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Report

Genome Scans Provide Evidence for Low-HDL-C Loci on Chromosomes 8q23, 16q24.1-24.2, and 20q13.11 in Finnish Families

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We performed a genomewide scan for genes that predispose to low serum HDL cholesterol (HDL-C) in 25 well-defined Finnish families that were ascertained for familial low HDL-C and premature coronary heart disease. The potential loci for low HDL-C that were identified initially were tested in an independent sample group of 29 Finnish families that were ascertained for familial combined hyperlipidemia (FCHL), expressing low HDL-C as one component trait. The data from the previous genome scan were also reanalyzed for this trait. We found evidence for linkage between the low-HDL-C trait and three loci, in a pooled data analysis of families with low HDL-C and FCHL. The strongest statistical evidence was obtained at a locus on chromosome 8q23, with a two-point LOD score of 4.7 under a recessive mode of inheritance and a multipoint LOD score of 3.3. Evidence for linkage also emerged for loci on chromosomes 16q24.1-24.2 and 20q13.11, the latter representing a recently characterized region for type 2 diabetes. Besides these three loci, loci on chromosomes 2p and 3p showed linkage in the families with low HDL-C and a locus on 2ptel in the families with FCHL.

Low serum HDL cholesterol (HDL-C), or hypo-α-lipoproteinemia, is the most frequently diagnosed dyslipidemia in patients with premature coronary heart disease (CHD) (Genest et al. 1992). The common form of low HDL-C that is associated with CHD is a typical complex disorder in which several genes and environmental factors affect the phenotype. Several candidate genes have been associated with low HDL-C in multiple sample groups (Davignon and Genest 1998). One of the most interesting findings indicated that allelic variants in the ATP-binding cassette transporter 1 gene (*ABC1* [MIM 205400; MIM 600046]) contribute to low HDL-C in four French-Canadian families (Brooks-Wilson et al. 1999; Rust et al. 1999). However, the significance of this or other candidate genes for the common form of low HDL-C has not been established. Here we report analyses of the first genome scan for low serum HDL-C performed in multiplex families from Finland. The sample group was selected to restrict both environmental and genetic heterogeneity. Finns descend from small founder populations that share a relatively homogeneous gene pool and environment (Peltonen et al. 1999). Excellent epidemiological data sets are an additional advantage, since these facilitate the adoption of age- and sex-specific population percentiles when defining affection status in family members (Porkka et al. 1994; Vartiainen et al. 1994).

The sample group with low HDL-C was collected in Helsinki and Turku University Central Hospitals in Finland. A total of 176 individuals, from 20 well-defined families with low HDL-C, were included in stage 1, and 5 additional families, with 43 individuals, were included in stage 2. Inclusion criteria for the probands with low HDL-C were an age of 30–60 years for both men and women, HDL-C levels <10th age- and sex-specific percentile of the Finnish population, and CHD that had been verified by either cor-

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Table 1

Clinical Characteristics of the Families with Low HDL-C

	Affected[a] (n = 104)	Unaffected (n = 115)
Age (years)	49.3 ± 15.7	43.7 ± 17.2
Sex (% males)	47	50
BMI (kg/m^2)	26.8 ± 4.1	24.7 ± 4.1
HDL-C (mmol/liter)	.86 ± .16	1.37 ± .34
TGs (mmol/liter)	1.69 ± .81	1.22 ± .59
TC (mmol/liter)	5.27 ± .97	5.46 ± 1.11
Apolipoproteins:		
A-I (mg/dl)	120 ± 16	147 ± 25
A-II (mg/dl)	34 ± 6	38 ± 6

NOTE.—All values except those for sex are expressed as mean ± SD. The affected group includes 25 probands with low HDL-C and 79 hypo-α-lipoproteinemic family members.

[a] HDL-C levels <10th age- and sex-specific percentile.

onary angiography (>50% stenosis of one or more coronary arteries) or myocardial infarction. All of the three following criteria had to be fulfilled for the diagnosis of myocardial infarction: (1) typical clinical symptoms; (2) definite electrocardiographic findings, according to the Minnesota coding (World Health Organization criteria) (Rose et al. 1982); and (3) elevated levels of the creatine-kinase enzyme, CK, and its cardiac isoenzyme, CK-MB. In addition to the probands, seven siblings of the probands and two parents had CHD. Additional lipid criteria for the probands were total cholesterol (TC) <6.3 mmol/liter in men and <6.0 mmol/liter in women and triglycerides (TGs) <2.3 mmol/liter in both sexes. To be selected for the study, the proband must have at least three accessible first-degree relatives. Exclusion criteria for the probands were type 1 or type 2 diabetes mellitus (DM), significant hepatic or renal diseases, untreated hypothyreosis, familial hypercholesterolemia, or a BMI >30 kg/m^2 (table 1). The lipid profiles shown in table 1 are consistent with those described elsewhere (Brooks-Wilson et al. 1999). The affected family members were identified as having low HDL-C, by use of the Finnish age- and sex-specific 10th population percentiles. Each study subject provided written informed consent prior to participating in the study. Any lipid-lowering medication was interrupted for 4 wk before the blood samples were taken. All samples were collected in accordance with the Helsinki declaration, and the ethics committees of the participating centers approved the study design. Serum TC, TGs, and HDL-C were measured as described elsewhere (Pajukanta et al. 1998, 1999). Apolipoproteins A-I and A-II were measured by an immunoturbidimetric method with commercial kits (Boehringer-Mannheim).

In stage 1, a total of 358 microsatellite markers (the modified Weber screening set, version 9.0) were genotyped. The genotyping was performed using LI-COR DNA 4200 Genetic Analyzer. The markers for denser maps were selected from the Genome Database; Cooperative Human Linkage Center; Center for Medical Genetics, Marshfield Medical Research Foundation; Genetic Location Database; and Généthon databases. Parametric linkage and nonparametric affected-sib-pair (ASP) analyses were performed for all markers (for details of the statistical analyses, see the legend for fig. 1). The complete two-point linkage results for all markers are available from our Web site (UCLA Human Genetics).

In stage 1, two-point LOD scores >1.0 were obtained for markers on chromosomes 1–3, 6–9, and 16–20. Figure 1 shows these results under either a parametric recessive mode of inheritance or the ASP analysis. The highest LOD score, 2.9 (recombination fraction [θ] = 0.10), was observed with the chromosome 3 marker D3S4545 by use of a dominant mode of inheritance. On chromosomes 1 and 9, two separate regions produced LOD scores >1.0. These two regions were located 72 cM and 10.7 cM apart, respectively. One of the regions on chromosome 1, located in the vicinity of the apolipoprotein A-II gene (*APOA2* [MIM 107670]), produced a LOD score of 2.1 with D1S2844. No additional markers were genotyped in this particular region, since it was fine mapped in our previous studies (Pajukanta et al. 1998; Lilja et al., in press).

In stage 2, the chromosomal regions that showed two-point LOD scores >1.0 in stage 1 were further studied by genotyping 67 additional markers and including five additional families with low HDL-C (fig. 2). The most significant linkage results on chromosomes 8, 16, 20,

Table 2

Two-Point and Multipoint Evidence for Linkage to Chromosome 8q23

Location	Position[a]	LOD Score[b]		Simwalk
		Pairwise[c]	ASP	Statistics A[d]
GAAT1A4	.0	.0 (.50)/.3 (.26)	.2/.5	1.3
D8S1132	8.9	2.3 (.10)/4.7 (.06)	1.4/3.1	3.3
D8S592	14.9	.1 (.32)/1.0 (.18)	.2/.9	2.0

NOTE.—For statistical analyses, see the legend for figure 1.

[a] Distance (in cM) from the first marker.

[b] The first LOD score is that for sample group with low HDL-C and the second (i.e., after the slash mark) is that for the pooled sample group.

[c] Maximum LOD scores for the two-point linkage analysis. The recombination fractions are given in parentheses.

[d] Results of the nonparametric-linkage analysis from Simwalk, version 2.80, for the pooled sample group. Statistic A is most powerful at detecting linkage to a recessive trait, statistic B is most powerful at detecting linkage to a dominant trait, and statistic C is a more general statistic that indicates if a few founder-alleles are overly represented among affecteds.

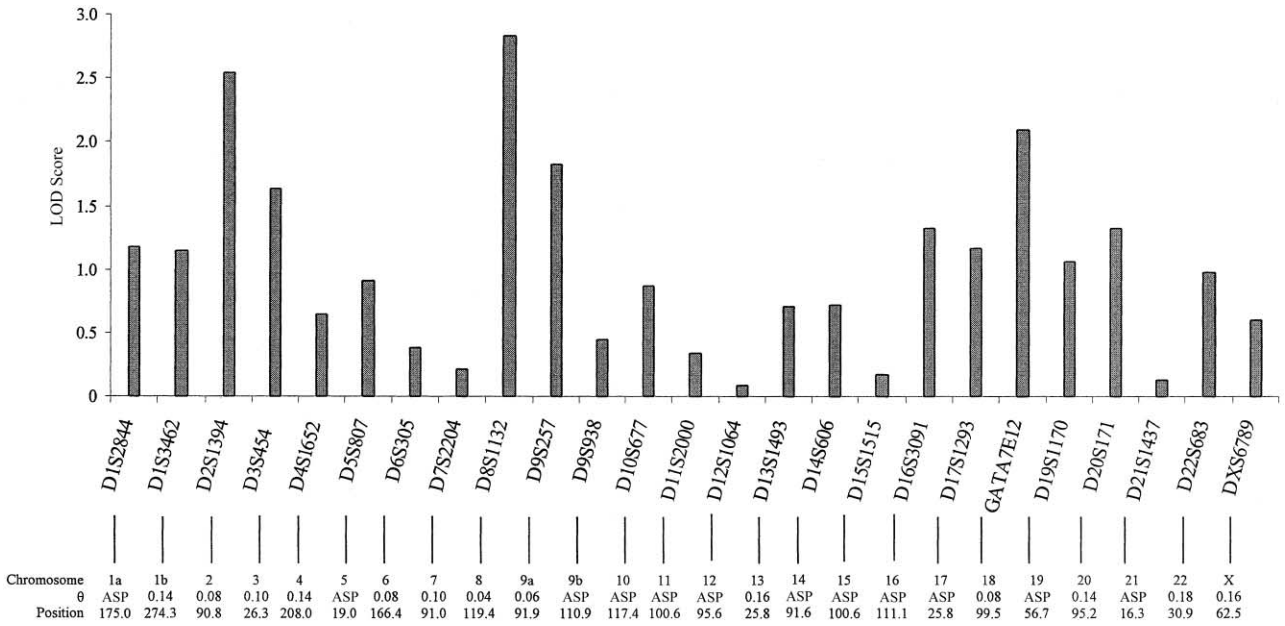

Figure 1 Highest two-point LOD scores in stage 1, for the sample group with low HDL-C, on each chromosome, as determined by use of either a recessive mode of inheritance or an ASP analysis. A dominant mode of inheritance yielded LOD scores that were typically slightly lower. The MLINK program of the LINKAGE package (Lathrop et al. 1984), version FASTLINK 4.1P (Cottingham et al. 1993; Schäffer et al. 1994), was used to perform the parametric linkage analyses. The parametric linkage analyses were performed with a dominant and recessive mode of inheritance by use of an affecteds-only strategy. Gene frequencies (reflecting an estimated population prevalence of ~1%) of 0.4% and 8% were used for the dominant and recessive mode of inheritance. For each marker, the allele frequencies were estimated from all individuals, by use of the DOWNFREQ program (Göring and Terwilliger 2000*b*). The ASP analysis was performed using the SIBPAIR program (Kuokkanen et al. 1996) of the ANALYZE package (Göring and Terwilliger 2000*a*). The two-point analyses were performed using the AUTOSCAN program, a helper program that enables a genomewide scan by a single computer analysis. Multipoint analyses were performed with the Simwalk program, version 2.80 (Sobel and Lange 1996). The Mendelian errors were checked with the PedCheck program (O'Connell and Weeks 1998). The observed inconsistencies were handled by rereading raw gel data; if errors still remained, the genotypes of the particular subjects involved were coded as zeros. On chromosomes 1 and 9, two separate regions produced LOD scores >1.0 and are indicated as 1a and 1b and 9a and 9b, respectively. The recombination fraction shown is that of the two-point maximum LOD score in the parametric linkage analysis. The position given is the distance (in cM) from pter, for each marker.

2p, and 3 are given in tables 2–5. For the remaining chromosomal regions, no further evidence for linkage was obtained in stage 2.

To further analyze the chromosomal regions on chromosomes 8, 16, 20, 2p, and 3, we performed linkage analyses, by use of low HDL-C as an affection status, in an independent sample group of 29 well-defined Finnish families with familial combined hyperlipidemia (FCHL) (table 6) (Pajukanta et al. 1999). In addition to elevated TC and TGs, low HDL-C is one of the component traits of FCHL. When coding the family members of the families with FCHL as affected, we used the same 10th-percentile HDL-C trait as had been used in our HDL-C scan. The data collection, laboratory measurements, and phenotype determinations for the families with low HDL-C or FCHL were performed in the same center, thereby making clinical and biochemical data in these two sample groups fully compatible.

When we analyzed the genome-scan data from the families with FCHL for the low-HDL-C trait, the three chromosomal regions on chromosomes 8q, 16q, and 20q that were identified in the families with low HDL-C provided some evidence for linkage. On chromosome 8q23, maximum LOD scores were observed with the same marker, D8S1132, in both the sample groups with low HDL-C and the sample groups with FCHL. The highest two-point LOD score in the families with FCHL was 1.6 ($\theta = 0.08$). On chromosome 16, D16S518 yielded a two-point LOD score of 1.1 ($\theta = 0.14$) and D16S403, located 67 cM centromeric from D16S518, yielded an ASP-LOD score of 1.1 in the sample group with FCHL. On chromosome 20, an ASP-LOD score of 1.7 was obtained with D20S481, located 36 cM centromeric from D20S171, which is the peak marker in the families with low HDL-C. The highest pairwise LOD scores for each chromosome in the sample group with FCHL are presented in figure 2.

To test if additional loci for low HDL-C could be identified in the families with FCHL, we reanalyzed

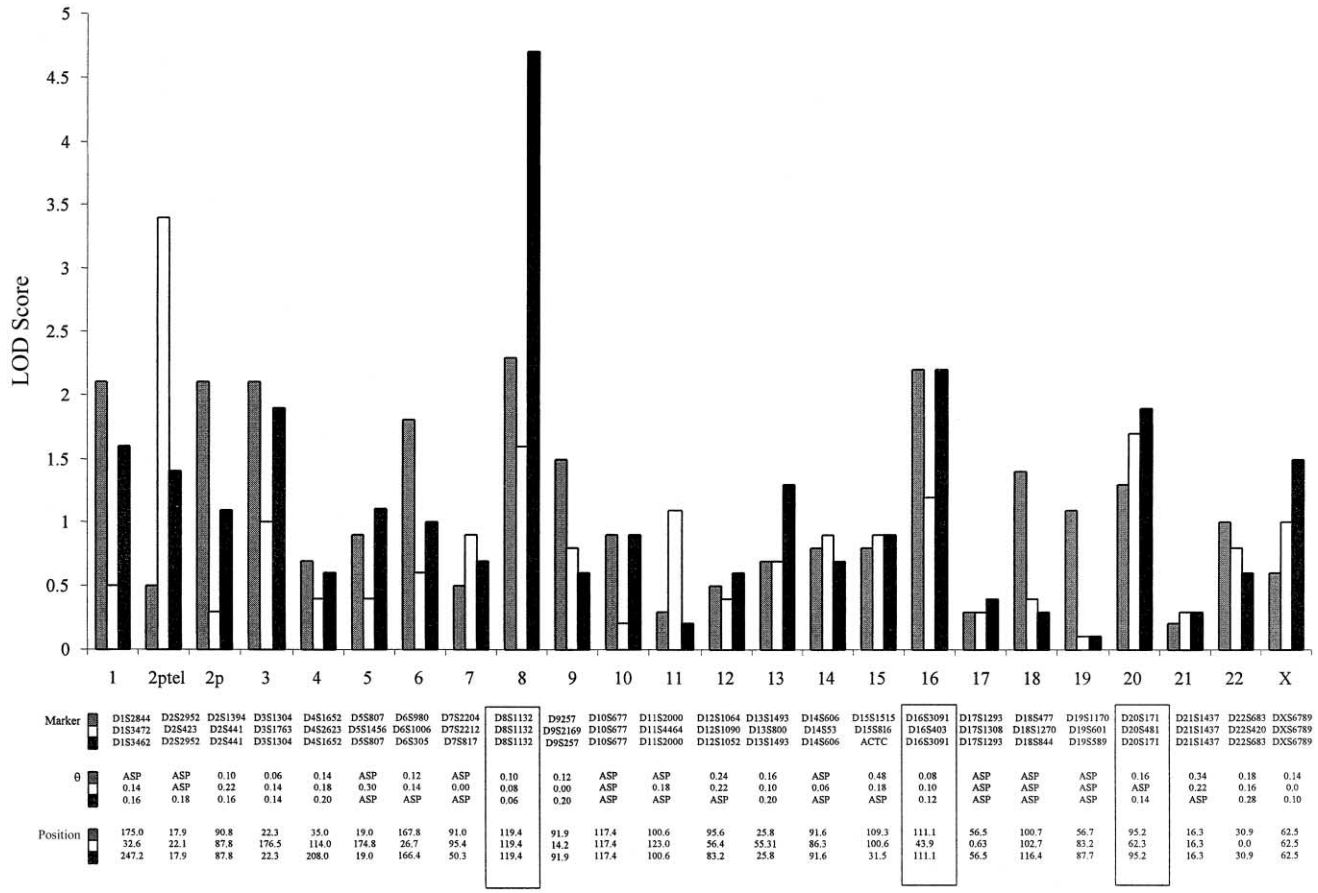

Figure 2 Highest two-point LOD scores in stage 2, for the three sample groups, on each chromosome. Gray columns show the two-point results for the sample group with low HDL-C, white columns show the results for the sample group with FCHL, and black columns show the results for the pooled sample group. The chromosome numbers are given below the *X*-axis. The boxes indicate the chromosomes on which the identified loci were supported by the pooled data analyses. On chromosome 2, two separate regions produced LOD scores >2.0 and are indicated as 2ptel and 2p. The complete linkage results for stage 2 are available from our Web site (UCLA Human Genetics). The markers that produced the highest LOD scores separately for each sample group are given below each chromosome. The recombination fraction and position are as explained in the legend for figure 1.

the data from the previous genome scan that was performed with 370 microsatellite markers (the Weber screening set, version 6.0) in 29 families with FCHL (Pajukanta et al. 1999). Using the 10th-percentile HDL-C trait as an affection status in the families with FCHL, we observed a promising finding for the low HDL-C on chromosome 2ptel, with D2S423, which yielded an ASP-LOD score of 3.4, and D2S2952, which is located 4.2 cM telomeric and which yielded a LOD score of 1.2 ($\theta = 0.12$). For the families with low HDL-C, D2S423 yielded a two-point LOD score of 0.0 ($\theta = 0.48$), and D2S2952 yielded a LOD score of 0.9 ($\theta = 0.12$) (table 7).

A pooled data analysis of the families with low HDL-C and FCHL was performed using low HDL-C as the diagnostic trait. The highest LOD score, 4.7 ($\theta = 0.06$), was obtained with D8S1132, on chromosome 8q23. A multipoint analysis provided supportive evidence, with LOD scores >3.0 (table 2). On chromosome 16, D16S3091 yielded a two-point LOD score of 2.2 ($\theta = 0.12$) in the pooled data analysis, yielding some additional evidence for this region (table 3). On chromosome 20, a LOD score of 1.9 ($\theta = 0.14$) was obtained with D20S171 (table 4). The chromosomal regions identified in only one of the sample groups (chromosomes 2p and 3p, in the families with low HDL-C, and 2ptel, in the families with FCHL) did not gain any further support in these pooled data analyses. The HOMOG program (Ott 1991) provided no statistical evidence for locus heterogeneity among families with low HDL-C or FCHL for any tested marker.

Although our study design of the genomewide scan was selected to identify linked regions for a qualitative

Table 3

Two-Point and Multipoint Evidence for Linkage to Chromosome 16q24.1-24.2

Location	Position	LOD Score		Simwalk Statistics C
		Pairwise	ASP	
D16S3040	.0	.1 (.32)	.1	1.1
D16S505[a]	4.5	1.5 (.12)/1.3 (.18)	1.8/1.5	1.2
D16S3091[a]	6.7	1.9 (.08)/2.2 (.12)	1.8/1.9	1.2
D16S402	9.1	.2 (.34)	.6	.9
D16S3061	17.0	.0 (.50)	.0	.5

Note.—The position and linkage results are as explained in table 2.
[a] Also genotyped in the sample group with FCHL.

Table 4

Two-Point and Multipoint Evidence for Linkage to Chromosome 20q13.11

Location	Position	LOD Score		Simwalk Statistics A
		Pairwise	ASP	
D20S120	.0	.8 (.20)	.9	1.2
D20S102	3.5	.4 (.20)	.4	1.1
D20S171[a]	8.7	1.3 (.16)/1.9 (.14)	1.3/1.4	1.7
D20S94	11.0	.4 (.26)	.3	1.4
D20S173	11.1	.6 (.20)	.2	1.4

Note.—The position and linkage results are as explained in table 2.
[a] Also genotyped in the sample group with FCHL.

trait, we also analyzed the quantitative measures, HDL-C and TGs, by variance-component methods that utilized SOLAR version 1.6.7 (Almasy and Blangero 1998). Additional covariates in the model were sex, age, BMI, ascertainment status (i.e., family with HDL-C or FCHL), and proband status. A logarithmic transformation of the variable was used if needed. No significant linkage results emerged from these analyses. For HDL-C, the highest LOD score, 1.94, was obtained on chromosome 13 with D13S1493 in a two-point analysis. (The qualitative analysis for this marker resulted in a LOD score of 1.32 in the pooled sample group.) For TGs, the highest LOD score, 1.52, was obtained on chromosome 8 in a multipoint analysis, 50 cM from the p-telomere. (The qualitative analysis for this region did not show positive results.) This TG region is located ~70 cM from the peak linkage markers on chromosome 8q23, which were obtained using the qualitative analysis. All results for the variance-component analyses are available from our Web site (UCLA Human Genetics). The genotyping strategy was designed to maximize the information obtained from the affected individuals in the large pedigrees. The variance-component analyses can therefore use only the variation within this group, thus reducing our power to detect loci with this method.

We also investigated the contribution of the *ABC1* gene to low HDL-C in the families with low HDL-C. Two markers, D9S257 and D9S938, that flank the *ABC1* region yielded LOD scores of 1.8 ($\theta = 0.06$) and 1.3 ($\theta = 0.06$). Results of the family-based association analyses—haplotype-based haplotype relative risk and transmission/disequilibrium tests (Terwilliger and Ott 1992)—were nonsignificant. Next, we constructed haplotypes (D9S53-*ABC1*-D9S306-D9S1866-D9S938-D9S1784-D9S1677) that spanned a 21.8-cM region, and we monitored for shared haplotypes among the affected family members. Only five families revealed potential cosegregation, and, consequently, genomic DNA from the five probands was subjected to sequencing of the coding region of *ABC1*. Sequence analyses identified four polymorphisms that have previously been characterized: the sequence variants corresponding to R219K, in exon 7; V825I, in exon 17; I883M, in exon 18; and R1587K, in exon

Table 5

Two-Point and Multipoint Evidence for Linkage to Chromosomes 2p and 3p

Location	Position	LOD Score		Simwalk Statistics B
		Pairwise	ASP	
Chromosome 2p:				
D2S441[a]	.0	1.0 (.14)/1.2 (.16)	.6/.7	1.3
D2S1394[a]	3.0	2.1 (.10)/1.1 (.20)	1.8/1.1	1.5
D2S286	6.2	.4 (.20)	.4	1.2
D2S2114	7.9	.1 (.28)	.0	1.0
Chromosome 3p:				
D3S3050[b]	.0	.1 (.30)	.0	.6
D3S1620	.8	.0 (.50)	.0	.7
D3S1304[a]	8.6	2.1 (.06)/1.9 (.12)	1.0/1.2	1.1
D3S4545	12.5	.5 (.22)	.7	1.1
D3S1597	16.2	.0 (.50)	.0	.5

Note.—Linkage evidence was obtained mainly from the families with low HDL-C. The position and linkage results are as explained in table 2.
[a] Also genotyped in the sample group with FCHL.
[b] Genotyped only in the sample group with FCHL.

35 (Clee et al. 2001). None of the nucleotide changes showed cosegregation with low HDL-C in these families.

Our analyses of well-defined Finnish families with low HDL-C or FCHL revealed six loci that are potentially important for the regulation of the HDL-C levels, on chromosomes 2ptel, 2p, 3p, 8q23, 16q24.1-24.2, and 20q13.11. Three of these loci were supported by pooled data analyses of the families with low HDL-C and FCHL, whereas loci on chromosomes 2p and 3p appeared to be specific to the families with low HDL-C and another locus on chromosome 2ptel was seen only in the analysis of the families with FCHL. The most statistically significant result was observed on chromosome 8q23, with a two-point LOD score of 4.7 in the pooled data analysis under a recessive mode of inheritance. This chromosomal region has previously been linked to the regulation of serum-HDL-C levels in a genome scan of a population cohort of Mexican American families, who were not ascertained for the low-HDL-C trait (Almasy et al. 1999). Our most significant markers are located 20 cM centromeric from their peak markers. These results, obtained independently both in a population-based sample group and in well-defined families with low HDL-C, implicate the involvement of one or more genes in this region in the regulation of HDL-C.

On chromosome 16q, markers on an 18-cM region showed suggestive evidence for linkage in the pooled data analysis. Some evidence for linkage to this region has also been reported in Dutch families with FCHL (Aouizerat et al. 1999). Finally, on chromosome 20q, markers spanning a 33-cM region produced suggestive LOD scores. Previous analyses in both mouse studies and human studies have indicated that chromosome 20q harbors multiple loci that contribute to body adiposity, fasting insulin levels, and type 2 DM (Bowden et al. 1997; Lembertas et al. 1997; Ghosh et al. 2000). Low HDL-C is a common feature in type 2 DM, and these findings may suggest the presence of one or more loci on 20q12-13 that are involved in HDL-C metabolism. Our results (1) have identified loci for low HDL-C in the pooled data analysis of two Finnish sample groups that were ascertained for overlapping traits and (2) have suggested a partially shared genetic background for the low-HDL-C and FCHL traits.

Table 6

Clinical Characteristics of the Families with FCHL

	Affected[a] (n = 64)	Unaffected (n = 75)
Age (years)	49.0 ± 14.1	45.0 ± 16.8
Sex (% males)	48	39
BMI (kg/m^2)	28.3 ± 4.1	25.5 ± 3.6
HDL-C (mmol/liter)	.94 ± .25	1.57 ± .42
TG (mmol/liter)	3.24 ± 2.52	2.02 ± 1.24
TC (mmol/liter)	6.78 ± 1.32	6.85 ± 1.27
Apolipoprotein:		
A-I (mg/dl)	125 ± 21	163 ± 25
A-II (mg/dl)	38 ± 9	43 ± 7

NOTE.—All values except those for sex are expressed as mean ± SD. The affected group includes 21 probands with FCHL and 43 hypo-α-lipoproteinemic family members.

[a] HDL-C levels <10th age- and sex-specific percentile.

Table 7

Two-Point and Multipoint Evidence for Linkage to Chromosome 2ptel

Location	Position	LOD Score		Simwalk Statistics B
		Pairwise	ASP	
D2S1780	.0	.0 (.50)	.0/.0	.8
D2S2952[a]	6.0	1.2 (.10)/1.4 (.18)	.7/1.1	1.4
D2S423[a]	10.2	2.8 (.0)/1.1 (.18)	3.4/.5	1.5
D2S1400[a]	15.7	.7 (.12)/.1 (.34)	.4/.0	1.2

NOTE.—Linkage evidence was obtained mainly from the families with FCHL. The position and linkage results are as explained in table 2, except that, in the "LOD Score" columns, the first LOD score is that for the sample group with FCHL and second (i.e., after the slash mark) is that for the pooled sample group.

[a] Also genotyped in the sample group with FCHL.

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Electronic-Database Information

Accession numbers and URLs for data in this report are as follows:

AUTOSCAN 1.0, http://www.genetics.ucla.edu/software/autoscan/index.html

Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/

Cooperative Human Linkage Center, The, http://lpg.nci.nih.gov/CHLC/ (for map)

Genetic Location Database (LDB), The, http://cedar.genetics.soton.ac.uk/public_html/ldb.html

Genome Database, The, http://www.gdb.org/

Généthon, http://www.genethon.fr/genethon_en.html
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for apolipoprotein A-II [MIM 107670] and *ABC1* [MIM 205400; MIM 600046])
UCLA Human Genetics, http://www.genetics.ucla.edu/hdl/ (for complete results of the linkage analyses)

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