sex groups (see Methods).

An overview of the variance component-based linkage results for the LDL-C, HDL-C, and triglyceride phenotypes is given in **Fig. 1**. Numerous peaks with LOD scores greater than 1.75 are observed for LDL-C, including on chromosomes 1q43, 3q23, 11q13-q24, 13q32, 15q26, 18q21, and 19q13. The highest peak among them is located on chromosome 19q13, with a LOD score of 3.59 for a marker within the gene coding apoE. The peak on chromosome 11q was quite broad and encompassed a 1-LOD support interval (1 LOD unit reduction from the peak) of ~40 cM. In contrast, only one chromosomal region reaches the significance level of linkage for HDL-C. However, this peak located on chromosome 12q14 provided the highest LOD score observed in the study (LOD = 4.06). In the case of triglycerides, four genomic regions exceeded the 1.75 LOD score threshold: 2p14, 5q14, 11p13, and 11q24. Although interesting, these peaks did not reach the magnitude of those observed for LDL-C and HDL-C. Remarkably, the two peaks for triglycerides on chromosome 11 did not overlap with the large one observed for LDL-C.

Linkage was also tested using singlepoint and multipoint allele-sharing methods. All chromosomal regions with a variance-component LOD score of ⩾1.75 or an allele-sharing P value of ⩽0.0023 are reported in **Table 2** for the four lipid traits. Six, 17, 9, and 13 markers showed suggestive evidence of linkage with at least one of the methods used for total cholesterol, LDL-C, HDL-C, and triglycerides, respectively. Among all of these markers, only seven of them provided suggestive evidence of linkage (LOD ⩾ 1.75 or $P \leqslant 0.0023$) with both the allele-sharing and the variance-components linkage methods. These markers are highlighted in Table 2 and correspond to chromosome regions 1q43, 15q26.1, and 19q13.32 for LDL-C, 12q14.1 for HDL-C, and 2p14, 11p13, and 11q24.1 for triglycerides. All singlepoint and multipoint results around these chromosomal regions are provided in the supplemental table. Although some markers provided fairly good evidence of linkage with total cholesterol, results were inconsistent across linkage methods (Table 2). Positional candidate genes in the seven regions identified as most promising in addition to the large 11q region for LDL-C are summarized in **Table 3**.

DISCUSSION

The present study confirms the existence of multiple loci influencing blood lipids and lipoproteins. Based on this genome-wide scan, evidence of linkage was found on chromosome regions 1q43, 11q13-q24, 15q26.1, and 19q13.32 for LDL-C, 12q14.1 for HDL-C, and 2p14, 11p13, and 11q24.1 for triglycerides. Some of these regions have been previously linked to lipid-related phenotypes, whereas others represent new findings. In genome-wide linkage studies, independent replication of positive findings is important to distinguish between true and false positives (4). For complex traits, determining whether a given study has replicated an initial study's findings is difficult. It has been demonstrated that the location estimate may be many centimorgans away from the true locus (30). Given this variation in position, it is difficult to distinguish between random variation around a single locus and the presence of multiple genetic signals. Despite these limitations, we present in **Table 4** the positive findings reported by previous genome scans on lipid-related phenotypes that are located around (and potentially replicated) the chromosomal regions identified in the current study.

The peak observed on 1q43 for LDL-C in this study represents a newly identified locus. The 1q region is a well-recognized region for familial combined hyperlipidemia (FCHL) (31–33) and has also been linked to cholesterol (6) and apoA-II levels (34) as well as with lipoprotein [a] concentrations (35). However, our peak on 1q is more distal from the centromere compared with peaks found in the other studies. Multiple peaks were observed on chromosome 11, including two for triglycerides and another large one for LDL-C. Genome-wide evidence of linkage has also been demonstrated on this chromosome for LDL-C

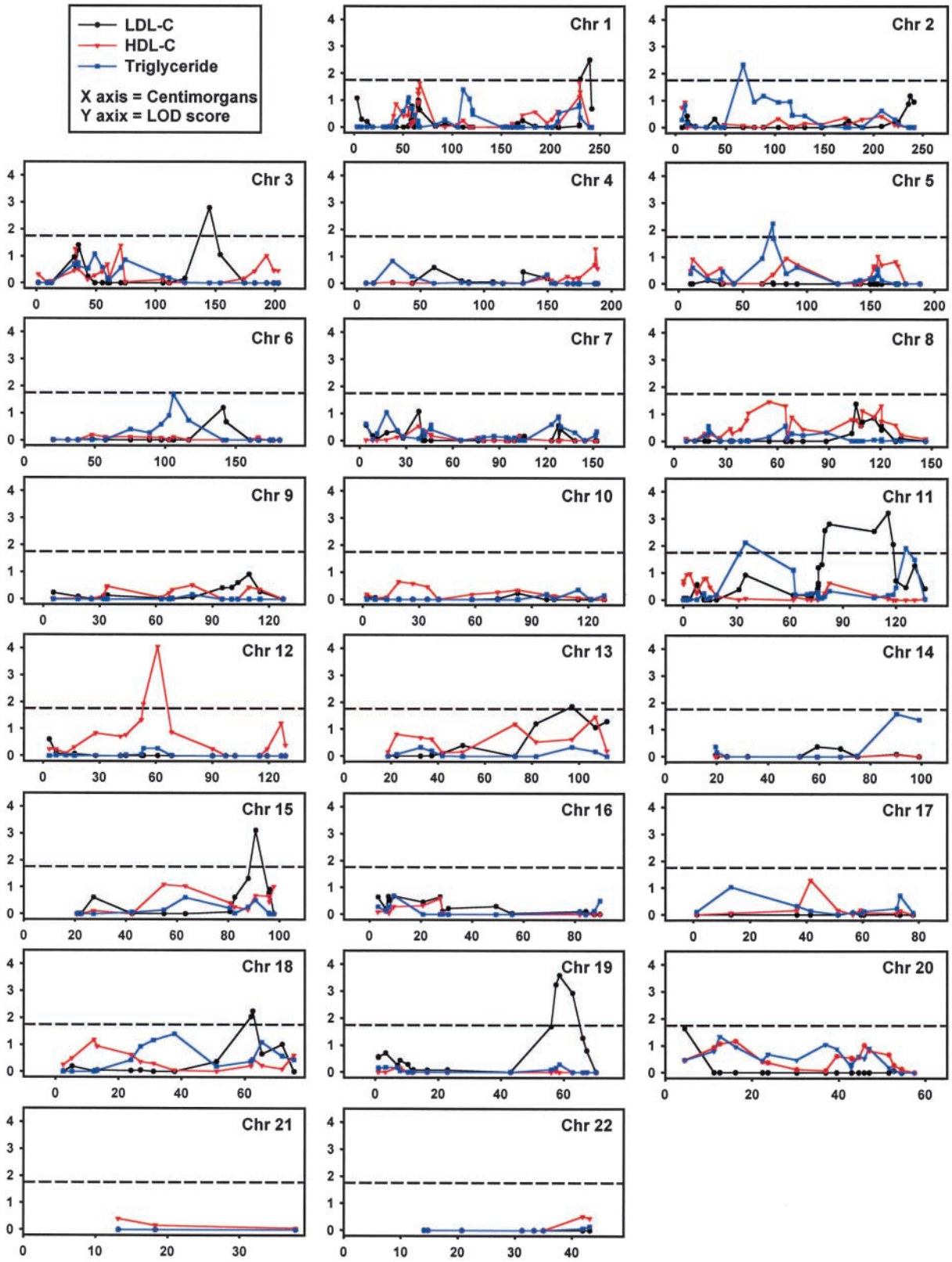

Fig. 1. Variance-component linkage results for all autosomal chromosomes (Chr) with LDL-cholesterol (LDL-C), HDL-C, and triglyceride phenotypes. Logarithm of the odds (LOD) scores are presented on the *y* axis, and genetic distances are presented on the *x* axis in centimorgans. The three traits are adjusted for the effects of age, age^2, age^3, gender, and body mass index. The horizontal dashed line represent a LOD score of 1.75.

TABLE 2. Summary of *P* values of <0.0023 from the allele-sharing method (singlepoint and multipoint) or LOD scores of >1.75 from the variance-component method

Phenotype	Chromosome	Distance	Marker[a]	*P*		LOD Score
				Singlepoint	Multipoint	
		cM				
Cholesterol	1	239.8	D1S547	0.000208	0.000437	1.21
	2	241.2	D2S2968	0.042940	0.030438	2.04
	15	90.8	D15S652	**0.000077**	0.036295	0.73
	16	20.9	D16S403	0.001993	0.018806	0.96
	18	71.9	ATA82B02	**0.000059**	0.002177	1.15
	20	4.5	D20S482	0.001804	0.039883	0.46
LDL-C	1	230.4	D1S3462	0.026331	0.005501	1.79
	1	239.8	**D1S547**	**0.000008**	**0.000078**	2.50
	3	145.1	D3S1764	0.028576	0.012546	2.79
	11	79.8	D11S911	0.327252	0.004652	2.57
	11	82.3	D11S2002	0.012992	0.001407	2.81
	11	107.8	D11S2000	0.040486	0.001069	2.55
	11	115.7	DRD2	0.009048	0.001213	**3.22**
	11	118.5	UCP3	0.325612	0.022330	2.06
	13	97.0	D13S793	0.007766	0.015280	1.85
	15	90.8	**D15S652**	0.000315	0.000288	**3.11**
	18	62.0	D18S38	0.051564	0.005764	2.04
	18	62.5	MC4R	0.150490	0.005014	2.24
	18	71.9	ATA82B02	0.001517	0.017365	1.01
	19	57.5	D19S178	0.012600	0.000617	**3.24**
	19	58.6	**APOE**	**0.000005**	0.000241	**3.59**
	19	62.8	GYS1	0.194859	0.001568	2.93
	20	4.5	D20S482	**0.000013**	0.000690	1.64
HDL-C	2	171.7	D2S1776	0.001052	0.005608	0.35
	12	53.4	D12S398	0.042114	0.004348	1.93
	12	61.0	**D12S334**	0.002204	0.000746	**4.06**
	12	68.5	D12S375	0.002196	0.001407	0.88
	16	7.4	D16S287	0.000251	0.313383	0.21
	18	12.3	D18S542	0.061955	0.000717	1.19
	18	13.3	MC5R	0.121424	0.002061	0.94
	20	45.9	D20S197	0.015407	0.001505	1.01
	20	47.0	D20S176	0.627925	0.000466	0.81
Triglyceride	1	111.2	D1S2860	0.000586	0.001153	1.39
	1	117.7	ATP1A1	0.247956	0.002042	1.05
	1	229.3	AGT	0.000893	0.008674	0.82
	2	67.8	**D2S441**	**0.000009**	0.001346	2.32
	4	149.6	UCP	**0.000043**	0.189994	0.33
	5	73.5	D5S1501	0.036299	0.004120	2.23
	5	73.9	CART	**0.000068**	0.015052	1.67
	7	151.6	NOS	0.000848	0.072359	0.21
	8	20.0	LPL	0.001273	0.032691	0.55
	8	88.3	D8S1119	0.001159	0.126362	0.31
	11	31.3	ATA34E08	0.022495	0.000330	1.69
	11	34.9	**D11S1392**	0.000105	**0.000009**	2.11
	11	125.6	**D11S4464**	0.001204	0.001890	1.93

P values of ≤0.0001 and logarithm of the odds (LOD) scores of ≥3.00 are shown in boldface.

[a] Markers showing suggestive evidence of linkage ($P \leq 0.0023$ or LOD score ≥ 1.75) with the three linkage methods used are shown in boldface.

in the NHLBI Family Heart Study (9). In addition, suggestive linkages have been reported for total cholesterol levels in the Rochester Family Heart Study (36), for FCHL in Dutch families (37), and for increased apoB levels in Finnish families (18) (Table 4). In addition, dense marker linkage analysis restricted to a specific region (11q23) of chromosome 11 has provided evidence of linkage with hypoalphalipoproteinemia (16). For chromosome 15, the peak observed on the q-terminal side for LDL-C overlapped with the newly identified locus for autosomal recessive hypercholesterolemia observed in Sardinian families (38). A QTL for unesterified HDL_{2b}-C reported in the San Antonio Family Heart Study is also located close to the LDL-C signal observed in the present study (39). One of the strongest signals in this genome scan was found on 19q13 with LDL-C. This region has produced genome-wide evidence of linkage with different lipid-related phenotypes before including LDL-C among the Hutterites population (8), triglyceride in Utah families (20), and apoE levels in the Rochester Family Heart Study (36). A suggestive QTL that influences variation in cholesterol concentrations of large LDL particles (LDL-2) has also been mapped at this location in the San Antonio Family Heart Study (40). The highest LOD score for the present genome scan was observed on 12q with HDL-C. No QTLs for lipid-related phenotypes have been reported around

TABLE 3. Positional candidate genes within chromosomal regions showing suggestive evidence of linkage with the three linkage methods

Phenotypes	Chromosome Region	Marker	LOD Score	Candidate Genes (Distance from the Marker in Mb[a])
LDL-C	1q43	D1S547	2.50	ABCB10 (−11.7), GGPS1 (−6.2)
	11q14.1	D11S2002	2.81	LRP5 (−11.6), CPT1A (−11.2), UCP2 (−6.3), UCP3 (−6.2)
	11q23.2	DRD2	3.22	ACAT1/SOAT1 (−5.5), APOA1 (3.4), APOC3 (3.4), APOA4 (3.4), APOA5 (3.3)
	15q26.1	D15S652	3.11	CYP11A (−18.3)
	19q13.32	APOE	3.59	LRP3 (−11.7), LIPE (−2.5), APOC4 (0), APOE (0), APOC1(0), APOC2 (0)
HDL-C	12q14.1	D12S334	4.06	SOAT2 (−7.3), APOF (−4.4), LRP1 (−3.5), CYP27B1 (−3.2)
Triglyceride	2p14	D2S441	2.32	FABP1 (19.6)
	11p13	D11S1392	2.11	ABCC8 (−17.6), LRP4 (12.6)
	11q24.1	D11S4464	1.93	ACAT1 (−15.4), APOA1 (−6.6), APOC3 (−6.6), APOA4 (−6.6), APOA5 (−6.6), ACAD8 (11)

ABC, ATP binding cassette; ACAD8, acyl-CoA dehydrogenase family, member 8; APO, apolipoprotein; CPT1A, carnitine palmitoyltransferase 1A; CYP, cytochrome P450; FABP1, fatty acid binding protein 1; GGPS1, geranylgeranyl diphosphate synthase 1; LIPE, hormone-sensitive lipase; LRP, low density lipoprotein receptor-related protein; SOAT, sterol *O*-acyltransferase; UCP, uncoupling protein.

[a] Distances separating the marker and the candidate genes are taken from the bioinformatic site of the University of California, Santa Cruz (http://genome.ucsc.edu/). Negative or positive values indicate that the gene is located downstream or upstream from the marker, respectively.

this area, suggesting that this locus represents a newly identified region influencing HDL-C levels. Finally, despite being of lesser magnitude, the 2p region provided consistent evidence of linkage for triglyceride levels. This region is near the locus suggested for low HDL-C (11), unesterified HDL_{2a}-C level (39), and triglyceride/HDL ratio (41).

In contrast, some of the most promising regions linked to lipid-related phenotypes reported to date were not replicated. This is the case for total cholesterol on 19p (5), for HDL-C-related phenotypes on 5q (10), 9p (12), and 16q (14, 15), and for triglyceride levels on 10p (18) and 15q (19). The lack of replication in these regions is not surprising and could be attributable to a variety of reasons. First, the previous genome-scan studies were conducted in populations with a variety of ethnic backgrounds and that were ascertained for different reasons. Thus, there may be etiological heterogeneity. Second, it is conceivable that similar phenotypes may not have common causes and different lipoprotein/lipid genes may operate in different subsets of families. In addition, multiple interacting loci or environmental factors are likely to participate in the regulation of these phenotypes. As a consequence, complex genetic and environmental contexts may be required for lipoprotein/lipid genes to be expressed. Accordingly, replication of a previously significant linkage can be difficult to achieve when dealing with complex quantitative traits such as blood lipids.

Other than the single gene defects known to cause dyslipidemia (3), little is known about the specific major ge-

TABLE 4. Possible replication of the current chromosomal regions identified with those from previous genome scans on lipid-related phenotypes

Chromosome	Location[a]	Study	Phenotypes	LOD Score
	Mb			
1q	239.8	This report	LDL-C	2.5
2p	68.4	This report	Triglyceride	2.3
	73.1	Finnish families (11)	HDL-C	2.1
	75.5–88	Northeastern Indian (41)	Triglyceride/HDL ratio	1.9
	85.1	San Antonio FHS (39)	Unesterified HDL_{2a}-C	2.3
11	30.2	Rochester FHS (36)	Cholesterol	1.8
	36.2	This report	Triglyceride	2.1
	46.3	National Heart, Lung, and Blood Institute FHS (9)	LDL-C	3.7
	60.9	Dutch families (37)	Familial combined hyperlipidemia	2.6
	79.8–130.6	This report	LDL-C	3.2
	125.6	Finnish families (18)	Apolipoprotein B	1.8
	125.6	This report	Triglyceride	1.9
12q	61	This report	HDL-C	4.1
15q	81.5	San Antonio FHS (39)	Unesterified HDL_{2b}-C	2.5
	88.3–92.7	Sardinian families (38)	Familial hypercholesterolemia	3.3
	89	This report	LDL-C	3.1
19q	31	Hutterites (8)	LDL-C	$P = 0.0001$
	34.7–58.6	Rochester FHS (36)	Apolipoprotein E	4.2
	35.8–45.1	San Antonio FHS (40)	LDL-2	1.9
	45.1–46.1	Utah families (20)	Triglyceride	3.2
	46.1	This report	LDL-C	3.6

FHS, family heart study.

[a] The physical distance is the location of the marker(s) that defines the peak or is closest to the signal and is obtained from the genome browser of the University of California, Santa Cruz (http://genome.ucsc.edu).

netic determinants of blood lipids. From this genome-wide scan analysis, a number of promising candidate genes can be located in the vicinity of the genomic regions showing evidence of linkage. These candidates as well as their distances from the peak are provided in Table 3. First, the strong evidence of linkage on chromosome 19q comes from a marker located within the apoE gene. It is well known that genetic variations in this particular gene modulate plasma lipid levels (42). Nevertheless, there are other genes within this region worth mentioning. Indeed, the apoE gene lies in a cluster of apolipoprotein genes containing apoC-I, apoC-II, and apoC-IV. These apolipoproteins are constituents of lipoproteins and serve as activators for enzymes. The hormone-sensitive lipase gene is also located under the 19q peak. Finally, the large genetic distance (35 Mb) separating the LDL receptor gene from the peak rules out its possible involvement in this signal.

Interesting candidate genes are also located under the broad peak observed on 11q. The width of this peak, covering more than one-third of the total chromosome (LOD $\geq$ 1.00), may be attributable to the major effect of a gene or may indicate overlapping peaks that are caused by more than one gene. The ACAT1 gene, known to be involved in the esterification of intracellular cholesterol, is located near the highest point of the peak (115.7 cM). Even closer to the signal is the apoA-I/apoC-III/apoA-IV gene cluster. Additional candidate genes are located in the 80 cM region of the peak (Table 3). Thus, the number of candidate genes in that region suggests the existence of more than one gene being causative. Promising genes were also located within the HDL-C locus on 12q. Particularly interesting is the apoF gene, which encodes a protein product known to inhibit the cholesteryl ester transfer protein-mediated transfer of triglyceride and cholesterol between plasma lipoproteins (43). However, the LDL receptor-related protein 1, known to bind apoE-containing lipoproteins, is also close to the signal.

In summary, despite the candidate genes/regions identified to date, the specific loci acting on the variability of serum lipids in individuals who have not been selected for lipid disorders are still unknown. This genome scan presented evidence of linkage for lipid-related traits on eight chromosomal regions: 1q43, 11q13-q24, 15q26.1, and 19q13.32 for LDL-C, 12q14.1 for HDL-C, and 2p14, 11p13, and 11q24.1 for triglyceride levels. Most of these regions have been linked to lipoprotein/lipid traits before. However, the highest signal (LOD = 4.1 at 12q14.1) observed in this genome scan for HDL-C level represents a newly identified region. Interesting candidate genes are located within this chromosomal region and the other regions identified. These positional candidate genes represent hypotheses to be tested in future studies.

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