review

Compendium of genome-wide scans of lipid-related phenotypes: adding a new genome-wide search of apolipoprotein levels[S]

Yohan Bossé,[*,†] Yvon C. Chagnon,[§] Jean-Pierre Després,[*,†,] Treva Rice,[††] D. C. Rao,[††] Claude Bouchard,[§§] Louis Pérusse,[***] and Marie-Claude Vohl[1,*,†]**

Lipid Research Center,* Laval University Medical Research Center, Québec, Canada; Department of Food Sciences and Nutrition,† Laval University; Laval University Robert-Giffard Research Center,§ Beauport; The Québec Heart Institute,** Québec, Canada; Division of Biostatistics,†† Washington University School of Medicine, St. Louis, MO; Pennington Biomedical Research Center,§§ Baton Rouge, LA; and Division of Kinesiology,*** Department of Social and Preventive Medicine, Laval University, Québec, Canada

Abstract **The genetic dissection of complex inherited diseases is a major challenge. Despite limited success in finding genes, substantial data based on genome-wide scan strategies is now available for a variety of diseases and related phenotypes. This can perhaps best be appreciated in the field of lipid and lipoprotein levels, where the amount of information generated is becoming overwhelming. We have created a database containing the results from whole-genome scans of lipid-related phenotypes undertaken to date. The usefulness of this database is demonstrated by performing a new autosomal genomic scan on apolipoprotein B (apoB), LDL-apoB, and apoA-I levels, measured in 679 subjects of 243 nuclear families. Linkage was tested using both allele-sharing and variance-component methods. Only two loci provided support for linkage with both methods: a LDL-apoB locus on 18q21.32 and an apoA-I locus on 3p25.2. Adding those findings to the database highlighted the fact that the former is reported as a lipid-related locus for the first time, whereas the latter has been observed before. However, concerns arise when displaying all data on the same map, because a large portion of the genome is now covered with loci supported by at least suggestive evidence of linkage.**—Bossé, Y., Y. C. Chagnon, J-P. Després, T. Rice, D. C. Rao, C. Bouchard, L. Pérusse, and M-C. Vohl. **Compendium of genome-wide scans of lipid-related phenotypes: adding a new genome-wide search of apolipoprotein levels. *J. Lipid Res.* 2004.** 45: **2174–2184.**

Supplementary key words lipoproteins • quantitative trait locus • cardiovascular risk factors • linkage • dyslipidemia

Mapping genes involved in complex human diseases is one of the major challenges in human genetics. With the increasing incidence of chronic diseases in industrialized societies, finding these genes is clinically and economically relevant. During the past few years, considerable research resources have been deployed to study the genetic causes of complex human diseases to better understand their pathogenesis and, ultimately, improve prevention strategies, diagnostic tools, and therapies (1). Encouraged by the early success in the identification of genes responsible for monogenic diseases, many investigators have embraced genome-scan strategies. This trend has resulted in an enormous amount of information, which is now typically difficult to synthesize and interpret for a given complex disease.

The importance ascribed to lipid and lipoprotein levels in risk estimation and in the treatment of coronary heart disease (CHD) (2) has stimulated molecular studies to investigate the genetic causes underlying human variation in these traits. A large number of genome-wide screens of serum lipid-related phenotypes have been performed to date, and a review of such studies seems timely. Because linkage results must be replicated to be credible (3), a compendium of published quantitative trait loci (QTLs) may facilitate the identification of replicated findings. To provide an example on how such information can be useful, we add the results of a new genome scan of apolipoprotein B (apoB) and apoA-I levels to this compendium.

ApoB and apoA-I levels are good markers of CHD risk (4, 5). A number of studies have clearly established that genetic factors contribute to interindividual differences in apolipoprotein levels. An elegant study comparing identical and fraternal twins reared together with twins reared apart has shown that a large portion of the variance in

Manuscript received 26 July 2004 and in revised form 26 August 2004.

Published, JLR Papers in Press, September 17, 2004.
DOI 10.1194/jlr.R400008-JLR200

Abbreviations: apoB, apolipoprotein B; CHD, coronary heart disease; cM, centimorgan; IBD, identical by descent; LOD, logarithm of the odds; QFS, Québec Family Study; QTL, quantitative trait locus.

[1] To whom correspondence should be addressed.
e-mail: marie-claude.vohl@crchul.ulaval.ca

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

apoB and apoA-I levels is attributable to genetic factors, with heritability estimates greater than 50% (6). In addition, based on complex segregation analyses, major gene effects have been reported for these two phenotypes (7, 8). Mutations in genes that encode apoB, LDL receptor, and ABCA1 have been implicated in monogenic disorders altering plasma apolipoprotein levels, including familial hypobetalipoproteinemia [Online Mendelian Inheritance in Man (OMIM) 605019], familial hypercholesterolemia (OMIM 143890), and hypoalphalipoproteinemia (OMIM 604091). However, these mutations do not account for the variation in plasma apoB and apoA levels in the general population. In an attempt to identify the responsible genes, a large number of association and linkage studies have been performed with candidate genes. These studies have been difficult to interpret because of conflicting results, lack of replication, and the occurrence of positive findings only in specific subgroups. Perhaps the highest linkage signal for apoB levels was reported in Dutch pedigrees on chromosome 1p31 [logarithm of the odds (LOD) = 4.7] (9). Other suggestive linkages (LOD > 1.7) have been found on chromosome 12q24 for apoA-I (10) and on 1p, 11q24, 21q21, and Xq23 for apoB (11, 12). However, other genome-wide scans failed to identify QTLs for apoB levels (10, 13). To search for additional loci influencing apoB and apoA-I levels or to replicate previous findings, we performed an autosomal genome scan among 243 nuclear families participating in the Québec Family Study (QFS).

MATERIALS AND METHODS

Population

Subjects were participants in the QFS, an ongoing project with French-Canadian families investigating the genetics of obesity and its comorbidities (14). In this study, 679 subjects of 243 nuclear families had apolipoprotein measurements available. This cohort represents a mixture of random sampling and ascertainment through obese (body mass index > 32 kg/m^2) probands. **Table 1** presents the characteristics of subjects in each of the sex and generation groups. The study was approved by the Laval University Medical Ethics Committee, and all subjects provided written informed consent. All procedures followed were in accordance with institutional guidelines.

Apolipoprotein measurements

Blood samples were obtained from an antecubital vein in the morning after a 12 h overnight fast. The apolipoprotein measurements were performed with the rocket immunoelectrophoretic method (15). ApoB concentrations were measured in plasma, whereas LDL apoB and apoA-I concentrations were measured in the infranatant (d > 1.006 g/ml) obtained after separation of very low density lipoprotein from the plasma by ultracentrifugation. The measurements were calibrated with reference standards obtained from the Centers for Disease Control and Prevention (Atlanta, GA).

Linkage analysis

A total of 443 markers spanning the 22 autosomal chromosomes with an average intermarker distance of 7.2 centimorgan (cM) were genotyped as described by Chagnon et al. (16). The apolipoprotein traits were adjusted for the effects of age (up to cubic polynomial to allow for nonlinearity), gender, and body mass index using a stepwise multiple regression procedure retaining only significant covariates ($P < 0.05$) as described previously (17). Adjustments of the phenotypes were performed using SAS (version 8.2).

We conducted quantitative trait linkage analyses using both allele-sharing and variance-component methods. For the allele-sharing method, we used the new Haseman-Elston regression-based method (18), which models the mean corrected cross-product of the sibs' trait values instead of the squared sib pair trait difference used in the original method (19). Two-point and multipoint (at 1 cM intervals) estimates of alleles shared identical by descent (IBD) were generated using GENIBD software, and linkage was tested using SIBPAL2 software from the S.A.G.E. 4.0 statistical package (20). The maximum number of sib pairs was 347. Empirical P values of the test statistic were also computed using a Monte Carlo permutation procedure with 10,000 replicate permutations for genomic regions containing two-point linkage markers with suggestive evidence of linkage ($P < 0.0023$). Linkage was also performed with a variance-component model using the QTDT (quantitative transmission disequilibrium test) computer program (21). Under this model, a phenotype is influenced by the additive effects of a QTL (q), a residual familial component attributable to polygenes (g), and a residual nonfamilial component (e). Hypothesis testing was performed with the likelihood ratio test. The likelihood of the null hypothesis is obtained by restricting the additive genetic variance attributable to the QTL (σ_q) equal to zero ($\sigma_q = 0$). The test is conducted by contrasting this restricted model with the alternative, in which σ_q is estimated ($\sigma_q \neq 0$). The difference in minus twice the log likelihoods between the null and alternative hypotheses is approximately distributed as a Chi-square, which allowed LOD score computation as $\chi^2/(2 \log_e 10)$. We have taken a LOD score of $\geq$3.00 ($P \leq 0.0001$) as evidence of linkage and a LOD score of $\geq$1.75 ($P \leq 0.0023$) as evidence of suggestive linkage (22). We have also retained LOD scores of $\geq$1.18 ($P \leq 0.01$) to identify potential independent confirmation of a previously reported significant linkage (23).

Database

The initial search for genome-wide scan publications on lipid-related phenotypes was accomplished with keywords (genome scan + lipoprotein and linkage + lipoprotein + genome) at the bioinformatics site of the National Center for Biotechnology In-

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

Variable	Fathers (n = 132)	Mothers (n = 175)	Sons (n = 164)	Daughters (n = 208)
Age (years)	54.1 ± 9.7	50.9 ± 9.2	27.2 ± 10.8	28.8 ± 11.6
Body mass index (kg/m^2)	29.5 ± 6.3	30.5 ± 8.5	27.4 ± 7.8	28.3 ± 9.4
Total apoB (g/l)	1.13 ± 0.22	1.02 ± 0.24	0.89 ± 0.23	0.87 ± 0.20
LDL-apoB (g/l)	1.00 ± 0.20	0.90 ± 0.21	0.80 ± 0.21	0.77 ± 0.19
ApoA-I (g/l)	1.20 ± 0.17	1.33 ± 0.20	1.19 ± 0.16	1.24 ± 0.17

apoB, apolipoprotein B. Values are means ± SD.

formation (www.ncbi.nlm.nih.gov). The publication list was completed and verified by examination of both the discussion section and the reference list of the publication found in the initial search. The search focused on results published before the end of April 2003 and excluded abstracts presented at meetings.

A whole-genome scan Excel database for lipid-related phenotypes was established. The database contained bibliographic details (first author, source, and years), study population (ethnicity), ascertainment scheme, phenotypic traits, sample size details (number of individuals, sib pairs, and families), linkage analysis methods, and results. Any evidence of linkage, from suggestive and better (LOD score ≥ 1.7 or $P \leq 0.0023$) was treated as an observation (a hit). Results were entered in the database with the name of the linked marker/gene, its location (megabase and chromosomal band), and its maximum LOD score or Z score or P value. For most studies, markers were provided in the papers and were those defining the peak or were the closest to the signal. When the marker's name or the specific location of the QTL (hits)

TABLE 2. Summary of LOD scores ≥ 1.18 or P values ≤ 0.01

Trait	Chromosome Band[a]	Distance	Marker	P[b]		LOD Score
				Two-Point (Empirical P Value)	Multipoint	
		cM				
Total apoB	2q33.3	208.3	D2S1384	0.004439	NS	NS
	6p22.3	30.8	D6S2439	NS	NS	1.32
	6p21.33	38.0	TNFα	NS	NS	1.28
	6p21.1	48.1	D6S1017	NS	NS	1.34
	6q23.1	143.2	D6S1040	NS	NS	1.35
	15q26.1	90.8	D15S652	0.007851	NS	NS
	18q21.32	62.0	D18S38	0.005121	NS	NS
	19q13.2	56.0	LIPE	0.009221	0.009682	NS
	19q13.32	58.6	APOE	**0.002271** (0.022600)	NS	NS
	20p13	4.5	D20S482	0.002712	NS	NS
LDL-apoB	1q42.2	230.4	D1S3462	NS	0.009261	NS
	1q43	239.8	D1S547	0.005565	0.006285	NS
	2q35	221.7	D2S434	NS	NS	1.31
	4q21.23	88.0	D4S1534	0.007840	NS	NS
	7q32.1	127.9	D7S1875	0.008742	NS	NS
	11q22.3	107.8	D11S2000	NS	NS	1.28
	12p13.32	3.3	D12S372	0.006271	0.009195	NS
	13q32.1	97.0	D13S793	0.006976	NS	NS
	18q21.32	62.0	D18S38	0.004792	0.007469	**2.05**
	18q21.32	62.5	MC4R	NS	NS	1.33
	19q13.2	56.0	LIPE	**0.001798** (0.097400)	0.003889	NS
	19q13.32	58.6	APOE	**0.001581** (0.051000)	NS	NS
	20p13	4.5	D20S482	**0.000051** (0.003200)	0.005086	NS
ApoA-I	3p25.2	12.6	D3S1259	**0.000022** (0.040200)	**0.000161**	1.21
	4q31.1	149.6	UCP1	NS	**0.000800**	NS
	4q31.21	153.0	D4S1586	NS	**0.000001**	NS
	5q21.3	138.0	D5S1453	**0.000084** (0.038600)	NS	NS
	5q31.3	158.7	D5S1480	**0.001577** (0.009200)	NS	NS
	5q33.2	169.8	D5S497	0.003630	NS	NS
	7p22.2	4.2	D7S3056	0.002641	NS	NS
	9q31.3	100.2	D9S1835	**0.000086** (0.052600)	NS	NS
	9q33.3	115.2	D9S282	**0.000450** (0.011689)	NS	NS
	10q21.1	58.2	D10S1221	**0.001651** (0.005800)	NS	NS
	11p15.1	18.6	SUR	**0.000900** (0.001300)	NS	NS
	11q13.2	72.1	D11S4136	NS	**0.001624**	NS
	12q24.21	115.0	D12S2070	**0.000026** (0.021000)	**0.000176**	NS
	12q24.23	119.1	D12S395	NS	0.008953	NS
	13q33.3	106.9	D13S796	NS	**0.000008**	NS
	15q11.2	21.9	D15S63	**0.000001** (0.001100)	NS	NS
	16p13.13	3.4	D16S748	NS	**0.002019**	NS
	16p13.11	6.5	D16S405	NS	**0.000091**	NS
	16p12.3	7.4	D16S287	NS	0.005713	NS
	16p13.11	7.6	D16S764	**0.000428** (0.072000)	NS	NS
	16p11.2	30.8	D16S753	NS	0.007298	NS
	16q12.1	49.3	D16S261	NS	**0.000518**	NS
	16q12.2	55.6	D16S3253	NS	**0.000006**	NS
	16q22.2	81.9	D16S2624	**0.001318** (0.336600)	NS	NS
	19q12	43.1	D19S433	NS	0.005224	NS
	20q13.2	51.6	D20S480	NS	0.002670	NS
	20q13.2	52.7	D20S120	NS	0.004233	NS
	22q13.31	41.9	D22S274	0.006556	NS	NS

LOD, logarithm of the odds.

[a] Chromosome bands are from the Human Genome browser of the University of California, Santa Cruz (http://genome.ucsc.edu/).

[b] Markers showing suggestive evidence of linkage ($P \leq 0.0023$ or LOD ≥ 1.75) are in boldface, and markers showing evidence of linkage ($P \leq 0.0001$ or LOD ≥ 3.00) are in boldface and underlined. NS, $P > 0.01$ or LOD < 1.18.

was not available in the original paper, the authors were contacted and asked to provide the missing information. To identify possible replication and compared loci across studies, the location of each linked marker/gene was positioned on a single map provided by the Human Genome browser of the University of California, Santa Cruz (assembly, June 2002; http://genome.ucsc.edu). When a two-stage strategy was reported in the publication, the *P* value of the second stage was favored unless it did not reach the criteria to be included in Table 4 (criteria based on whole-genome scan). This decision was made to take the best out of these studies considering that the criteria for claiming significant linkage are different between the first and second stages of the analysis. Similarly, when multiple linkage methods were used in the same publication, the most significant result was kept for the database.

To evaluate whether QTLs were randomly distributed across the genome, we regressed the observed hit ratio against the expected hit ratio as reported previously (24). The observed hit ratio of each chromosome was obtained as number of hits on a specific chromosome/number of hits across all chromosomes × 100; the expected hit ratio of each chromosome was obtained as number of genes on a specific chromosome/total number of genes in the genome × 100. The gene content of each chromosome and for the whole genome are from Venter et al. (25). A significant association (positive slope) between the observed and expected hit ratios would suggest that the positive linkages reported in the literature are distributed randomly across the genome. In contrast, if the association is missing, it would suggest that the observed hits are concentrated within specific chromosomes containing the genes controlling lipid and lipoprotein levels.

RESULTS

Genome scan on apoB, LDL-apoB, and apoA-I in the QFS cohort

Detailed results for all chromosomes and phenotypes are available in the three supplementary tables online. **Table 2** summarizes the markers showing weak to moderate evidence of linkage ($P \leq 0.01$ or LOD score ≥ 1.18) with the allele-sharing (two-point and multipoint) and the variance-component linkage methods. The highest variance-component LOD score was obtained for LDL-apoB on chromosome 18q21.32 (LOD = 2.05) (**Fig. 1**). Hits were also observed by the variance-component method for total apoB on 6p22.3-p21.1 and 6q23.1, for LDL-apoB on 2q35 and 11q22.3, and for apoA-I on 3p25.2.

In this study, the new Haseman-Elston linkage method yielded more genetic loci. For LDL-apoB, single-point evidence of linkage was observed on 20p13. In addition, the apoE and LIPE locus on 19q13 suggested the presence of a susceptibility locus for LDL-apoB as well as for apoB levels. The search for loci influencing apoA-I concentrations has been the most productive. Indeed, single-point linkages were demonstrated in five genomic regions: 3p25.2 (**Fig. 2**), 5q21.3, 9q31.3, 12q24.21, and 15q11.2. Suggestive evidence was also observed on 10q21.1, 11p15.1, 16p13.11, and 16q22.2. Multipoint linkage analysis, on the other hand, revealed strong evidence of linkage ($P < 0.000001$) on a 2 cM region (151–153 cM) flanked by UCP1 and D4S1586 markers. Additional multipoint linkages were observed on 13q33.3 and 16p13.11, with the strongest signals observed with markers D13S796 and D16S405, respectively. Finally, a multipoint linkage was observed on 16q12, with the highest peak ($P = 0.000003$) located between marker D16S261 and D16S3253 at 54.4 cM.

Most of the strong linkage evidence observed with the allele-sharing linkage method (both single point and multipoint) was not supported by the variance-component method. Only two loci, one at 18q21.32 (marker D18S38; Fig. 1) for LDL-apoB and the other at 3p25.2 (D3S1259; Fig. 2) for apoA-I, were supported by both the allele-sharing and the variance-component methods. These findings were added to the accumulating database derived from the published genome-wide scans for lipid-related phenotypes.

Descriptive statistics of the database containing published genome-wide scans for lipid-related phenotypes

The database included 32 citations published from 1998 through 2003. Phenotypes incorporated in the database

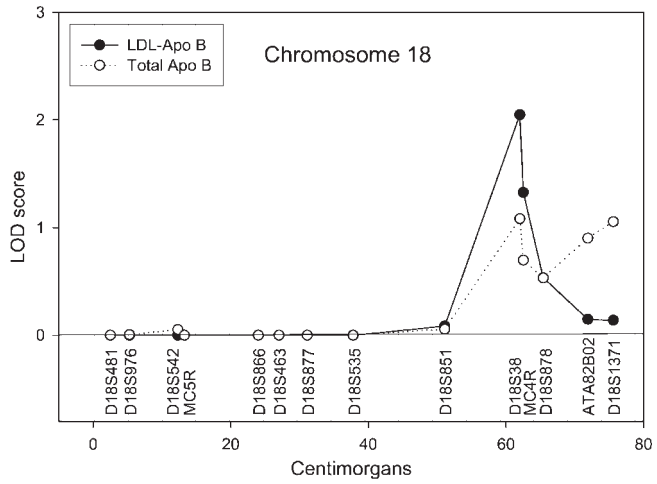

Fig. 1. Variance-component-based linkage results for chromosome 18 with the total apolipoprotein B (apoB) and the LDL-apoB phenotypes. The two traits are adjusted for the effects of age, age^2, age^3, gender, and body mass index. LOD, logarithm of the odds.

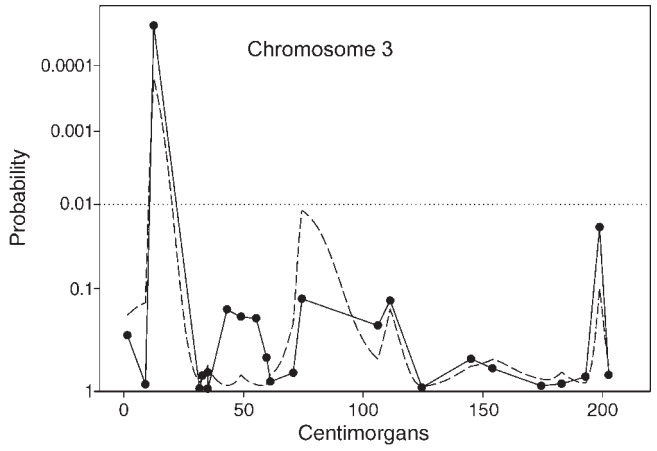

Fig. 2. Two-point (solid line) and multipoint (dashed line) sib pairs linkage analysis for chromosome 3 with the apoA-I phenotype. ApoA-I is adjusted for the effects of age, age^2, age^3, gender, and body mass index. The horizontal dotted line is a reference corresponding to $P = 0.01$.

and the number of genome scans for each phenotype are presented in **Table 3**. The most frequently studied phenotypes were total cholesterol (n = 10), LDL-cholesterol (n = 11), HDL-cholesterol (n = 18), and triglyceride (n = 16). Studies of familial hypercholesterolemia, familial combined hyperlipidemia, and familial hypobetalipoproteinemia typically used a disease affliction status (affected or unaffected) based on lipid and nonlipid criteria. The other phenotypes were treated as either quantitative or qualitative variables. The study design, the sample size, and the linkage methods varied greatly between studies. Only 15.6% of the investigations were conducted among families ascertained randomly. The remaining were ascertained based on specific clinical criteria such as familial combined hyperlipidemia, familial hypercholesterolemia, familial hypobetalipoproteinemia, CHD, myocardial infarction, low HDL-cholesterol concentrations, hypertension, obesity, and type 2 diabetes. Few studies were from genetically isolated populations, such as the Hutterites, North-Eastern Indian, and Pima Indians.

Table 4 presents a summary of the loci providing evidence of linkage from the compendium of whole-genome scans. A total of 152 hits were identified, which suggests that an average of 4.8 positive loci per study reached the suggestive threshold of significance ($P \leq 0.0023$ or LOD $\geq$ 1.7). To evaluate whether positive loci were randomly distributed across the genome, we plotted the observed number of hits against the expected number of hits for chromosomes 1–22 (**Fig. 3**) (see Materials and Methods). A close relationship between positive loci and theoretical gene content was apparent. This suggests that the null hypothesis of random linkage across the genome cannot be rejected. On the other hand, some chromosomes showed an increased number of observed hits relative to expected hits. Indeed, chromosomes 21, 13, 15, and 2 had observed-to-expected hit ratios of 2.7, 2.4, 1.8, and 1.5, respectively.

DISCUSSION

The avalanche of information anticipated from whole-genome linkage scans (23) has certainly been confirmed for the field of blood lipids and lipoproteins. The accumulating information may soon be overwhelming even for the scientists. Here, we have produced a summary of the loci providing evidence of linkage from published genome-wide scans carried out on blood lipid-related phenotypes (Table 4). We believe that such a compendium will be useful to others in the field. For instance, it may help investigators to access quickly the data on linkage for a specific genomic region or a particular phenotype. We have integrated all linkage signals on the same map to facilitate comparisons across studies.

To provide an example of the usefulness of this compendium, we performed a new genome-wide search of apoB, LDL-apoB, and apoA-I levels. The results suggested the existence of a susceptibility locus for LDL-apoB on 18q21.32 and a second one for apoA-I on 3p25.2. Additional linkages were observed with the allele-sharing linkage method, but the lack of consistency across linkage methods made the significance of these findings quit doubtful. From Table 4, we can easily identify the other QTLs that have been reported in the same regions from previous genome-wide scan studies. Interestingly, the apoA-I locus on 3p overlaps with the locus for low HDL-cholesterol levels reported in Finnish families (26) and with the locus for LDL-3 (phenotype defined as the cholesterol concentration in small LDL particles) observed in Mexican Americans (27). The re-

TABLE 3. Whole-genome scans of lipid-related phenotypes

Phenotype	No. of Studies	References
CH	10	10–12, 40–46
LDL-CH	11	13, 27, 40–42, 44–49
HDL-CH	18	10, 12, 13, 26, 40–43, 45, 46, 48–55
TG	16	10–13, 26, 40, 41, 43, 45, 46, 48, 49, 51, 54, 56, 57
Non-HDL-CH	1	13
CH/HDL-CH	1	10
LDL-CH/HDL-CH	2	45, 55
TG/HDL-CH	4	10, 45, 55, 57
TG/apoC-III	1	13
Total apoB	5	10–13, this study
LDL-apoB	1	This study
ApoA-I	2	10, this study
ApoA-II	1	10
ApoC-II	1	10
ApoC-III	2	10, 13
ApoE	1	10
Lp[a]	2	48, 49
FCHL	3	11–13
FH	5	44, 58–61
FHBL	1	28
HDL subfractions	1	29
LDL subfractions	1	27
LDL-PPD	2	17, 54

CH, cholesterol; FCHL, familial combined hyperlipidemia; FH, familial hypercholesterolemia; FHBL, familial hypobetalipoproteinemia; LDL-PPD, LDL peak particle diameter; Lp[a], lipoprotein [a]; TG, triglyceride.

TABLE 4. Evidence for the presence of linkage with lipid-related phenotypes from genome-wide scan studies: status as April 2003

Markers or Genes	Location[a]	Chromosome Band[a]	Samples	Phenotypes	*P*, *Z*, or LOD Values	References
	Mb					
D1S1608, 3735	4.3–65.1	1p36.32-p31.3	31 subjects; 1 kindred	FH	LOD = 6.8	58
D1S214, 228	6.5–13.4	1p36.31-p36.21	576 subjects; 42 families	LDL-C	LOD = 2.4	45
D1S2826, 513	18.1–31.1	1p36.13-p35.2	74 subjects; 1 kindred	FH	LOD = 3.1	44
D1S552, 2843	18.8–20.1	1p36.13-p36.12	Twins and parents	Cholesterol	LOD = 1.8	44
				LDL-C	LOD = 1.9	44
D1S2725, 2787	21.7–27.3	1p36.12-p35.3	17 subjects; 2 families	FH	LOD = 5.3	60
D1S233, 193	31.3–43	1p35.2-q34.2	576 subjects; 42 families	Ratio LDL/HDL	LOD = 2.1	45
D1S2892, 2722	40.2–41.6	1p34.2	1 pedigree; 12 families	FH	LOD = 3.1	61
D1S405	58.7	1p32.1	383 sib pairs; 75 families	TG	$Z = 3.1$	40
LEPR	65.9	1p31.2	681 subjects; 236 nuclear families	LDL-PPD	LOD = 2.6	17
D1S1665	74.4	1p31.1	269 subjects; 48 families	ApoB (qualitative)	LOD = 2.0	12
D1S484	158.6	1q23.3	383 sib pairs; 75 families	Cholesterol	$Z = 3.4$	40
D1S1679	160	1q23.3	1,406 subjects; 513 families	Lp[a]	LOD = 3.8	49
D1S104	161.3	1q23.3	269 subjects; 48 families	TG (qualitative)	LOD = 2.8	12
				FCHL	LOD = 2.5	12
D1S2623[b]	180.4	1q25.3	649 sib pairs	HDL-C	LOD = 2.1	41
D1S547	239.8	1q43	930 subjects; 292 nuclear families	LDL-C	LOD = 2.5	46
D2S2211[b]	7.3	2p25.1	649 sib pairs	Cholesterol	LOD = 2.2	41
D2S2952	7.9	2p25.1	269 subjects; 48 families	ApoB (qualitative)	LOD = 1.8	12
				TG (qualitative)	LOD = 1.8	12
			240 subjects; 18 families	FCHL	LOD = 2.6	13
D2S423	9.7	2p25.1	269 subjects; 48 families	FCHL	LOD = 2.2	12
			29 families	HDL-C (qualitative)	LOD = 3.4	26
D2S1788	36.2	2p22.3	547 sibs; 188 nuclear families	TG	LOD = 1.7	43
D2S441	68.4	2p14	930 subjects; 292 nuclear families	TG	LOD = 2.3	46
D2S1394	73.1	2p13.2	25 families	HDL-C (qualitative)	LOD = 2.1	26
D2S286, 2216	75.5–88	2p12-p11.2	535 subjects; 99 families	Ratio TG/HDL	LOD = 1.9	55
D2S1790	85.1	2p11.2	477 subjects; 10 pedigrees	Unesterified HDL_{2a}-C	LOD = 2.3	29
D2S410	113.4	2q14.1	485 subjects; 1 pedigree	TG	$P = 0.000006$	56
			451 subjects; 1 pedigree	TG	$P = 0.000006$	48
D2S1391	183.2	2q32.1	201 subjects; 42 families	TG (qualitative)	LOD = 2.3	11
D2S1384	203.4	2q33.3	681 subjects; 236 nuclear families	LDL-PPD	LOD = 2.3	17
D2S338	235.3	2q37.2	31 subjects; 1 kindred	FH	LOD = 2.2	58
D2S338, 125	235.3–240.3	2q37.2-q37.3	576 subjects; 42 families	HDL-C	LOD = 2.3	45
D2S2968	236.1	2q37.3	930 subjects; 292 nuclear families	Cholesterol	LOD = 2.0	46
D3S2387, 2403	1-13.1	3p26.3-p25.2	470 subjects; 10 pedigrees	LDL-3	LOD = 2.6	27
D3S1304	6.8	3p26.1	25 families	HDL-C (qualitative)	LOD = 2.1	26
D3S1259	12	3p25.2	679 subjects; 243 nuclear families	ApoA-I	$P = 0.000022$	This study
D3S2407, 1578	40.7–52.9	3p22.1-p21.2	38 subjects; 1 family	FHBL	LOD = 3.3	28
D3S2406	71.7	3p13	547 sibs; 188 nuclear families	TG	LOD = 1.8	43
D3S2406, 2459	71.7–98.9	3p13-q12.3	1,702 subjects; 332 families	Ratio TG/HDL-C	LOD = 1.8	57
D3S1271	97.4	3q12.2	535 subjects; 99 families	Ratio TG/HDL	LOD = 2.1	55
D3S2459, 1310	98.9–111.6	3q12.3-q13.31	31 subjects; 1 kindred	FH	LOD = 1.9	58
D3S1764	136.1	3q23	930 subjects; 292 nuclear families	LDL-C	LOD = 2.8	46
D3S3053	168.8	3q26.31	590 sibs; 201 nuclear families	HDL-C	LOD = 2.6	43
D3S1754, 1311	174.4–193	3q26.32-q29	470 subjects; 10 pedigrees	LDL-3	LOD = 4.1	27
D4S3007[b]	6.7	4p16.1	622 sib pairs	HDL-C	LOD = 2.0	41
D4S2397	27.4	4p15.2	681 subjects; 236 nuclear families	LDL-PPD	LOD = 2.2	17
D4S3248	59.8	4q13.1	477 subjects; 10 pedigrees	Unesterified HDL_{3a}-C	LOD = 2.6	29
D4S1647, 1644	99.7–142.6	4q23-q31.21	470 subjects; 10 pedigrees	LDL-3	LOD = 4.1	27
D4S2623	111.3	4p25	269 subjects; 48 families	TG (qualitative)	LOD = 1.8	12
D4S2368	169.5	4q32.3	1482 subjects; 232 pedigrees	ApoA-II	LOD = 2.4	10
D5S2849	3.5	5p15.33	2799 subjects; 500 families	LDL-C	LOD = 1.9	47
D5S593[b]	4.4	5p15.33	649 sib pairs	HDL-C	LOD = 2.7	41
D5S1470	32.3	5p13.3	1,027 subjects; 101 families	HDL-C	LOD = 3.6	50
D5S2500	58.9	5q11.2	1,482 subjects; 232 pedigrees	ApoA-II	LOD = 2.1	10
D5S427	63.1	5q12.1	576 subjects; 42 families	Cholesterol	LOD = 2.1	45
D5S1501	77.3	5q14.1	681 subjects; 236 nuclear families	LDL-PPD	LOD = 2.4	17
			930 subjects; 292 nuclear families	TG	LOD = 2.2	46
D5S1505	118.8	5q23.1	240 subjects; 18 families	HDL-C	LOD = 2.4	54
D5S1456	169.3	5q35.1	477 subjects; 10 pedigrees	Unesterified HDL_{2b}-C	LOD = 2.8	29
D5S211, 408	173.5–180.1	5q35.2-q35.3	576 subjects; 42 families	LDL-C	LOD = 2.0	45
D6S282	43.2	6p21.1	535 subjects; 99 families	HDL-C	LOD = 2.0	55
D6S257	55.9	6p12.1	96 subjects; 1 pedigree	Cholesterol (qualitative)	LOD = 2.0	42
D6S1717[b]	99.5	6q16.2	622 sib pairs	HDL-C	LOD = 1.8	41
D6S1003, 1277	144.2–163.7	6q24.2-q27	470 subjects; 10 pedigrees	LDL-3	LOD = 2.9	27
D6S305	161.6	6q26	451 subjects; 1 pedigree	Lp[a]	$P < 0.000001$	48
			1,406 subjects; 513 families	Lp[a]	LOD = 27.0	49
D7S691, 479	41.7–94.9	7p14.1-q21.3	418 subjects; 27 families	TG	LOD = 2.1	51
D7S520*, 820	63.4-82.3	7q11.21-q21.11	470 subjects; 10 pedigrees	LDL-3	LOD = 2.1	27

TABLE 4. (*Continued*)

Markers or Genes	Location[a]	Chromosome Band[a]	Samples	Phenotypes	*P*, *Z*, or LOD Values	References
	Mb					
D7S653, 471	70.5–110.5	7q11.22-q31.1	418 subjects; 27 families	HDL-C	LOD = 1.7	51
D7S1824, 688	138.3–146.8	7q34-q36.1	418 subjects; 27 families	TG	LOD = 1.9	51
D7S2195, 3058	142.1–152.8	7q35-q36.2	1,702 subjects; 332 families	TG	LOD = 1.8	57
D7S2195, 3058	142.1–152.8	7q35-q36.2	1,702 subjects; 332 families	Ratio TG/HDL-C	LOD = 2.5	57
D8S1477	32	8p12	477 subjects; 10 pedigrees	Unesterified HDL_{2b}-C	LOD = 2.1	29
D8S259, 1121	33–35.6	8p12	472 subjects; 10 families	HDL-C	LOD = 2.0	53
D8S1132	106.4	8q23.1	25 + 29 families	HDL-C (qualitative)	LOD = 4.7	26
D8S1128	127.6	8q24.21	477 subjects; 10 pedigrees	Unesterified HDL_{2a}-C	LOD = 4.9	29
D9S921	10.7	9p23	269 subjects; 48 families	HDL-C (qualitative)	LOD = 2.1	12
D9S925, 741	18.5–23.4	9p22.2-p21.3	415 subjects; 27 families	HDL-C	LOD = 3.4	52
IFNA	21.8	9p21.3	485 subjects; 1 pedigree	TG	$P = 0.000043$	56
D9S1122	70.7	9q21.2	1,406 subjects; 513 families	TG	LOD = 1.9	49
D10S1220	51.5	10q11.23	269 subjects; 48 families	TG (qualitative)	LOD = 3.3	12
D10S568	52.6	10q21.1	269 subjects; 48 families	HDL-C (qualitative)	LOD = 2.0	12
D10S1221	56.3	10q21.1	201 subjects; 42 families	TG (qualitative)	LOD = 3.2	11
D10S520, 521	95.3–108.3	10q23.33-q25.1	2,799 subjects; 500 families	LDL-C	LOD = 2.5	47
D10S169	131.3	10q26.3	201 subjects; 42 families	FCHL	LOD = 2.3	11
				Cholesterol (qualitative)	LOD = 2.6	11
D11S1324[b]	30.2	11p14.1	1,482 subjects; 232 pedigrees	Cholesterol	LOD = 1.8	10
D11S1392	36.2	11p13	930 subjects; 292 nuclear families	TG	LOD = 2.1	46
D11S1993	46.3	11p12	2,799 subjects; 500 families	LDL-C	LOD = 3.7	47
D11S1985	60.9	11q12.1	240 subjects; 18 families	FCHL	LOD = 2.6	13
D11S911, 912	79.8–130.6	11q13.5-q24.3	930 subjects; 292 nuclear families	LDL-C	LOD = 3.2	46
D11S4464	125.6	11q24.1	201 subjects; 42 families	ApoB (qualitative)	LOD = 1.8	11
			930 subjects; 292 nuclear families	TG	LOD = 1.9	46
D12S334	61	12q14.1	930 subjects; 292 nuclear families	HDL-C	LOD = 4.1	46
PAH	102.4	12q23.2	477 subjects; 10 pedigrees	Unesterified HDL_{2a}-C	LOD = 2.1	29
D12S1091, 378	104.2–123.4	12q23.3-q24.31	383 sib pairs; 75 families	TG	$Z = 3.0$	40
D12S2070	115	12q24.21	1,482 subjects; 232 pedigrees	ApoA-I	LOD = 2.0	10
D13S171, 263	31.2–40.1	13q13.1-q14.11	576 subjects; 42 families	HDL-C	LOD = 2.0	45
D13S1493	32	13q13.1	25 + 29 families	HDL-C	LOD = 1.9	26
			1,027 subjects; 101 families	HDL-C	LOD = 2.4	50
D13S800	71.8	13q22.1	201 subjects; 42 families	TG (qualitative)	LOD = 1.9	11
D13S156, 158	72.6–102.3	13q22.1-q33.1	96 subjects; 1 pedigree	Cholesterol (qualitative)	LOD = 5.7	42
			222 pairs of twins	Cholesterol	$P = 0.0002$	42
				LDL-C	$P = 0.0002$	42
				HDL-C	$P = 0.004$	42
D13S1300, 1266	91–101.5	13q31.3-q33.1	74 subjects; 1 kindred	FH	LOD = 3.1	44
D13S793	96.3	13q32.1	930 subjects; 292 nuclear families	LDL-C	LOD = 1.9	46
D14S53	74.4	14q24.3	681 subjects; 236 nuclear families	LDL-PPD	LOD = 2.8	17
D15S11, 659	20.5–41.9	15q11.2-q21.1	418 subjects; 27 families	TG	LOD = 3.9	51
D15S1007	29	15q14	535 subjects; 99 families	Ratio LDL/HDL	LOD = 1.7	55
D15S1040[b]	29.4	15q14	649 sib pairs	TG	LOD = 1.9	41
ACTC, D15S659	30.4–41.9	15q14-q21.1	470 subjects; 10 pedigrees	LDL-1	LOD = 1.8	27
D15S659	41.9	15q21.1	240 subjects; 18 families	LDL-PPD	LOD = 2.2	54
D15S643	55.3	15q22.2	477 subjects; 10 pedigrees	Unesterified HDL_{2a}-C	LOD = 3.3	29
D15S653	81.5	5q25.3	477 subjects; 10 pedigrees	Unesterified HDL_{2b}-C	LOD = 2.5	29
D15S963, 207	88.3–92.7	15q26.1-q26.2	5 families	FH	LOD = 3.3	59
D15S652	89	15q26.1	930 subjects; 292 nuclear families	LDL-C	LOD = 3.1	46
D16S769	25.6	16p12.1	269 subjects; 48 families	TG (qualitative)	LOD = 1.9	12
D16S3136	41.1	16q12.1	535 subjects; 99 families	Ratio TG/HDL	LOD = 1.7	55
D16S2624, 518	62.6–69.1	16q22.2-q23.1	472 subjects; 10 families	HDL-C	LOD = 4.3	53
D16S518, 3091	69.1–73.8	16q23.1-q23.3	560 subjects; 73 families	HDL-C (qualitative)	LOD = 3.6	12
D16S3091	73.8	16q23.3	25 + 29 families	HDL-C (qualitative)	LOD = 2.2	26
D17S938[b]	6.6	17p13.2	622 sib pairs	TG	LOD = 1.8	41
D17S1290	56.1	17q23.2	1,406 subjects; 513 families	LDL-C	LOD = 2.3	49
D17S1291	63.8	17q24.1	383 sib pairs; 75 families	TG	$Z = 2.6$	40
D17S1535, 928	72.5–79	17q25.1-q25.3	31 subjects; 1 kindred	FH	LOD = 2.7	58
D17S1301	72.7	17q25.1	681 subjects; 236 nuclear families	LDL-PPD	LOD = 6.8	17
044XG3	77.7	17q25.3	2,799 subjects; 500 families	LDL-C	LOD = 2.3	47
D17S928	79	17q25.3	1,482 subjects; 232 pedigrees	Ratio total cholesterol/HDL-C	LOD = 2.5	10
D18S843	8.7	18p11.22	451 subjects; 1 pedigree	Lp[a]	$P = 0.000069$	48
D18S38	58.4	18q21.32	679 subjects; 243 nuclear families	LDL-apoB	LOD = 2.1	This study
D19S247, 209	3.2–3.4	19p13.3	576 subjects; 42 families	Ratio TG/HDL	LOD = 2.1	45
D19S1034, 219	6.2–46.6	19p13.3-q13.32	998 sibs; 292 nuclear families	Cholesterol	LOD = 3.9	43
D19S916	9.2	19p13.2	38 subjects; 1 family	FHBL	LOD = 1.7	28
D19S714, 433	16.1–31	19p13.12-q12	470 subjects; 10 pedigrees	LDL-1	LOD = 2.3	27
D19S433	31	19q12	451 subjects; 1 pedigree	LDL-C	$P = 0.00011$	48
D19S245, 254	34.7–58.6	19q13.11-q13.43	1,482 subjects; 232 pedigrees	ApoE	LOD = 4.2	10
D19S587, 178	35.8–45.1	19q13.12-q13.31	470 subjects; 10 pedigrees	LDL-2	LOD = 1.9	27

TABLE 4. (*Continued*)

Markers or Genes	Location[a]	Chromosome Band[a]	Samples	Phenotypes	*P*, *Z*, or LOD Values	References
	Mb					
D19S178, APOCII	45.1–46.1	19q13.31-q13.32	576 subjects; 42 families	TG	LOD = 3.2	45
APOE	46.1	19q13.32	930 subjects; 292 nuclear families	LDL-C	LOD = 3.6	46
D20S103	0.5	20p13	38 subjects; 1 family	FHBL	LOD = 1.8	28
D20S900[b]	7.3	20p12.3	622 sib pairs	TG	LOD = 2.8	41
D20S171	57.5	20q13.32	25 + 29 families	HDL-C (qualitative)	LOD = 1.9	26
D21S1437	18.3	21q21.1	201 subjects; 42 families	ApoB (qualitative)	LOD = 2.2	11
D21S263	28.8	21q22.11	535 subjects; 99 families	Ratio LDL/HDL	LOD = 2.0	55
D21S1246	37.4	21q22.2	2,799 subjects; 500 families	LDL-C	LOD = 2.7	47
D21S1260[b]	39.4	21q22.3	622 sib pairs	Cholesterol	LOD = 2.3	41
D21S1411[b]	40.7	21q22.3	622 sib pairs	LDL-C	LOD = 1.7	41
D22S1161	45.6	22q13	31 subjects; 1 kindred	FH	LOD = 2.0	58
DXS6804	107.3	Xq23	201 subjects; 42 families	ApoB (qualitative)	LOD = 1.9	11

FCHL, familial combined hyperlipidemia; FH, familial hypercholesterolemia; FHBL, familial hypobetalipoproteinemia; HDL-C, HDL-cholesterol; LDL-1,2,3,4, cholesterol concentration in four LDL size fractions (LDL-1, 26.4–29.0 nm; LDL-2, 25.5–26.4 nm; LDL-3, 24.2–25.5 nm; LDL-4, 21.0–24.2 nm); LDL-C, LDL-cholesterol; LDL-PPD, LDL peak particle diameter; Lp[a], lipoprotein [a]; NA, not available; TG, triglyceride. When two markers per line are shown, these give the interval within which the peak is located.

[a] The physical and genetic locations of markers and genes are from the Genome Browser of the University of California, Santa Cruz (http://genome.ucsc.edu).

[b] When the authors provided only the location of linkage (in genetic distance) without mentioning the name of the marker, we identified a possible marker within the region showing evidence of linkage from the genetic map used by the authors.

gion is also close to the locus for familial hypobetalipoproteinemia (28). In contrast, the LDL-apoB locus (18q21.32) observed in this study represents a newly identified locus. Although some genome-wide scans have been performed on apoB levels before (9–11), this study was the first to investigate the LDL-apoB subfraction. Genome-wide scans with subphenotypes have been successful in the past (27, 29) and may explain the identification of this new locus on 18q21.32.

Our biggest challenge in the compilation of Table 4 was the choice of a significance level for inclusion of a linkage result. This question is related to the ongoing debate concerning significance levels appropriate for reporting evidence of linkage from genome-wide scans of complex traits (23, 30–34). With the emergence of genome-wide scans to identify loci underlying complex traits, geneticists have proposed a refinement of the originally proposed LOD score of 3 threshold (35). Although some advocated a continuation of the more stringent guideline to control false-positives (23), others suggested more flexible guidelines to hunt down genes with small effects believed to be involved in complex traits (31). Rao (32) proposed a middle ground, for the purpose of carrying out follow-up studies, to deal with both false-positive and false-negative claims. The recommendation was to increase tolerance from one false-positive in 20 genomic scans assuming a continuous map, as suggested by Lander and Kruglyak (23), to one per scan assuming a more realistic map density of 400 markers, and to additionally rely on replication. These modifications set the nominal *P* value to 0.0023, which corresponds to a LOD score of 1.75 (22, 36). However, it is interesting that this new threshold corresponded to what was called "putative" linkage by Thomson (31) and "suggestive" linkage by Lander and Kruglyak (23). Accordingly, all point-wise significance levels below this threshold were included in Table 4.

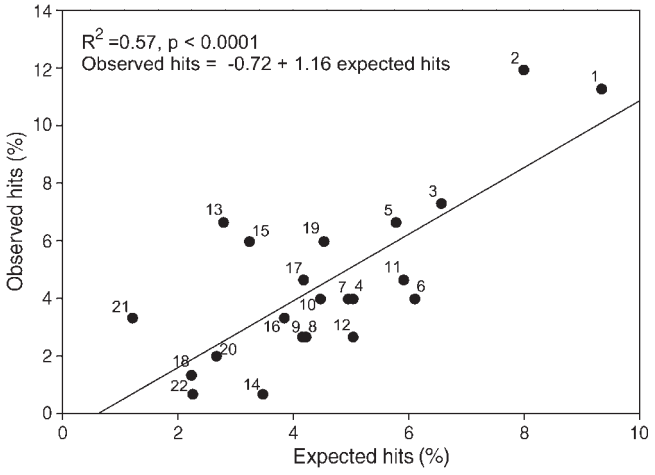

Fig. 3. Regression analysis of observed and expected hits on the autosomal chromosomes. The observed hit ratio of each chromosome was obtained as number of hits on a specific chromosome/all 152 hits × 100, and the expected hit ratio of each chromosome was obtained as number of genes on a specific chromosome/total number of genes in the genome × 100. The gene content of each chromosome and the genome are from Venter et al. (25).

For complex traits, independent replication of an earlier finding gives substantial credibility to the results. Accordingly, it is a standard practice in the literature to compare the newly identify loci with those previously published even if the lipid-related phenotypes are not the same. However, this practice is questionable considering the large number of genome scans performed to date and the uncertainty about the location estimates of a QTL. Indeed, determining whether a given study has replicated an earlier finding is not simple, particularly when different markers have been used. When do we accept that two location estimates in a genomic region represent the same QTL? This issue has been addressed before, and it has been proposed that the location estimate may sometimes be several centimorgan away from the true locus (37). In fact,

the 95% confidence interval of the location estimate can span tens of centimorgan depending on family size and number, penetrance of locus, and heterogeneity. Based on the above, the cumulative evidence from genome-wide screens for lipid-related phenotypes now covers a very large portion of the genome (Table 4). It is likely that the entire genome will be covered with at least suggestive evidence of linkage in a few years, and replication of findings will be guaranteed in future genome-wide scans if the lipid-related phenotypes are grouped together. This phenomenon is not unique to lipid-related phenotypes. The evolution of the human obesity gene map is a good example of this trend, with more than 300 genes, markers, and chromosomal regions that have now been associated or linked with human obesity phenotypes (38).

Despite the large number of QTLs reported to date, a coherent and comprehensive picture of the loci contributing to variations in lipid and lipoprotein has not been achieved. This is demonstrated by the inability to reject the hypothesis of random positive linkage (Fig. 3). We have learned that the genetic mechanisms underlying the predisposition to favorable or unfavorable plasma lipoprotein-lipid levels are more complicated than previously thought. The emergence of such a large number of potential susceptibility loci for lipid-related phenotypes should be interpreted with caution and used carefully before claiming replication. It is commonly accepted that a P value of less than 0.01 from an independent study sample is sufficient to declare replication of an earlier significant linkage (23). However, a large part of the data in Table 4 is only suggestive linkage, which implies that some of the loci are false-positives. In addition, given the large number of genome scan reports and the inability to precisely localize the loci (37), many regions are likely to be replicated solely by chance. For example, more than 30 loci reached the $P <$ 0.01 threshold in the present genome scan study of apolipoprotein levels, and many of them could be considered replicated linkage. New strategies to deal with these issues are urgently needed.

CONCLUSION

In summary, the identification of genes for complex human diseases and their associated biological traits has had limited success to date. This limited success may be explained by genetic heterogeneity, incomplete penetrance, epistasis, phenocopy and pleiotropy (39), and undoubtedly other factors. In this paper, we provide a compendium of previous results from genome scan studies of lipid-related phenotypes. We have recorded a large number of loci covering a large portion of the genome. The number of false-positives is difficult to assess but is likely to be high because positive findings are more frequently published. Because of this publication bias, a lot of positive hits presented in Table 4 will eventually turn out to be false-positives. Accordingly, even though a single tool summarizing the extensive literature on the subject may prove to be useful, it should be used with caution. Caution is also advised for claiming replication, because a large number of loci have been reported and the probability of claiming replication just by chance is getting high. We also report a new genome scan of apolipoprotein levels. Linkage was tested using both allele-sharing and variance-component methods. Many loci provided weak to moderate evidence of linkage, but only two QTLs were supported by both analytical methods.

This study was supported by the Canadian Institutes of Health Research (MT-13960 and GR-15187). The authors express their gratitude to the subjects for their excellent collaboration and to the staff of the Physical Activity Sciences Laboratory for their contribution to the study. Y.B. is the recipient of a studentship from the Canadian Institutes of Health Research. M-C.V. is a research scholar from the Fonds de la Recherche en Santé du Québec. C.B. is supported in part by the George A. Bray Chair in Nutrition. J-P.D. is chair professor of human nutrition, lipidology, and prevention of cardiovascular disease supported by Provigo and Pfizer Canada. The results presented in this paper were obtained using the program package S.A.G.E., which is supported by a United States Public Health Service Resource Grant (1 P41 RR03655) from the National Center for Research Resources.

REFERENCES

1. Risch, N. J. 2000. Searching for genetic determinants in the new millennium. *Nature.* **405:** 847–856.
2. ATP. 2001. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *J. Am. Med. Assoc.* **285:** 2486–2497.
3. Province, M. A. 2001. Sequential methods of analysis for genome scans. *Adv. Genet.* **42:** 499–514.
4. Walldius, G., I. Jungner, I. Holme, A. H. Aastveit, W. Kolar, and E. Steiner. 2001. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS Study): a prospective study. *Lancet.* **358:** 2026–2033.
5. Lamarche, B., S. Moorjani, P. J. Lupien, B. Cantin, P. M. Bernard, G. R. Dagenais, and J. P. Despres. 1996. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec Cardiovascular Study. *Circulation.* **94:** 273–278.
6. Heller, D. A., U. de Faire, N. L. Pedersen, G. Dahlen, and G. E. McClearn. 1993. Genetic and environmental influences on serum lipid levels in twins. *N. Engl. J. Med.* **328:** 1150–1156.
7. Hasstedt, S. J., L. Wu, and R. R. Williams. 1987. Major locus inheritance of apolipoprotein B in Utah pedigrees. *Genet. Epidemiol.* **4:** 67–76.
8. Moll, P. P., V. V. Michels, W. H. Weidman, and B. A. Kottke. 1989. Genetic determination of plasma apolipoprotein AI in a population-based sample. *Am. J. Hum. Genet.* **44:** 124–139.
9. Allayee, H., K. L. Krass, P. Pajukanta, R. M. Cantor, C. J. van der Kallen, R. Mar, J. I. Rotter, T. W. de Bruin, L. Peltonen, and A. J. Lusis. 2002. Locus for elevated apolipoprotein B levels on chromosome 1p31 in families with familial combined hyperlipidemia. *Circ. Res.* **90:** 926–931.
10. Klos, K. L., S. L. Kardia, R. E. Ferrell, S. T. Turner, E. Boerwinkle, and C. F. Sing. 2001. Genome-wide linkage analysis reveals evidence of multiple regions that influence variation in plasma lipid and apolipoprotein levels associated with risk of coronary heart disease. *Arterioscler. Thromb. Vasc. Biol.* **21:** 971–978.
11. Pajukanta, P., J. D. Terwilliger, M. Perola, T. Hiekkalinna, I. Nuotio, P. Ellonen, M. Parkkonen, J. Hartiala, K. Ylitalo, J. Pihlajamaki, K. Porkka, M. Laakso, J. Viikari, C. Ehnholm, M. R. Taskinen, and L. Peltonen. 1999. Genomewide scan for familial combined hyperlipidemia genes in Finnish families, suggesting multiple suscepti-

bility loci influencing triglyceride, cholesterol, and apolipoprotein B levels. *Am. J. Hum. Genet.* **64:** 1453–1463.
12. Pajukanta, P., H. Allayee, K. L. Krass, A. Kuraishy, A. Soro, H. E. Lilja, R. Mar, M. R. Taskinen, I. Nuotio, M. Laakso, J. I. Rotter, T. W. De Bruin, R. M. Cantor, A. J. Lusis, and L. Peltonen. 2003. Combined analysis of genome scans of Dutch and Finnish families reveals a susceptibility locus for high-density lipoprotein cholesterol on chromosome 16q. *Am. J. Hum. Genet.* **72:** 903–917.
13. Aouizerat, B. E., H. Allayee, R. M. Cantor, R. C. Davis, C. D. Lanning, P. Z. Wen, G. M. Dallinga-Thie, T. W. de Bruin, J. I. Rotter, and A. J. Lusis. 1999. A genome scan for familial combined hyperlipidemia reveals evidence of linkage with a locus on chromosome 11. *Am. J. Hum. Genet.* **65:** 397–412.
14. Bouchard, C. 1996. Genetic epidemiology, association, and sib-pair linkage: results from the Québec Family Study. *In* Molecular and Genetic Aspects of Obesity. G. A. Bray and D. H. Ryan, editors. Louisiana State University Press, Baton Rouge, LA. 470–481.
15. Laurell, C. B. 1966. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Anal. Biochem.* **15:** 45–52.
16. Chagnon, Y. C., I. B. Borecki, L. Perusse, S. Roy, M. Lacaille, M. Chagnon, M. A. Ho-Kim, T. Rice, M. A. Province, D. C. Rao, and C. Bouchard. 2000. Genome-wide search for genes related to the fat-free body mass in the Quebec Family Study. *Metabolism.* **49:** 203–207.
17. Bosse, Y., L. Perusse, J. P. Despres, B. Lamarche, Y. C. Chagnon, T. Rice, D. C. Rao, C. Bouchard, and M. C. Vohl. 2003. Evidence for a major quantitative trait locus on chromosome 17q21 affecting low-density lipoprotein peak particle diameter. *Circulation.* **107:** 2361–2368.
18. Elston, R. C., S. Buxbaum, K. B. Jacobs, and J. M. Olson. 2000. Haseman and Elston revisited. *Genet. Epidemiol.* **19:** 1–17.
19. Haseman, J. K., and R. C. Elston. 1972. The investigation of linkage between a quantitative trait and a marker locus. *Behav. Genet.* **2:** 3–19.
20. S.A.G.E. 1999. Statistical Analysis for Genetic Epidemiology, release 4.0. Department of Epidemiology and Biostatistics, Rammelkamp Center for Education and Research, Metro Health Campus, Case Western Reserve University, Cleveland, OH.
21. Abecasis, G. R., L. R. Cardon, and W. O. Cookson. 2000. A general test of association for quantitative traits in nuclear families. *Am. J. Hum. Genet.* **66:** 279–292.
22. Rao, D. C., and M. A. Province. 2000. The future of path analysis, segregation analysis, and combined models for genetic dissection of complex traits. *Hum. Hered.* **50:** 34–42.
23. Lander, E., and L. Kruglyak. 1995. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat. Genet.* **11:** 241–247.
24. Altmuller, J., L. J. Palmer, G. Fischer, H. Scherb, and M. Wjst. 2001. Genomewide scans of complex human diseases: true linkage is hard to find. *Am. J. Hum. Genet.* **69:** 936–950.
25. Venter, J. C., M. D. Adams, E. W. Myers, P. W. Li, R. J. Mural, G. G. Sutton, H. O. Smith, M. Yandell, C. A. Evans, R. A. Holt, J. D. Gocayne, P. Amanatides, R. M. Ballew, D. H. Huson, J. R. Wortman, Q. Zhang, C. D. Kodira, X. H. Zheng, L. Chen, M. Skupski, G. Subramanian, P. D. Thomas, J. Zhang, G. L. Gabor Miklos, C. Nelson, S. Broder, A. G. Clark, J. Nadeau, V. A. McKusick, and N. Zinder. 2001. The sequence of the human genome. *Science.* **291:** 1304–1351.
26. Soro, A., P. Pajukanta, H. E. Lilja, K. Ylitalo, T. Hiekkalinna, M. Perola, R. M. Cantor, J. S. Viikari, M. R. Taskinen, and L. Peltonen. 2002. Genome scans provide evidence for low-HDL-C loci on chromosomes 8q23, 16q24.1-24.2, and 20q13.11 in Finnish families. *Am. J. Hum. Genet.* **70:** 1333–1340.
27. Rainwater, D. L., L. Almasy, J. Blangero, S. A. Cole, J. L. VandeBerg, J. W. MacCluer, and J. E. Hixson. 1999. A genome search identifies major quantitative trait loci on human chromosomes 3 and 4 that influence cholesterol concentrations in small LDL particles. *Arterioscler. Thromb. Vasc. Biol.* **19:** 777–783.
28. Yuan, B., R. Neuman, S. H. Duan, J. L. Weber, P. Y. Kwok, N. L. Saccone, J. S. Wu, K. Y. Liu, and G. Schonfeld. 2000. Linkage of a gene for familial hypobetalipoproteinemia to chromosome 3p21.1-22. *Am. J. Hum. Genet.* **66:** 1699–1704.
29. Almasy, L., J. E. Hixson, D. L. Rainwater, S. Cole, J. T. Williams, M. C. Mahaney, J. L. VandeBerg, M. P. Stern, J. W. MacCluer, and J. Blangero. 1999. Human pedigree-based quantitative-trait-locus mapping: localization of two genes influencing HDL-cholesterol metabolism. *Am. J. Hum. Genet.* **64:** 1686–1693.
30. Witte, J. S., R. C. Elston, and N. J. Schork. 1996. Genetic dissection of complex traits. *Nat. Genet.* **12:** 355–356; author reply 357–358.
31. Thomson, G. 1994. Identifying complex disease genes: progress and paradigms. *Nat. Genet.* **8:** 108–110.
32. Rao, D. C. 1998. CAT scans, PET scans, and genomic scans. *Genet. Epidemiol.* **15:** 1–18.
33. Morton, N. E. 1998. Significance levels in complex inheritance. *Am. J. Hum. Genet.* **62:** 690–697.
34. Curtis, D. 1996. Genetic dissection of complex traits. *Nat. Genet.* **12:** 356–358.
35. Morton, N. E. 1955. Sequential tests for the detection of linkage. *Am. J. Hum. Genet.* **7:** 277–318.
36. Rao, D. C., and C. Gu. 2001. False positives and false negatives in genome scans. *Adv. Genet.* **42:** 487–498.
37. Roberts, S. B., C. J. MacLean, M. C. Neale, L. J. Eaves, and K. S. Kendler. 1999. Replication of linkage studies of complex traits: an examination of variation in location estimates. *Am. J. Hum. Genet.* **65:** 876–884.
38. Chagnon, Y. C., T. Rankinen, E. E. Snyder, S. J. Weisnagel, L. Perusse, and C. Bouchard. 2003. The human obesity gene map: the 2002 update. *Obes. Res.* **11:** 313–367.
39. Lander, E. S., and N. J. Schork. 1994. Genetic dissection of complex traits. *Science.* **265:** 2037–2048.
40. Reed, D. R., E. Nanthakumar, M. North, C. Bell, and R. A. Price. 2001. A genome-wide scan suggests a locus on chromosome 1q21-q23 contributes to normal variation in plasma cholesterol concentration. *J. Mol. Med.* **79:** 262–269.
41. Coon, H., M. F. Leppert, J. H. Eckfeldt, A. Oberman, R. H. Myers, J. M. Peacock, M. A. Province, P. N. Hopkins, and G. Heiss. 2001. Genome-wide linkage analysis of lipids in the Hypertension Genetic Epidemiology Network (HyperGEN) Blood Pressure Study. *Arterioscler. Thromb. Vasc. Biol.* **21:** 1969–1976.
42. Knoblauch, H., B. Muller-Myhsok, A. Busjahn, L. Ben Avi, S. Bahring, H. Baron, S. C. Heath, R. Uhlmann, H. D. Faulhaber, S. Shpitzen, A. Aydin, A. Reshef, M. Rosenthal, O. Eliav, A. Muhl, A. Lowe, D. Schurr, D. Harats, E. Jeschke, Y. Friedlander, H. Schuster, F. C. Luft, and E. Leitersdorf. 2000. A cholesterol-lowering gene maps to chromosome 13q. *Am. J. Hum. Genet.* **66:** 157–166.
43. Imperatore, G., W. C. Knowler, D. J. Pettitt, S. Kobes, J. H. Fuller, P. H. Bennett, and R. L. Hanson. 2000. A locus influencing total serum cholesterol on chromosome 19p: results from an autosomal genomic scan of serum lipid concentrations in Pima Indians. *Arterioscler. Thromb. Vasc. Biol.* **20:** 2651–2656.
44. Al-Kateb, H., S. Bahring, K. Hoffmann, K. Strauch, A. Busjahn, G. Nurnberg, M. Jouma, E. K. Bautz, H. A. Dresel, and F. C. Luft. 2002. Mutation in the ARH gene and a chromosome 13q locus influence cholesterol levels in a new form of digenic-recessive familial hypercholesterolemia. *Circ. Res.* **90:** 951–958.
45. Elbein, S. C., and S. J. Hasstedt. 2002. Quantitative trait linkage analysis of lipid-related traits in familial type 2 diabetes: evidence for linkage of triglyceride levels to chromosome 19q. *Diabetes.* **51:** 528–535.
46. Bosse, Y., Y. C. Chagnon, J. P. Despres, T. Rice, D. C. Rao, C. Bouchard, L. Perusse, and M. C. Vohl. 2004. Genome-wide linkage scan reveals multiple susceptibility loci influencing lipid and lipoprotein levels in the Quebec Family Study. *J. Lipid Res.* **45:** 419–426.
47. Coon, H., J. H. Eckfeldt, M. F. Leppert, R. H. Myers, D. K. Arnett, G. Heiss, M. A. Province, and S. C. Hunt. 2002. A genome-wide screen reveals evidence for a locus on chromosome 11 influencing variation in LDL cholesterol in the NHLBI Family Heart Study. *Hum. Genet.* **111:** 263–269.
48. Ober, C., M. Abney, and M. S. McPeek. 2001. The genetic dissection of complex traits in a founder population. *Am. J. Hum. Genet.* **69:** 1068–1079.
49. Broeckel, U., C. Hengstenberg, B. Mayer, S. Holmer, L. J. Martin, A. G. Comuzzie, J. Blangero, P. Nurnberg, A. Reis, G. A. Riegger, H. J. Jacob, and H. Schunkert. 2002. A comprehensive linkage analysis for myocardial infarction and its related risk factors. *Nat. Genet.* **30:** 210–214.
50. Peacock, J. M., D. K. Arnett, L. D. Atwood, R. H. Myers, H. Coon, S. S. Rich, M. A. Province, and G. Heiss. 2001. Genome scan for quantitative trait loci linked to high-density lipoprotein cholesterol: the NHLBI Family Heart Study. *Arterioscler. Thromb. Vasc. Biol.* **21:** 1823–1828.
51. Duggirala, R., J. Blangero, L. Almasy, T. D. Dyer, K. L. Williams, R. J. Leach, P. O'Connell, and M. P. Stern. 2000. A major susceptibility locus influencing plasma triglyceride concentrations is located on chromosome 15q in Mexican Americans. *Am. J. Hum. Genet.* **66:** 1237–1245.

52. Arya, R., R. Duggirala, L. Almasy, D. L. Rainwater, M. C. Mahaney, S. Cole, T. D. Dyer, K. Williams, R. J. Leach, J. E. Hixson, J. W. MacCluer, P. O'Connell, M. P. Stern, and J. Blangero. 2002. Linkage of high-density lipoprotein-cholesterol concentrations to a locus on chromosome 9p in Mexican Americans. *Nat. Genet.* **30:** 102–105.
53. Mahaney, M. C., L. Almasy, D. L. Rainwater, J. L. VandeBerg, S. A. Cole, J. E. Hixson, J. Blangero, and J. W. MacCluer. 2003. A quantitative trait locus on chromosome 16q influences variation in plasma HDL-C levels in Mexican Americans. *Arterioscler. Thromb. Vasc. Biol.* **23:** 339–345.
54. Allayee, H., K. M. Dominguez, B. E. Aouizerat, R. M. Krauss, J. I. Rotter, J. Lu, R. M. Cantor, T. W. de Bruin, and A. J. Lusis. 2000. Contribution of the hepatic lipase gene to the atherogenic lipoprotein phenotype in familial combined hyperlipidemia. *J. Lipid Res.* **41:** 245–252.
55. Francke, S., M. Manraj, C. Lacquemant, C. Lecoeur, F. Lepretre, P. Passa, A. Hebe, L. Corset, S. L. Yan, S. Lahmidi, S. Jankee, T. K. Gunness, U. S. Ramjuttun, V. Balgobin, C. Dina, and P. Froguel. 2001. A genome-wide scan for coronary heart disease suggests in Indo-Mauritians a susceptibility locus on chromosome 16p13 and replicates linkage with the metabolic syndrome on 3q27. *Hum. Mol. Genet.* **10:** 2751–2765.
56. Newman, D. L., M. Abney, H. Dytch, R. Parry, M. S. McPeek, and C. Ober. 2003. Major loci influencing serum triglyceride levels on 2q14 and 9p21 localized by homozygosity-by-descent mapping in a large Hutterite pedigree. *Hum. Mol. Genet.* **12:** 137–144.
57. Shearman, A. M., J. M. Ordovas, L. A. Cupples, E. J. Schaefer, M. D. Harmon, Y. Shao, J. D. Keen, A. L. DeStefano, O. Joost, P. W. Wilson, D. E. Housman, and R. H. Myers. 2000. Evidence for a gene influencing the TG/HDL-C ratio on chromosome 7q32.3-qter: a genome-wide scan in the Framingham study. *Hum. Mol. Genet.* **9:** 1315–1320.
58. Hunt, S. C., P. N. Hopkins, K. Bulka, M. T. McDermott, T. L. Thorne, B. B. Wardell, B. R. Bowen, D. G. Ballinger, M. H. Skolnick, and M. E. Samuels. 2000. Genetic localization to chromosome 1p32 of the third locus for familial hypercholesterolemia in a Utah kindred. *Arterioscler. Thromb. Vasc. Biol.* **20:** 1089–1093.
59. Ciccarese, M., A. Pacifico, G. Tonolo, P. Pintus, A. Nikoshkov, G. Zuliani, R. Fellin, H. Luthman, and M. Maioli. 2000. A new locus for autosomal recessive hypercholesterolemia maps to human chromosome 15q25-q26. *Am. J. Hum. Genet.* **66:** 453–460.
60. Eden, E. R., R. P. Naoumova, J. J. Burden, M. I. McCarthy, and A. K. Soutar. 2001. Use of homozygosity mapping to identify a region on chromosome 1 bearing a defective gene that causes autosomal recessive homozygous hypercholesterolemia in two unrelated families. *Am. J. Hum. Genet.* **68:** 653–660.
61. Varret, M., J. P. Rabes, B. Saint-Jore, A. Cenarro, J. C. Marinoni, F. Civeira, M. Devillers, M. Krempf, M. Coulon, R. Thiart, M. J. Kotze, H. Schmidt, J. C. Buzzi, G. M. Kostner, S. Bertolini, M. Pocovi, A. Rosa, M. Farnier, M. Martinez, C. Junien, and C. Boileau. 1999. A third major locus for autosomal dominant hypercholesterolemia maps to 1p34.1-p32. *Am. J. Hum. Genet.* **64:** 1378–1387.