Am. J. Hum. Genet. 69:117–123, 2001

Quantitative-Trait-Locus Analysis of Body-Mass Index and of Stature, by Combined Analysis of Genome Scans of Five Finnish Study Groups

Markus Perola,[1,5,*] Miina Öhman,[1,*] Tero Hiekkalinna,[5] Jenni Leppävuori,[1] Päivi Pajukanta,[5] Maija Wessman,[2,3] Markku Koskenvuo,[7] Aarno Palotie,[2,5,6] Kenneth Lange,[5] Jaakko Kaprio,[4,8] and Leena Peltonen[1,5]

[1]Department of Molecular Medicine, National Public Health Institute, and Departments of [2]Clinical Chemistry, [3]Biosciences, Division of Genetics, and [4]Public Health, University of Helsinki, Helsinki; Departments of [5]Human Genetics, Gonda Neuroscience and Genetics Research Center, and [6]Pathology and Laboratory Medicine, University of California–Los Angeles; [7]Department of Public Health, University of Turku, Turku, Finland; and [8]Department of Public Health and General Practice, University of Oulu, Oulu, Finland

In recent years, many genomewide screens have been performed, to identify novel loci predisposing to various complex diseases. Often, only a portion of the collected clinical data from the study subjects is used in the actual analysis of the trait, and much of the phenotypic data is ignored. With proper consent, these data could subsequently be used in studies of common quantitative traits influencing human biology, and such a reanalysis method would be further justified by the nonbiased ascertainment of study individuals. To make our point, we report here a quantitative-trait-locus (QTL) analysis of body-mass index (BMI) and stature (i.e., height), with genotypic data from genome scans of five Finnish study groups. The combined study group was composed of 614 individuals from 247 families. Five study groups were originally ascertained in genetic studies on hypertension, obesity, osteoarthritis, migraine, and familial combined hyperlipidemia. Most of the families are from the Finnish Twin Cohort, which represents a population-wide sample. In each of the five genome scans, ~350 evenly spaced markers were genotyped on 22 autosomes. In analyzing the genotype data by a variance-component method, we found, on chromosome 7pter (maximum multipoint LOD score of 2.91), evidence for QTLs affecting stature, and a second locus, with suggestive evidence for linkage to stature, was detected on chromosome 9q (maximum multipoint LOD score of 2.61). Encouragingly, the locus on chromosome 7 is supported by the data reported by Hirschhorn et al. (in this issue), who used a similar method. We found no evidence for QTLs affecting BMI.

Introduction

The pedigrees collected for genome scans for complex diseases are typically ascertained via probands who manifest either clinically verified disease or extreme values for a quantitative risk factor. Multiple phenotypic variables, including stature of and weight of study subjects, are often either recorded as part of a basic medical history or are determined by a routine physical examination. In statistical analysis, these traits are usually ignored or incorporated either as covariates predictive of the disease or as associated risk factors. Even though these quantitative traits may not be clinically important enough to warrant independent genome scans, they are often interesting for the understanding of human biology and, as such, are worthy targets for quantitative-trait-locus (QTL) mapping. In the mapping of QTLs for such secondary traits, care must be taken to avoid ascertainment biases; for instance, if the secondary trait is strongly correlated with the original disease, naïve analysis may lead to false-positive results (Göring and Terwilliger 2000). To a large extent, these biases can be circumvented by (*a*) selecting those secondary traits that are only weakly correlated with the disease or the risk factor, (*b*) conditioning on the proband's secondary traits in analysis, and (*c*) pooling of study samples ascertained for different diseases.

Body-mass index (BMI) and stature are good examples of quantitative traits with high heritability (Solomon et al. 1983; Korkeila et al. 1991; Allison et al. 1996; Preece 1996; Silventoinen et al. 2000). Here we use these traits in a proof-of-principle study using genotypes produced in five separate genomewide scans originally performed for osteoarthritis (Leppävuori et al. 1999), familial combined hyperlipidemia (FCHL) (Pajukanta et al. 1999), hypertension (Perola et al. 2000), obesity (Öhman et al. 2000), and migraine (Wessman et al. 1998). Two suggestive loci controlling height are

Received March 2, 2001; accepted for publication May 14, 2001; electronically published June 15, 2001.

Address for correspondence and reprints: Dr. Leena Peltonen, UCLA Department of Human Genetics, Gonda Neuroscience and Genetics Research Center, Room 6506, 695 Charles E. Young Drive South, Box 708822, Los Angeles, CA 90095-7088. E-mail: lpeltonen@mednet.ucla.edu

* The first two authors contributed equally to this work.

0002-9297/2001/6901-0013$02.00

apparent from our data analysis, one of which overlaps with a locus also identified by an independent study (Hirschhorn et al. 2001 [in this issue]).

Subjects, Material, and Methods

Study Groups

The combined study group comprised 614 individuals from 247 Finnish families. Most of the families analyzed are from the Finnish Twin Cohort (Kaprio 1994). The concordant DZ twin pairs were ascertained according to explicit clinical criteria (Wessman et al. 1998; Leppävuori et al. 1999; Öhman et al. 2000; Perola et al. 2000) The families with FCHL were chosen from the European Multicenter Study on Familial Dyslipidemias (Pajukanta et al. 1997; Porkka et al. 1997) and are not from the Finnish Twin Cohort. The probands in this study were patients at Finnish University Hospitals who had been diagnosed as having at-risk lipid profiles and premature coronary heart disease (Pajukanta et al. 1997). The study groups were supplemented by recruiting the probands' available parents and siblings. A more detailed description of the patient selection is available elsewhere (Wessman et al. 1998; Leppävuori et al. 1999; Pajukanta et al. 1999; Öhman et al. 2000; Perola et al. 2000). This combined study group included the following: from the osteoarthritis study group, 94 individuals from 31 families; from the obesity study group, 236 individuals from 87 families; from the migraine study group, 108 individuals from 47 families; from the hypertension study group, 139 individuals from 47 families; and, from the FCHL study group, 174 individuals from 35 families. The number of nonfounders with phenotypic data (which produce the most information for linkage) is given, for each project, in table 1; individuals with no phenotypic data but with genotypic data were included, for phase information. Only 34 pedigree founders—all from the FCHL study group—had phenotypic data.

All the study subjects from the Finnish Twin Cohort Study have replied to queries about stature and weight, in health questionnaires mailed in 1981, 1990, or later. The nontwin family members were identified, and they responded to the disease-specific questionnaires. In addition, participants in the obesity study group and participants in the FCHL study group were clinically examined from 1990 onward. Of the individuals in the study, 57% were measured, for stature and weight, in clinical research centers; the remaining 43% were from the Finnish Twin Cohort. The questionnaire method used in the Finnish Twin Cohort Study has previously been validated for both stature (Silventoinen et al. 2000) and weight (Korkeila et al. 1991). The most recent reported weight was used. All study participants provided both informed consent to genetic studies of specific traits and permission to access their health records. The blood samples were bar coded on their arrival at the laboratory, and personal information identifying patients and their families was not made available to the investigators performing the genetic studies.

Genotyping

DNA was extracted from EDTA-anticoagulated whole blood according to standard procedures. In the five genome scans, ~350 microsatellite markers—included in the Weber screening set version 6 (Sheffield et al. 1995) and spaced, on average, 10.0 cM apart—were genotyped on 22 autosomes. The estimated average heterozygosity for the markers was .76. The fluorescently labeled PCR products were electrophoretically separated on an ABI 377XL automated DNA sequencer (Perkin Elmer), with analysis by Applied Biosystems' GENESCAN 2.1 software (Perkin Elmer), or on an ALFexpress automated laser-fluorescence DNA sequencer (Pharmacia Biotech). Analysis and assignment of the marker alleles were performed with GENOTYPER 2.0 (Perkin Elmer) or with Allele Links (Pharmacia Biotech), by two persons independently for each marker. The genetic-map construction was based on the Marshfield linkage maps (Broman et al. 1998). These baseline data were consistent both with the maps used elsewhere (Wessman et al. 1998;

Table 1

Demographic Characteristics of the Study Groups

Study Group	No. of Individuals			Age[a] (years)		BMI (kg/m^2)				Stature (cm)			
	Female	Male	Total	Mean (SD)	Range	Mean (SD)	Range	Skewness[b]	Kurtosis[b]	Mean (SD)	Range	Skewness[b]	Kurtosis[b]
Arthrosis	50	15	65	58.4 (11.4)	20–80	26.2 (4.2)	17.4–39.9	.37	.79	166.5 (7.8)	152–186	.56	−.11
FCHL	78	63	141	47.5 (12.6)	20–76	37.2 (4.0)	17.4–37.2	.73	.62	168.2 (9.2)	148–191	.13	−.64
Hypertension	68	34	102	56.1 (8.5)	39–74	25.5 (3.1)	18.6–33.5	.42	.29	166.1 (8.8)	150–186	.02	−.60
Migraine	78	9	87	42.6 (7.1)	32–62	24.1 (3.8)	17.4–37.9	−.25	−.14	164.7 (5.8)	151–182	.48	.38
Obesity	122	63	185	49.9 (8.9)	21–72	36.7 (6.1)	22.3–56.6	.38	.37	166.2 (7.7)	144–194	.26	−.14
All	396	184	580	50.4 (11.2)	20–80	29.4 (6.9)	17.4–56.6	.10	−.41	166.5 (8.4)	144–194	.27	−.25

Note.—Only nonfounder individuals for whom both genotypic and phenotypic data were available were included.

[a] Individuals <20 years of age were excluded.

[b] After corrections (i.e., substitution of square root of stature and reciprocal of BMI).

Leppävuori et al. 1999; Pajukanta et al. 1999; Öhman et al. 2000; Perola et al. 2000) and with our own marker-to-marker linkage data in the families.

Statistical Analysis

Preliminary statistical analysis of the genotypes was performed by SAS 8.01 (SAS Institute). BMI was defined as weight/(height)^2. In the combined study group, stature and BMI were not normally distributed. Because QTL mapping relies on normality, we replaced stature with its square root and replaced BMI with its reciprocal. For purposes of covariate adjustment, the study participants' ages computed were those when their stature and weight were recorded or measured. Genotyped markers were checked for incompatibilities, by the programs PedCheck (O'Connell and Weeks 1998) and MENDEL (Lange et al. 1988). Most Mendelian errors could be resolved unambiguously; the remaining errors were handled by excluding from linkage analysis, at all markers, the families with errors. QTL mapping was done by the program Solar 1.6.7 (Almasy and Blangero 1998), which incorporates the variance-component program FISHER (Lange et al. 1988). Since subjects from the obesity study group who had BMI $\geq$30.0 kg/m^2 and subjects from the hypertension study group who had BMI <27.0 kg/m^2 were originally selected according to their BMI, they were, for ascertainment correction, labeled as probands in the Solar analyses. Because some markers were used in only a subset of the scans, in the present study we omit the two-point LOD scores and present only multipoint LOD scores. The list of markers genotyped in each study group is given at our website, Additional Tables for the Study. To determine which study groups contributed most to identification of loci, each study group was analyzed again, after the primary analyses for both phenotypes.

Results

The mean age of the 580 individuals genotyped in the five genome scans was 50.4 years (SD 11.2) (table 1). Females were 68% of the study group, and males were 32% of the study group. Although the stature and weight of individuals <20 years of age were excluded from the QTL analysis, the genotypes of these individuals were retained to help to determine the genotypes and the linkage phases of older family members, as were the genotypes of all other persons with genotypic data in the pedigrees. The full results of the QTL analyses are given at our website, Additional Tables for the Study.

BMI

The BMIs of females and males in the combined study group were 28.9 kg/m^2 (SD 6.9) and 29.9 kg/m^2 (SD 6.4), respectively. Given the inclusion of participants from the obesity study group, it is hardly surprising that analysis of variance shows a significant BMI difference among the study groups ($P < .0001$). The heritability of BMI in the combined study group was .55 (standard error [SE] .09). BMI values were adjusted for age and for sex, in the final model, by regressing age against sex and then transforming to z scores, separately, for each sex, by calculating the number of SD above or below the mean. The highest multipoint LOD score for BMI, 1.29, was found on chromosome 5, 34 cM from the pter (fig. 1). To control for ascertainment bias, we also analyzed the study group without including genotypes collected in the obesity group's scan. The highest LOD score, 1.04, was again found on chromosome 5, 23 cM from pter. The multipoint LOD scores for BMI are given at our website, Additional Tables for the Study. On the basis of variance-component analysis, variation in the chromosome 1 region would account for 36% of the variation in BMI, with a residual additive genetic component of 21% and with a random environmental contribution of 43% (Comuzzie et al. 1997; Almasy and Blangero 1998). When the study groups were analyzed separately, a LOD score of 2.05, for the migraine study group, was found on chromosome 5; therefore, this group has the greatest contribution to this positive result.

Stature

The mean statures of females and of males in the combined study group were 162.3 cm (SD 6.0) and 175.0 cm (SD 6.1) (table 1), respectively. Analysis of variance did not show a significant stature difference between the five study groups ($P = .14$). The heritability of stature in the combined study group was .69 (SE .08). Sex ($P < .0001$)

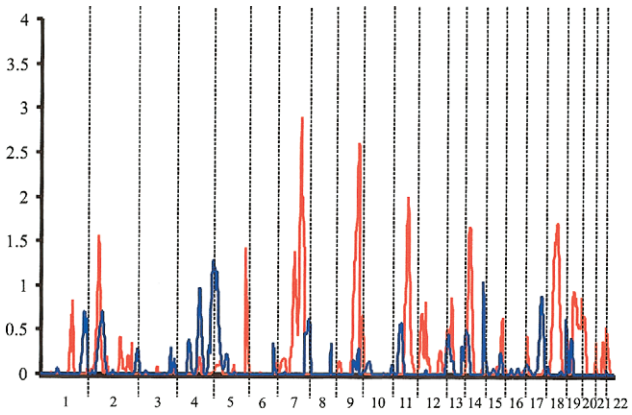

Figure 1 LOD scores for QTLs for stature and BMI. The red curve (computed by Solar 1.6.7) represents the multipoint LOD scores for a QTL determining stature, and the blue curve represents the genomewide multipoint LOD score for a QTL determining BMI (both are adjusted for age and for sex). The border of each autosome is indicated by dotted lines.

and age ($P = .0002$) were significantly correlated with stature and, thus, were included in the final analytical model in QTL analysis. Stature had an inverse correlation with age, for both sexes. The stature data were adjusted by regressing stature against age, for each sex separately. These age-corrected square roots of stature were then transformed to z scores by calculating the number of SDs above or below the mean. Figure 1 plots the multipoint LOD scores computed by Solar 1.6.7. Multipoint LOD scores for individual chromosomes can be viewed at our website, Additional Tables for the Study. The highest multipoint LOD score for stature, 2.91, was found on chromosome 7, 164 cM from the pter (fig. 2). Another suggestive LOD score, 2.61, was found on chromosome 9, 159 cM from the 9pter (fig. 3). According to variance-component analysis, variation in the chromosome 7 region would account for 34% and 33% of the variation in stature, in the linked regions on chromosomes 7 and 9, respectively, with a residual additive genetic component of 14% and with a random environmental contribution of 19%. When the study groups were analyzed separately, a multipoint LOD score of 2.3, for the hypertension study group, was found on chromosome 7; therefore, this group has the greatest contribution to this positive result. In figures 1 and 2, we have also indicated the multipoint findings that Hirschhorn et al. (2001 [in this issue]) have reported for these chromosomes, to facilitate comparison between the study groups.

Genomewide P *Values*

To assess the relative significance of our results, we permuted age- and sex-corrected phenotypes and recalculated the multipoint LOD scores by using these permuted phenotypes. The adjustments, for age and sex covariates, that were used in the permuted scans were the same as those used in the original data analysis. Phenotype permutation was confined to the siblings within each family. Since not all individuals were genotyped for all markers, the phenotypes, rather than the genotypes, were permuted. In our 100 permuted genome scans, we found the maximum multipoint LOD score, ≥ 2.91, 14 times, which results in an empiric P value of .14. LOD scores ≥ 2.61 were seen 32 times ($P = .32$). Only four of these permuted genome scans showed a combination of two or more LOD scores that were >2.61 ($P = .04$).

Discussion

Once panels of evenly distributed, informative markers became available for genomewide scans, the search for genes predisposing to complex diseases commenced with great enthusiasm. Unfortunately, few real successes in gene identification have yet been reported (Weiss and Terwilliger 2000). One explanation for these failures is the information loss that occurs when quantitative complex traits are dichotomized, according to accepted diagnostic criteria, into yes/no disease states. With the ad-

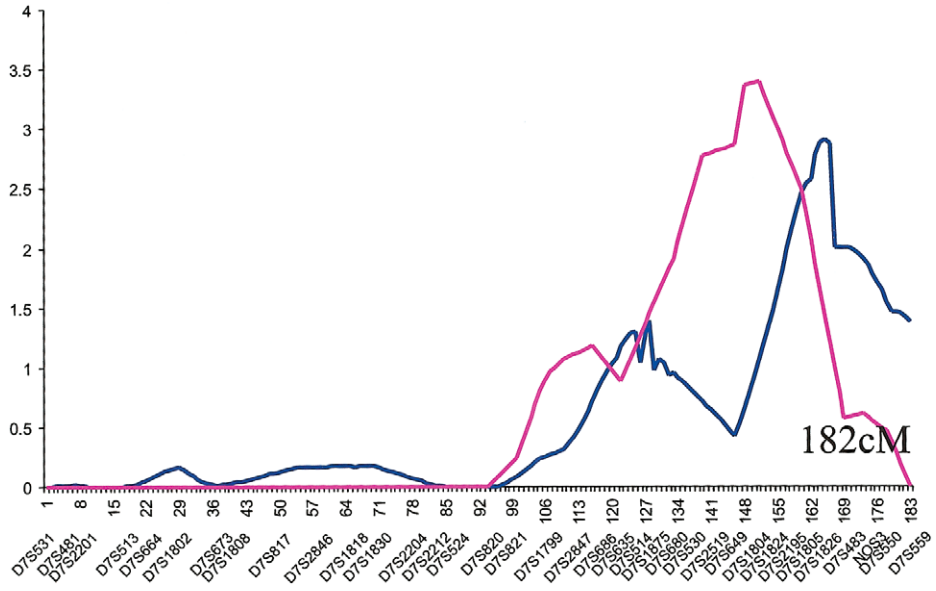

Figure 2 LOD scores for QTLs for stature and BMI: chromosome 7. The blue curve expands the genomewide multipoint-LOD-score curves in figure 1, to chromosome 7 alone. For comparison, the pink curve represents the results reported by Hirschhorn et al. (2001 [in this issue]) for their Swedish study group, as discussed in the text. The numbers below the horizontal axis indicate distance (in cM) from 7pter.

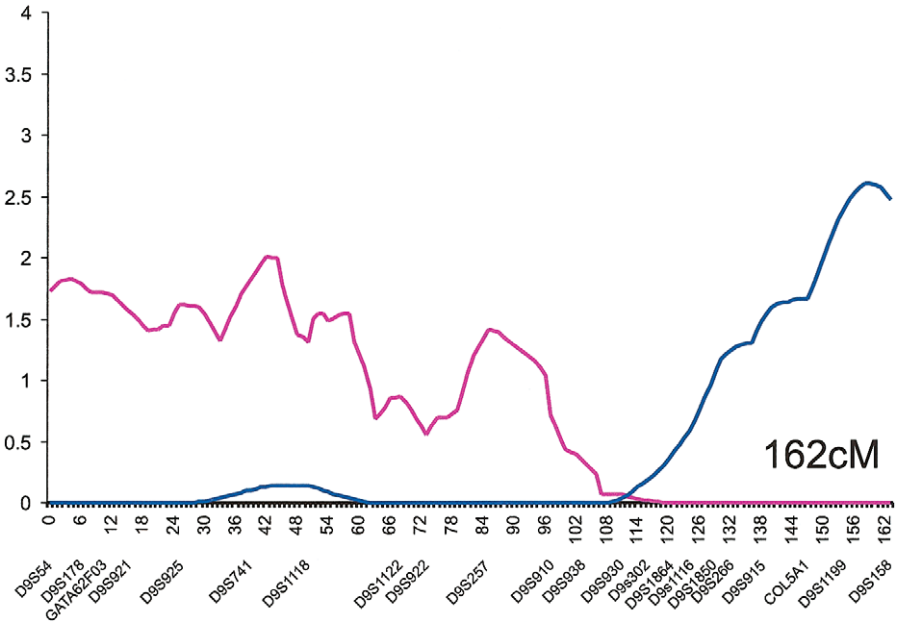

Figure 3 LOD scores for QTLs for stature and BMI: chromosome 9. The blue curve expands the genomewide multipoint-LOD-score curves in figure 1, to chromosome 9 alone. For comparison, the pink curve represents the results reported by Hirschhorn et al. (2001 [in this issue]) for their Botnian study group, as discussed in the text. The numbers below the horizontal axis indicate distance (in cM) from 9pter.

vent of more-advanced QTL-mapping methods (Almasy and Blangero 1998), there is now no excuse for wasting the precious quantitative information collected via these scans. Similarly, most of the routine phenotypic and clinical data collected in genetic studies are not used in the subsequent analyses. Typically, the disease traits are analyzed, and most of the ancillary data are disregarded. Clearly, exploiting the secondary traits should not be allowed if study participants have not provided informed consent for genetic analysis of all phenotypic data. If, however, proper, informed consent has been given, use of all the available phenotypic data has a tremendous potential to expose important features of biological variation. The present study has conducted the kind of meta-analysis commonly employed in epidemiology.

Our analysis of QTLs of BMI and of stature combines information from five genomewide scans performed in Finland. The selected variables analyzed were stature (i.e., height) and relative weight (i.e., BMI). In our combined study group of 614 individuals, we found suggestive evidence for linkage between stature and a QTL on chromosome 7q. This intriguing result is consistent with the linkage peak reported by Hirschhorn et al. (2001 [in this issue]) for a Swedish study group. The two peaks on this chromosome that were reported by these two studies are remarkably close. Unfortunately, neither the pedigrees from western Finland (specifically, Botnia) nor the pedigrees from Helsinki, in southern Finland, provide much evidence for linkage to this 7qter region, in the study by Hirschhorn et al. (2001 [in this issue]). Our strategy is somewhat different from that of Hirschhorn et al. (2001 [in this issue]); whereas they analyzed their scans separately, we combined the raw data of five scans and analyzed the geno- and phenotypes together. Also, all the scans in our study were ascertained for different phenotypes, and, although most study groups ascertained are from the genetically isolated Finland, the contribution of subisolates varies greatly and can have an effect on contribution of different loci (Kittles et al. 1998). The two study groups with matching linkage peaks on this chromosome 7 region are among the largest in these two studies, indicating the real significance of this locus. Another region that, in our study, showed some evidence for linkage, on chromosome 9, was not replicated as successfully by Hirschhorn et al. (2001 [in this issue]); however, in the analysis of complex traits, the peak points for the same gene locus can widely vary between different studies (Terwilliger and Göring 2000). The intervals supporting linkage to stature QTLs on chromosomes 7 and 9 remain quite wide, and, thus, it is not relevant to list any obvious positional candidate genes, at this stage. We did not see any evidence for linkage to chromosome 20, where a previous linkage for stature has been reported (Thompson et al. 1995).

The suggestive area for a dichotomized phenotype (i.e., obesity) reported, elsewhere (Öhman et al. 2000),

in a group from the present study, was not replicated in the present study. Also, we found no peaks in the regions reported in several genomewide scans for different variants of weight (Comuzzie et al. 1997; Hager et al. 1998; Hanson et al. 1998; Lee et al. 1999). A previous candidate-gene study (Mitchell et al. 1999) in a population similar to that in the present study (i.e., one comprising mostly individuals not ascertained for obesity) linked BMI to chromosome 8. We could not replicate this finding. As a quantitative trait, BMI is preferred to weight, because stature affects weight nonlinearly. BMI serves as an economic surrogate for relative obesity. Our positive evidence for two QTLs affecting stature in our combined study group is not balanced by equally convincing evidence for QTLs affecting BMI. It is possible that this divergence reflects the heritability difference (i.e., .70 vs. .55) between these two traits. The adult stature of individuals is usually attained during puberty and remains essentially the same throughout adulthood, whereas adult BMI may fluctuate considerably throughout adulthood. The numerous environmental factors affecting adult BMI levels make a single measurement of weight a less reliable indicator of genetic influence than is a single measurement of stature. Although genes affecting BMI doubtless exist, the study groups—or pedigrees—necessary for detection of a QTL for BMI may be significantly larger than the combined study group assembled here.

The stature heritability found in our data closely matches the heritabilities—.77 (95% confidence interval [95%CI] .73–.82) among Finnish men and .76 (95%CI .71–.80) among Finnish women—reported by Silventoinen et al. (2000). This consistency suggests that nonadditive genetic influences on stature are rather small, if present at all. The heritability difference between stature and BMI may partially explain why linkage to stature but not to BMI was detected. It is interesting that familial risk ratios for extreme obesity tend to be higher than familial risk ratios for moderate obesity (Allison et al. 1996; Lee et al. 1997).

To summarize, by combining collected genotypic data from previously performed genomewide scans for complex disease loci, we found, on chromosome 7, evidence for a QTL determining stature, in agreement with the results reported by Hirschhorn et al. (2001 [in this issue]), who used a similar analytical strategy. We also found, on chromosome 9, some evidence for QTLs affecting stature. Our results demonstrate that reanalyses of genome-scan data for common QTLs of variant traits can expose influencing loci. Data mining and meta-analysis of genotypes accumulated in numerous genome scans worldwide would be extremely useful in the mapping of many common traits and would increase the scientific value of these expensive endeavors. Pooled data analyses of representative study groups from different populations would be highly beneficial, not only for the pursuit of potential differences among populations but also for efficient restriction of the critical DNA regions of the QTL loci and for final gene identification. Potentially, this strategy could lead to the final identification of genes, so far successfully cloned only in plants (Frary et al. 2000).

Acknowledgments

We wish to thank all the patients and their families. This study was supported by The Finnish Academy grant 38332 (to J.K.) and by National Institutes of Health grants MH59498 and GM53275 (both to K.L.), by Helsinki University Central Hospital Research Fund TYH0054 (to A.P. and M.W.), by The Paulo Foundation (support to M.Ö., M.P., and M.W.), by The Finnish Cultural Foundation (support to M.P. and P.P.), by the Duodecim Foundation (support to M.Ö. and P.P.), by the Farmos Research Foundation (support to M.Ö.), by the Research Foundation of the University of Helsinki (support to M.Ö. and L.P.), by the Aarne Koskelo Foundation (support to M.Ö.), by the Helsingin Sanomat Centennial Foundation (support to M.P. and T.H.), and by the Finnish Heart Foundation (support to M.Ö., M.P., and P.P.). We would like to thank Dr. Rita Cantor for her helpful comments during the preparation of the manuscript.

Electronic-Database Information

URLs for data in this article are as follows:

Additional Tables for the Study, http://www.ktl.fi/lmgo/lmgo_wwwpub/siliconscan.htm (for full results of QTL analyses)

Finnish Twin Cohort Study, The, http://kate.pc.helsinki.fi/twin/twinhome.html (for detailed description of the Finnish Twin Cohort)

References

Allison D, Faith M, Nathan J (1996) Risch's lambda values for human obesity. Int J Obes Relat Metab Disord 20:990–999

Almasy L, Blangero J (1998) Multipoint quantitative trait linkage analysis in general pedigrees. Am J Hum Genet 62:1198–1211

Broman KW, Murray JC, Sheffield VC, White RL, Weber JL (1998) Comprehensive human genetic maps: individual and sex-specific variation in recombination. Am J Hum Genet 63:861–869

Comuzzie AG, Hixson JE, Almasy L, Mitchell BD, Mahaney MC, Dyer TD, Stern MP, MacCluer JW, Blangero J (1997) A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2. Nat Genet 15:273–276

Frary A, Nesbitt TC, Grandillo S, Knaap E, Cong B, Liu J, Meller J, Elber R, Alpert KB, Tanksley SD (2000) *fw2.2:* a quantitative trait locus key to the evolution of tomato fruit size. Science 289:85–88

Göring HH, Terwilliger JD (2000) Linkage analysis in the pres-

ence of errors III: marker loci and their map as nuisance parameters. Am J Hum Genet 66:1298–1309

Hager J, Dina C, Francke S, Dubois S, Houari M, Vatin V, Vaillant E, Lorentz N, Basdevant A, Clement K, Guy-Grand B, Froguel P (1998) A genome-wide scan for human obesity genes reveals a major susceptibility locus on chromosome 10. Nat Genet 20:304–308

Hanson RL, Ehm MG, Pettitt DJ, Prochazka M, Thompson DB, Timberlake D, Foroud T, Kobes S, Baier L, Burns DK, Almasy L, Blangero J, Garvey WT, Bennett PH, Knowler WC (1998) An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. Am J Hum Genet 63:1130–1138.

Hirschhorn JN, Lindgren CM, Daly MJ, Kirby A, Schaffner SF, Burtt NP Altshuler D, Parker A, Rioux JD, Platko J, Gaudet D, Hudson TJ, Groop LC, Lander ES (2001) Genomewide linkage analysis of stature in multiple populations reveals several regions with evidence of linkage to adult height. Am J Hum Genet 69:106–116 (in this issue)

Kaprio J (1994) Lessons from twin studies in Finland. Ann Med 26:135–139

Kittles RA, Perola M, Peltonen L, Bergen AW, Aragon RA, Virkkunen M, Linnoila M, Goldman D, Long JC (1998) Dual origins of Finns revealed by Y chromosome haplotype variation. Am J Hum Genet 62:1171–1179

Korkeila M, Kaprio J, Rissanen A, Koskenvuo M (1991) Effects of gender and age on the heritability of body mass index. Int J Obes 15:647–654

Lange K, Weeks D, Boehnke M (1988) Programs for pedigree analysis: MENDEL, FISHER, and dGENE. Genet Epidemiol 5:471–472

Lee JH, Reed DR, Li WD, Xu W, Joo EJ, Kilker RL, Nanthakumar E, North M, Sakul H, Bell C, Price RA (1999) Genome scan for human obesity and linkage to markers in 20q13. Am J Hum Genet 64:196–209

Lee J, Reed D, Price R (1997) Familial risk ratios for extreme obesity: implications for mapping human obesity genes. Int J Obes Relat Metab Disord 21:935–940

Leppävuori J, Kujala U, Kinnunen J, Kaprio J, Nissila M, Heliövaara M, Klinger N, Partanen J, Terwilliger JD, Peltonen L (1999) Genome scan for predisposing loci for distal interphalangeal joint osteoarthritis: evidence for a locus on 2q. Am J Hum Genet 65:1060–1067

Mitchell BD, Cole SA, Comuzzie AG, Almasy L, Blangero J, MacCluer JW, Hixson JE (1999) A quantitative trait locus influencing BMI maps to the region of the β-3 adrenergic receptor. Diabetes 48:1863–1867.

O'Connell JR, Weeks DE (1998) PedCheck: a program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet 63:259–266

Öhman M, Oksanen L, Kaprio J, Koskenvuo M, Mustajoki P, Rissanen A, Salmi J, Kontula K, Peltonen L (2000) Genome-wide scan of obesity in Finnish sibpairs reveals linkage to chromosome Xq24. J Clin Endocrinol Metab 85: 3183–3190

Pajukanta P, Porkka KV, Antikainen M, Taskinen MR, Perola M, Murtomaki-Repo S, Ehnholm S, Nuotio I, Suurinkeroinen L, Lahdenkari AT, Syvanen AC, Viikari JS, Ehnholm C, Peltonen L (1997) No evidence of linkage between familial combined hyperlipidemia and genes encoding lipolytic enzymes in Finnish families. Arterioscler Thromb Vasc Biol 17:841–850

Pajukanta P, Terwilliger J, Perola M, Hiekkalinna T, Nuotio I, Ellonen P, Parkkonen M, Hartiala J, Ylitalo K, Pihlajamäki J, Porkka K, Laakso M, Viikari J, Enholm C, Taskinen M-R, Peltonen L (1999) Genomewide scan for familial combined hyperlipidemia genes in Finnish families, suggesting multiple susceptibility loci influencing triglyceride, cholesterol, and apolipoprotein B levels. Am J Hum Genet 64: 1453–1463

Perola M, Kainulainen K, Pajukanta P, Terwilliger JD, Hiekkalinna T, Ellonen P, Kaprio J, Koskenvuo M, Kontula K, Peltonen L (2000) Genome-wide scan of predisposing loci for increased diastolic blood pressure in Finnish siblings. J Hypertens 18:1579–1585

Porkka KV, Nuotio I, Pajukanta P, Ehnholm C, Suurinkeroinen L, Syvanne M, Lehtimaki T, Lahdenkari AT, Lahdenpera S, Ylitalo K, Antikainen M, Perola M, Raitakari OT, Kovanen P, Viikari JS, Peltonen L, Taskinen MR (1997) Phenotype expression in familial combined hyperlipidemia. Atherosclerosis 133:245–253

Preece M (1996) The genetic contribution to stature. Horm Res 45 Suppl 2:56–58

Sheffield VC, Weber JL, Buetow KH, Murray JC, Even DA, Wiles K, Gastier JM, Pulido JC, Yandava C, Sunden SL (1995) A collection of tri- and tetranucleotide repeat markers used to generate high quality, high resolution human genome-wide linkage maps. Hum Mol Genet 4:1837–1844

Silventoinen K, Kaprio J, Lahelma E, Koskenvuo M (2000) Relative effect of genetic and environmental factors on body height: differences across birth cohorts among Finnish men and women. Am J Public Health 90:627–630

Solomon P, Thompson E, Rissanen A (1983) The inheritance of height in a Finnish population. Ann Hum Biol 10:247–256

Terwilliger JD, Göring HH (2000) Gene mapping in the 20th and 21st centuries: statistical methods, data analysis, and experimental design. Hum Biol 72:63–132

Thompson DB, Ossowski V, Janssen RC, Knowler WC, Bogardus C (1995) Linkage between stature and a region on chromosome 20 and analysis of a candidate gene, bone morphogenetic protein 2. Am J Med Genet 59:495–500

Weiss KM, Terwilliger JD (2000) How many diseases does it take to map a gene with SNPs? Nat Genet 26:151–157

Wessman M, Kallela M, Hovatta I, Marttila P, Kaunisto M, Koskenvuo M, Honkasalo M-L, Färkkilä M, Ott J, Kaprio J, Peltonen L, Palotie A (1998) A genome-wide search for genes predisposing to migraine in Finnish twins. Am J Hum Genet Suppl 63:A314