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The Genetic Dissection of Complex Traits in a Founder Population

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We estimated broad heritabilities (H^2) and narrow heritabilities (h^2) and conducted genomewide screens, using a novel association-based mapping approach for 20 quantitative trait loci (QTLs) among the Hutterites, a founder population that practices a communal lifestyle. Heritability estimates ranged from .21 for diastolic blood pressure (DBP) to .99 for whole-blood serotonin levels. Using a multipoint method to detect association under a recessive model we found evidence of major QTLs for six traits: low-density lipoprotein (LDL), triglycerides, lipoprotein (a) (Lp[a]), systolic blood pressure (SBP), serum cortisol, and whole-blood serotonin. Second major QTLs for Lp(a) and for cortisol were identified using a single-point method to detect association under a general two-allele model. The heritabilities for these six traits ranged from .37 for triglycerides to .99 for serotonin, and three traits (LDL, SBP, and serotonin) had significant dominance variances (i.e., $H^2 > h^2$). Surprisingly, there was little correlation between measures of heritability and the strength of association on a genomewide screen ($P > .50$), suggesting that heritability estimates per se do not identify phenotypes that are influenced by genes with major effects. The present study demonstrates the feasibility of genomewide association studies for QTL mapping. However, even in this young founder population that has extensive linkage disequilibrium, map densities <<5 cM may be required to detect all major QTLs.

Introduction

Despite the extensive efforts in laboratories around the world, in both the public and private sectors, to identify genes that influence common human diseases that have complex genetic etiologies, there have been relatively few successes to date (for examples, see reports by Horikawa et al. [2000], Hugot et al. [2001], and Tavtigian et al. [2001]). The difficulties in identifying genes for common diseases in humans result, in part, from the fact that these diseases are genetically heterogeneous conditions, with contributions from low-penetrant, common alleles and from environmental factors that are often unknown or unmeasurable. In addition, the true genetic models that underlie common phenotypes are not known. The total number of genes that influence susceptibility, as well as the number of genes that would be detectable in any particular sample and by any particular analytical approach, are unknown.

Nonetheless, ongoing debates about the best strategies for identifying common disease genes rely on assumptions about the underlying genetic models (Risch and Merikangas 1996; Kruglyak 1999; Wright et al. 1999). Whereas choices about the most efficient strategies would be more informed if the model were known, there is a dearth of knowledge about the true models that give rise to diseases with complex modes of inheritance. Estimates of risk ratios for relatives of affected individuals (such as the λ_R statistic) and of heritability provide some information on the relative importance of genetic and familial factors in comparison with nonshared environmental factors, but such estimates will not necessarily provide information on the relative contributions of specific genes or on the overall number of genes that contribute to susceptibility. Furthermore, the effects of shared environments among first-degree relatives cannot easily be disentangled from the effects of shared genes on phenotypic trait values among these same relatives. As a result, estimates of λ and of heritability often include the effects of a shared familial environment as well as shared genes, thereby inflating estimates of the contribution of genes to the phenotypic variance (Rice and Borecki 2001).

As a first step in dissecting the genetics of complex phenotypes, we examined the relationship between estimates of heritability and the strength of signals in genomewide screens for quantitative trait loci (QTL) in a founder population, the Hutterites. The Hutterites are a young founder population who practice a communal farming lifestyle. The small number of founders is expected to reduce the number of alleles that contribute to susceptibility, while the Hutterites' communal lifestyle attenuates, to a large degree, the confounding effects of environmental factors. In particular, all Hutterite communities eat a farming diet that is based on

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traditional recipes; individual household environments are nearly identical within colonies and differ little between colonies; and other lifestyle factors that are risks for common diseases are remarkably uniform within this community. The Hutterites in our study are connected by a known pedigree, and every pair of individuals is related through multiple lines of descent. By considering correlations between all pairs of individuals (not just first-degree relatives), we further reduce the effects of even small differences between familial environments on heritability estimates. As a result, estimates of heritability in this population are expected to more closely reflect the contribution of genetic variation. In addition, because nearly all pairs of Hutterites have nonzero probability of sharing two alleles identical by descent (IBD), we will have increased power to detect dominance variance in addition to the additive variance and will also have increased accuracy in estimation of the narrow heritabilities (h^2) and broad heritabilities (H^2) (Abney et al. 2000). Lastly, the Hutterites' recent origins and the resulting extensive linkage disequilibrium (LD) allows for genomewide LD (or association) mapping, which may be more powerful than linkage studies for identifying genes that contribute to common diseases (Cardon and Bell 2001).

As part of our genetic studies of complex traits in the Hutterites, we have measured 20 quantitative traits that are associated with asthma, diabetes mellitus, cardiovascular disease, hypertension, and autism. Genomewide screens with >500 autosomal markers have been completed in nearly 700 individuals who are related to one another in a single 13-generation 1,623-person pedigree (Abney et al. 2000; Ober et al. 2000). Variance-component analyses were used to estimate heritabilities (Abney et al. 2000, 2001). Association mapping for QTLs included a novel multipoint method for detecting recessive alleles and a single-point method that allows a general two-allele model. These analyses were conducted in the entire, intact 1,623-person pedigree. In earlier reports, we presented estimates of heritability for 10 of these traits (Abney et al. 2000, 2001). In the present report, we present an overview of the relationship between heritability and the ability to detect allelic associations to 20 quantitative traits in the Hutterites, and, from this information, we draw inferences about the underlying genetic models for these QTLs.

Material and Methods

Sample Composition and Evaluation of Phenotypes

The study subjects include 722 Hutterites who live on nine communal farms (colonies) in South Dakota. All Hutterites >5 years of age who were in the colony on the days of our visits were included in our studies. The mean age of the participants is 28.7 years (SD 17.0 years; range 6–89 years). The study participants are descendants of 64 Hutterite ancestors who were born between the early 1700s and the early 1800s in Europe (Ober et al. 1997). The mean inbreeding coefficient of the individuals in this sample is .034 (SD .015), slightly greater than that of first cousins once removed. However, because we do not know the relationships among all 64 ancestors and because some could have been related to each other, this may be an underestimate of the true inbreeding level in this population (Ober et al. 1997).

Subjects were evaluated for a variety of qualitative and quantitative phenotypes during trips to Hutterite colonies in 1994 and in 1997–1998. Individuals who were ⩾15 years old ($N = 526$) donated one blood sample and one urine sample after an overnight fast and donated one additional blood sample in the nonfasting state; individuals <15 years old donated a blood sample in the nonfasting state only. Six phenotypes—low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, lipoprotein (a) (Lp[a]), insulin, and serum cortisol—were assessed in fasting blood samples, and two (creatinine and kallikrein) were assessed in urine samples. All studies of each person were performed on the same day. Results of studies of qualitative, asthma-related traits have been reported elsewhere (Ober et al. 2000). The protocol for assessing 20 quantitative traits is described below.

In this sample, 11% of subjects had asthma, and 51% had atopy (Ober et al. 2000). Among individuals ⩾30 years of age, 28% had type 2 diabetes or impaired glucose tolerance, 34% had hypertension, and 58% were obese.

Immunoglobulin E (IgE).—Total serum IgE concentration was measured in duplicate in serum samples, using the Sanofi Diagnostic Pasteur's method (Pierson et al. 1998) and was expressed in International Units per milliliter. All measurements were repeated, again in duplicate, in a second independent assay. All four measurements were averaged to obtain a final value.

Lung function.—Spirometry was performed with the subject in a sitting position and wearing a nose clip. The best forced expiratory volume at one second (FEV_1) and forced vital capacity (FVC) were measured following criteria of the American Thoracic Society (1987). Results were expressed as a percentage of predicted values, corrected for height and gender.

Eosinophils.—Eosinophils were measured in whole blood on the basis of a differential blood count.

Lipids.—The determinations of total cholesterol, HDL, and triglyceride levels were performed in an automated Kodak Ektakem DT 60 unit, according to the manufacturer's instructions. LDL levels were calculated from the total cholesterol, triglyceride, and HDL cholesterol values, by the Friedewald formula: LDL =

totalcholesterol − [HDL + (triglycerides/5)]. The concentration of Lp(a) was determined using the protocol of Fless et al. (1989) and expressed the results in terms of milligrams of protein per deciliter of plasma.

Insulin.—Whole blood was collected in red top Vacutainer tubes after a 10-hour fast. The serum was separated by centrifugation and immediately frozen. Serum samples were shipped on dry ice to the laboratory, where they were stored at −70°C until the time of the assay. Insulin was assayed by a double-antibody technique (Morgan and Lazarow 1963) with a lower limit of sensitivity of 20 pmol/liter and an average intra-assay coefficient of variation of 6%. The cross-reactivity of proinsulin in the radioimmunoassay for insulin was ~40%.

Percent fat and fat-free mass (FFM).—Percent fat and FFM were determined by bioelectrical impedance analysis (BIA). Wrist-ankle BIA was measured using an RJL model 101A tetrapolar bioimpedance analyzer. Resistance and reactance were measured while subjects were lying supine, with their arms abducted at a 45° angle and their legs separated so that the thighs did not touch. Total body water (TBW) was calculated using the prediction equation of Kushner et al. (1992). FFM was calculated as TBW/0.73, and fat mass was calculated as weight (in kilograms) − FFM (Kushner et al. 1992).

Anthropometrics.—Height was measured, by use of a plastic stadiometer, to the nearest 3 mm, with the subject in stocking feet; weight was measured using a Tanita model TBF105 scale, with the subject wearing light clothing. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). Waist and hip circumferences were measured in centimeters, using a tape measure over light clothing.

Blood pressure.—Nurses measured blood pressure after the subject had been standing for ⩾5 min, using mercury-gravity sphygmomanometers and appropriately sized cuffs.

Serotonin.—Serotonin was measured in whole blood that was anticoagulated in EDTA and mixed by gentle inversion. Samples were immediately frozen and shipped on dry ice to the laboratory, where they were stored at −70°C until the time of batch assay. Whole-blood 5-hydroxytryptamine was analyzed by high-performance liquid chromatography, with fluorometric detection (Anderson et al. 1981); 5-hydroxytryptophan was used as an internal standard. Intra-assay and interassay coefficients of variation were 0.8% and 3.6%, respectively (Anderson et al. 1981).

Serum cortisol.—Cortisol was measured in fasting serum samples, by the method of Taylor et al. (1983).

Urine creatinine.—Proteins were measured in first-voided morning urine samples, by an automated modification of the pyrogallol red method (Hicks et al. 1979).

Urine kallikrein.—Kallikrein was measured in first-voided morning urine samples, by radioimmunoassay (Shimamoto et al. 1980).

Genetic markers

A genome screen, using 386 microsatellite markers (Screening Set 9), was completed by the NHLBI-funded Mammalian Genotyping Service, yielding a 9.1-cM map. Subjects were genotyped for >200 additional markers in selected regions of the genome, as described elsewhere (Ober et al. 2000).

Variance-Component Analyses

Estimating heritability.—Heritabilities for each quantitative trait were measured using variance-component analysis, as described elsewhere (Abney et al. 2000; 2001).

QTL mapping.— Association-based mapping methods were developed specifically to map QTLs in large inbred pedigrees. The effect of an allele is modeled as a main effect, while the relationships among all the Hutterites are taken into account by means of additive- and dominance-variance components of random polygenic effects. We include the major gene effect as a main effect to take advantage of the extensive LD in the Hutterites. Within this basic framework, we use two different approaches: a single-point method to detect association under a general two-allele model (of which additive, dominant, and recessive are all special cases) and a multipoint method to detect association under a recessive model (called the allele-specific homozygosity-by-descent [ASHBD] method). The ASHBD method takes advantage of the inbreeding present among the Hutterites. Locus-specific and genomewide significance are assessed by a novel permutation-based test that takes into account the relationships among individuals, as well as the number of tests performed per locus and across the entire genome, respectively. The methods are briefly described below; a separate manuscript detailing the properties of these methods is in preparation.

For the single-point general method, the model for association with a particular allele at a given locus is as follows: $Y = X\beta + G\gamma + \epsilon$, where Y is the transformed phenotype vector, X is a matrix of covariates (usually age, sex, and an intercept term), β is a vector of unknown parameters, G is a matrix with two columns (the first of which contains the number of copies of the given allele in each individual's genotype and the second of which is an indicator of homozygosity for the given allele for each individual), and γ is a vector of two unknown parameters. The vector ϵ is multivariate normal, with a mean of 0 and covariance matrix $2\Phi\sigma_A^2 + D\sigma_D^2 + I\sigma_E^2$. Here, σ_A^2 is additive variance, σ_D^2 is dominance variance, and σ_E^2 is environmental variance. The known matrices 2Φ and **D** are determined by the pedigree structure and

are calculated by the method of Abney et al. (2000). **I** is the identity matrix. The vector γ represents the effect of the given locus on the phenotype and parameterizes a general two-allele model. When the estimate γ^* of γ fell in the range $\gamma^*_1/\gamma^*_2 \approx -1$, we declared the model to be approximately dominant; when $|\gamma^*_1/\gamma^*_2|$ was 0–0.02, we declared the model to be approximately recessive; and, when $\gamma^*_1/\gamma^*_2 \geq 1$ or ≤ -1.5, we declared the model to be approximately additive. Detection of a major gene corresponds to rejection of the null hypothesis $\gamma = 0$. Conditional on the genotype data, the efficient score statistic for this test is approximately the F test for significance of γ in the generalized regression, in which maximum-likelihood estimates of the needed variance components under the null model are inserted. This test is performed for each allele at each locus.

For the ASHBD method, the model for association with a particular allele at a given locus is of the same mathematical form as shown above, but now G is a vector that gives, for each individual, the indicator of homozygosity by descent for a specific allele, and γ is an unknown scalar. As before, detection of a major gene corresponds to rejection of the null hypothesis $\gamma = 0$. In this case, unlike that of the previous model, G is not observed. To calculate an approximation to the efficient score statistic for this case, we first calculate, for each individual, the conditional probability of homozygosity by descent (autozygosity) for the particular allele at the locus, given the multipoint genotype data for the individual and the known pedigree relationship between the individual's parents. This is done by constructing a Markov approximation to the binary process that represents autozygosity/nonautozygosity for each individual and then applying a hidden Markov method. From this conditional probability, from the maximum-likelihood estimates of the needed variance components under the null model and from estimates of the other free parameters obtained by generalized regression, we calculate an approximation to the efficient score statistic. This test is performed for each allele at each locus.

Standard asymptotic theory combined with Bonferroni correction gives locus-specific P values, and, because the effect of interest is a main effect, these P values are fairly robust to deviations from normality of the residuals of the transformed phenotype values. In addition, to guard against such deviations from normality, we calculate P values by use of a permutation-based approach, in which we preserve the covariance structure due to relatedness among individuals. We first obtain the phenotypic residuals under the model with $\gamma = 0$. We then obtain a Cholesky-type decomposition of the estimated covariance matrix for these residuals and use it to linearly transform the phenotypic residuals to be approximately uncorrelated. We then permute the uncorrelated linearly transformed phenotypic residuals and transform them back, to construct new phenotype data for the individuals. For the case of multivariate normality, this is, asymptotically, a true permutation test, and, under deviations from normality, it would be expected to perform better than the theoretically determined P value. Our permutation-based assessment of significance allows us to obtain both locus-specific and genomewide P values, with appropriate correction for multiple tests. In fact, we find that the locus-specific P values from asymptotic theory are in close agreement with those from the permutation-based test. For obtaining genomewide P values, this method is applicable when positions of markers are independent of the observed association signals, under the null hypothesis (e.g., genome-screen data), whereas there is no such restriction for locus-specific P values.

Results

Heritability Studies

The population means and standard deviations and estimates of heritability (h^2 and H^2) for each quantitative trait are shown in table 1. The dominance variance of a trait measures the variance due to the interaction of the two alleles at a locus, summed over the genome. This is different from the additive variance, which measures the variance due to mean effects of single alleles. In addition, a nonzero dominance variance implies nonadditive effects at one or more loci, whereas a nonzero additive variance does not necessarily indicate that there are any QTLs that follow a strictly additive model, concepts that are discussed in detail in articles published elsewhere (Abney et al. 2000, 2001). Five traits had a significant dominance variance, thereby yielding estimates of broad heritability (H^2) that were larger than the estimates of narrow heritability (h^2): LDL, FFM, waist-hip ratio (WHR), SBP, and serotonin. The heritabilities of the remaining 15 traits could be accounted for entirely by additive genetic variances, and therefore the estimated broad and narrow heritabilities (H^2 and h^2, respectively) were the same. Two traits (WHR and SBP) had estimated narrow heritabilities of 0. However, the standard errors of these estimates were 0.10 and 0.15, respectively, putting their 95% confidence intervals (CIs) within the range of (in the case of WHR) or close to the lower estimate of (in the case of SBP) heritabilities in outbred populations.

For nearly all traits with additive variances only, estimates of heritability in the Hutterites are in the range of estimates in other populations (table 2). The lower heritability of the phenotype percent fat in the Hutterites compared with other populations (0.48 vs. 0.62–0.80) may reflect the inclusion of shared familial environment in previous estimates and the known importance of diet

Table 1

Attributes and Estimates of Narrow (h^2) and Broad (H^2) Heritabilities for 20 Quantitative Traits

Phenotype	*N*	Transformation	Covariates	Mean	SD	h^2	H^2
IgE	722	Log	Age, sex	97.6 IU/ml	254	.63	.63
FEV_1 (% predicted)	654	Log	Age, age^2	100.06	15.36	.35	.35
FEV_1/FVC	654	...	Age, sex	.96	.08	.41	.41
Eosinophilia	575	Log	Age, sex	.140 K/ml	.105	.32	.32
LDL	451	Cube root	Age	128.4 mg/dl	39.0	.36	.96
HDL	484	Cube root	Age, sex	47.3 mg/dl	13.8	.63	.63
Triglycerides	484	Log	Age, sex	134.5 mg/dl	92.3	.37	.37
Lp(a)	374	Log	Age, sex	2.88 mg/dl	3.64	.79	.79
Fasting insulin	497	Log of log	Age	99.34 pmol/liter	56.6	.32	.32
BMI	666	Log of log	Age, age^2, age^3, sex	24.5	6.1	.54	.54
Percent fat	663	...	Age, age^3, sex	30.61	10.83	.48	.48
FFM	664	Square root	Log (age), height^2, sex	45.0	13.3	.45	.76
WHR	514	Cube root	Age, sex	.86	.09	0	.86
Adult height	516	...	Age, sex	66.23 in	3.48	.83	.83
SBP	623	Log	Age, sex	122 mm Hg	14.4	0	.45
DBP	623	Square root	Age, age^2, sex	80 mm Hg	10.0	.21	.21
Cortisol	518	Log	Sex	22.2 μg/dl	6.2	.45	.45
Creatinine	526	Square root	Age, sex	162.9 mg/dl	68.8	.36	.36
Kallikrein	436	Cube root	Age	136.1 ng/day	162.0	.37	.37
Serotonin	567	Log	Age, sex	191 ng/ml	79	.52	.99

NOTE.—Means and standard deviations (SD) correspond to untransformed trait values. Traits with a significant dominance variance component are underlined. See Material and Methods section for full description of phenotypes.

and other lifestyle factors on this trait. The wide range of estimates for some traits is not surprising, because these estimates are derived from diverse population samples. Nonetheless, heritability estimates were considerably higher in the Hutterites than in other samples for three of four traits with dominance variances: LDL (.96 vs. .34–.50), FFM (.76 vs. .65), and WHR (.86 vs. .06–.50). This could result, in part, from an underestimation of heritabilities in previous studies if the dominance variance was present but not measured. Estimates of heritability for urinary creatinine, urinary kallikrein, and whole-blood serotonin have not been reported for other populations.

Genomewide Association Mapping

The most significant locus-specific *P* value on the genomewide screen and the corresponding genomewide *P* values are shown in table 3 and table 4, for each phenotype, by both the multipoint recessive and single-point general two-allele–model association tests. The ASHBD method tests the hypothesis that homozygosity by descent for a specific allele is significantly associated with the trait. The latter tests the hypothesis that a specific allele is associated with the trait value, where any two-allele model is allowed as the alternative model. For the general two-allele method, shown in table 4, we report an approximate model for the detected allele (additive, dominant, or recessive). The results of the full genome screen for these traits will be presented in separate reports.

Using the multipoint ASHBD method, we found that the strength of the most significant association, assessed by locus-specific and genomewide *P* values, varied dramatically across the traits, from a locus-specific *P* value of 5.8×10^{-6} (genomewide $P = .005$) for triglycerides to a locus-specific *P* value of 0.0041 (genomewide $P = .780$) for urinary creatinine. Loci for five traits (LDL, triglycerides, Lp(a), SBP, and serum cortisol) met genomewide significance ($P < .05$); for one trait (serotonin), the *P* value was so close to this threshold that it cannot be determined, on the basis of 1,000 simulations, whether it is above or below this threshold ($P = .044$; 95% CI 0.031–0.057). For one additional QTL (DBP), the *P* value was close enough to .10 that it could not be determined on the basis of 1,000 simulations whether it was above or below this threshold ($P = .117$; 95% CI 0.097–0.14). When ASHBD mapping was used, 3 of the 5 traits with a dominance variance and 3 of the 15 traits with only additive variances had loci with genomewide *P* values < .05. There were no particularly strong signals (all locus-specific *P* values >.001) across the genome for half the traits when the multipoint ASHBD mapping was used.

When the general two-allele model was applied, the strength of the most significant association varied from a locus-specific *P* value of 7.9×10^{-11} (genomewide $P < .001$) for Lp(a) to a locus-specific *P* value of .0075 (genomewide $P = .987$) for the ratio FEV_1/FVC. The best-fitting model for both traits was approximately additive. Loci for two traits—Lp(a) and cortisol—met genomewide significance ($P < .05$); the best-fitting model

Table 2

Heritability Estimates in the Hutterites and Other Populations for 17 Quantitative Traits

Phenotype[a]	H^{2b}	Heritability in Other Studies	References
IgE	.63	.47–.79	Hopp et al. 1984; Palmer et al. 2000
FEV_1 (% predicted)	.35	.06–.52	Palmer et al. 2000; Wilk et al. 2000; Whitfield et al. 1999
FEV_1/FVC	.41	.45	Wilk et al. 2000
Eosinophilia	.32	.30	Palmer et al. 2000
LDL	.96	.34–.50	Mitchell et al. 1996; Edwards et al. 1999
HDL	.63	.42–.83	Brenn 1994; Mitchell et al. 1996; Perusse et al. 1997; Edwards et al. 1999
Triglycerides	.37	.19–.55	Brenn 1994; Mitchell et al. 1996; Perusse et al. 1997; Edwards et al. 1999; Shearman et al. 2000
Lp(a)	.79	.51–.90	Mitchell et al. 1996; Rainwater et al. 1997; Scholz et al. 1999; Hong et al. 1995
Fasting insulin	.32	.35–.54	Mitchell et al. 1996; Narkiewicz et al. 1997
BMI	.54	.32–.59	Borecki et al. 1998; Cheng et al. 1998; Rice et al. 1997
Percent fat	.48	.62–.80	Rice et al. 1997; Faith et al. 1999
FFM	.76	.65	Rice et al. 1997
WHR	.86	.06–.50	Mitchell et al. 1996; Sellers et al. 1994; Selby et al. 1990
Height	.83	.66–.78	Silventoinem et al. 2000; Chatterjee et al. 1999; Luo et al. 1998
SBP	.45	.18–.54	Brenn et al. 1994; Mitchell et al. 1996; Rotimi et al. 1999; Cheng et al. 1998; An et al. 1999; Gu et al. 1998
DBP	.21	.28–.44	An et al. 1999; Rotimi et al. 1999; Mitchell et al. 1996; Gu et al. 1998; Brenn 1994
Cortisol	.45	.45	Saljukov et al. 1992; Meikle et al. 1988

NOTE.—No previous studies of heritability are available for the three traits included in the present study but not shown in this table.

[a] Traits for which $H^2 > h^2$ are underlined.

[b] Values from the present study.

was approximately additive in both cases. The additive loci that were significantly associated with Lp(a) and cortisol differed from the locus significantly associated with each of these traits by the ASHBD method. A QTL for one additional trait (BMI) had a *P* value close enough to .10 that it could not be determined on the basis of 1,000 simulations whether it was above or below this threshold ($P = .109$; 95% CI 0.090–0.13). The best-fitting model for BMI was approximately additive. Twelve traits showed no particularly strong evidence for association with alleles at any locus (all locus-specific *P* values >.001) by this method. For eight traits (IgE, FEV_1, FEV_1/FVC, eosinophils, HDL, height, urinary creatinine, and urinary kallikrein), no QTLs with a locus-specific *P* value <.001 were detected by use of either method.

The locus most associated with each trait by ASHBD mapping differed from the locus most associated by the general two-allele model for all but two traits. Alleles at D19S591 provided the best evidence for association with insulin, by both ASHBD and the general two-allele model; and alleles at D12S366 provided the best evidence for association with urinary creatinine, by both models. Additionally, despite correlations between many of these phenotypes, the locus most associated with each trait was unique in most cases. Only four pairs of traits were each associated with alleles at the same locus. These could represent the pleiotropic effects of allelic variants at a single linked QTL or alleles at multiple linked QTLs, each influencing variation in one trait. For example, SBP and DBP were associated with alleles at D11S1993; DBP and urinary creatinine were associated with alleles at D12S366; percent fat and BMI were associated with alleles at D14S1426; and serotonin levels and WHR were associated with alleles at D18S1371. The latter association is particularly intriguing, given the associations between serotonin and appetite regulation (Blundell 1984; Leibowitz and Shor-Posner 1986; De Fanti et al. 2001).

The relationship between estimates of heritability and strength of the signal on a genomewide screen is shown in figure 1 for each mapping approach. The heritability for the six traits that had QTLs with genomewide *P* values <.05 ranged from .37 (for triglycerides) to .99 (for serotonin). Unexpectedly, three traits with heritability estimates >.60 (adult height, HDL, and IgE) provided no particularly strong signals on a genomewide screen by either method. In fact, the estimate of heritability and the most significant locus-specific *P* value were not correlated (ASHBD: Spearman's $\rho = .127$, $P = .592$; general: Spearman's $\rho = -.108$, $P = .649$), indicating that heritability estimates per se are poor predictors of how easy it will be to detect a significant association on a genomewide screen.

Discussion

Dissecting the genetics of common diseases with complex modes of inheritance is a major challenge in human genetics (Lander and Schork 1994). A number of novel approaches for addressing the complexity of these con-

ditions and overcoming the methodological limitations inherent in studies of human families have been used, with varying degrees of success. A better understanding of the genetic models that underlie susceptibility would enhance our ability to "custom design" mapping and positional cloning strategies for complex phenotypes and would facilitate the search for susceptibility loci of many common diseases. Our studies in the Hutterites have allowed us to assess the genetics of a variety of quantitative phenotypes in a genetically homogeneous population that shares a relatively uniform environment. This allows us to make comparisons across phenotypes and to draw inferences about the genes that influence quantitative traits that are associated with susceptibility to common diseases.

The lack of correlation between estimates of heritability and the strength of signals on genomewide screens was surprising. Although the utility of heritability estimates as a measure of the overall importance of genetic factors influencing trait values has long been criticized (Morton 1974; Lewontin 1976), this measure is still often used to justify mapping studies or to prioritize traits for mapping. The results reported here demonstrate that heritability estimates do not reflect the underlying genetic models and therefore should be used cautiously when prioritizing phenotypes for mapping studies or when making decisions regarding appropriate analytical strategies. Among the six traits with genomewide significance, three had heritability estimates <.50, indicating that major genes influence the variation in some traits with relatively low heritabilities. The strong signals for cortisol, triglycerides, and SBP—despite their relatively low heritabilities—suggest the presence of at least one major QTL influencing variation in these traits. Our results for Lp(a) and serum cortisol suggest that there may even be two major QTLs for each trait, one detected by the ASHBD and one by the general two-allele method. On the other hand, some traits with relatively high estimates of heritability (e.g., adult height) may have many loci that each influence the trait value in small, and possibly negligible, ways. For these traits, traditional linkage approaches may have limited ability to dissect their genetic bases, and, in the present study, even association-based tests had little power.

Among traits with high heritabilities (>.60), the best signals on genomewide screens ranged from $P = .0037$ (IgE by the ASHBD method) to 7.8×10^{-11} (Lp[a] by general model). The large heritable component of some of these traits (such as height, HDL, and IgE) is apparently a result of the relatively small effects of many genes and may best fit a polygenic model in which variation is accounted for by the small effects of many loci. For others traits with high heritabilities (such as Lp(a), LDL, and serotonin), variation is likely a result of one or more major QTLs. Of course, height is the textbook example of a human polygenic trait, and the *LPA* locus maps to chromosome 6q27, just 1 cM from our most significant marker (Weitkamp et al. 1988). Genetic variation at the *LPA* locus is known to account for a substantial proportion of the phenotypic variation in Lp(a) levels (Boerwinkle et al. 1989). Our data are consistent with these findings and further suggest the presence of a second major locus for Lp(a).

Overall, more loci reached or approached genomewide significance by multipoint ASHBD mapping than by the general single-point method. Furthermore, whereas only 3 of the 10 loci with genomewide *P* values below or not significantly different from .10 were well approximated by an additive model, 7 of the loci reaching this level of significance were detected on the basis of a recessive model. These findings may indicate that the most important loci influencing quantitative trait variation are more often recessive than additive. If so, founder populations may be particularly well suited for QTL mapping studies, because the ability to detect loci with recessive alleles should be enhanced in these populations compared with outbred populations. On the other hand, we may have had better power to detect loci when we used the ASHBD method, because only these estimates were multipoint, whereas the general model was a single-point estimate.

A significant dominance variance was detected for five traits, indicating that at least one locus with a nonadditive effect influences trait values, and, in fact, the most significant loci for these five traits were recessive. Although proportionally more of the traits with nonzero dominance variances had at least one locus reaching a genomewide threshold of 5% than did traits with only additive variances (3 of 5 vs. 3 of 15), the numbers are too small to draw conclusions regarding the ease of mapping traits with dominance variances versus those with additive variances only. However, we note that the most significant association in this study was with a QTL that had an approximately additive genetic model for Lp(a), a trait whose distribution was accounted for entirely by additive genetic variance. In addition, among the eight QTLs that reached genomewide significance ($P < .05$), five corresponded to traits with additive variances only. Therefore, QTLs for phenotypes with significant dominance variances are not necessarily those that will be detected on genomewide screens.

Several additional factors specific to this study may have influenced our results. First, the fortuitous location of genetic markers relative to the location of the susceptibility loci likely influenced the ability to detect associations. For example, the framework marker D6S305 lies <1 cM from the *LPA* locus, which significantly affects Lp(a) levels (Weitkamp et al. 1988). The highly significant *P* value that we observed with this

Table 3

Results of Genomewide Screens for 20 QTLs: Analysis by Multipoint ASHBD

Trait	Locus	Allele Size (bp)	Distance from pter (cM)	Calculated P[a]	Permutation P[b]	GW P[b]
IgE	D3S1764[c]	233	153	.0037	.002	.780
FEV_1 (% predicted)	D11S1392[c]	212	43	.0017	.001	.527
FEV_1/FVC	D5S820[c]	198	160	.0038	.002	.846
Eosinophilia	D1S547[c]	304	268	.0026	.002	.752
LDL	D19S433[c]	211	52	.00011	<.001	.035
HDL	D18S535[c]	151	64	.0025	.002	.501
Triglycerides	D2S410[c]	170	125	5.8×10^{-6}	<.001	.005
Lp(a)	D18S843[c]	185	28	6.9×10^{-5}	<.001	.029
Insulin	D19S591[c]	108	10	.00091	.001	.343
BMI	D19S587	151	59	.0014	.003	.531
Percent fat	D1S3721[c]	212	73	.00031	.001	.148
FFM	D3S3547	224	55	.00088	<.001	.405
WHR	D7S817[c]	157	50	.0026	.004	.612
Adult height	D3S2459[c]	195	119	.0022	.001	.416
SBP	D8S1119[c]	182	101	7.0×10^{-5}	<.001	.031
DBP	D12S366	191	133	.00036	<.001	.117
Cortisol	D1S3723[c]	194	140	3.7×10^{-5}	<.001	.029
Creatinine	D12S366	189	133	.0041	.001	.780
Kallikrein	D17S1308[c]	308	1	.0038	.004	.822
Serotonin	D18S1371[c]	145	116	.00011	<.001	.044

NOTE.—Traits with genomewide $P < .05$ are underlined.

[a] Bonferroni-adjusted values.

[b] Based on 1,000 simulations.

[c] Framework marker.

Table 4

Results of Genomewide Screens for 20 QTLs: Analysis by General Two-Allele Model

Trait	Locus	Allele Size (bp)	Distance from pter (cM)	Calculated P[a]	Permutation P[b]	Best-Fitting Model	GW P[b]
IgE	D5S1505[c]	243	130	.0031	.005	Additive	.768
FEV_1 (% predicted)	D3S1768[c]	202	62	.0022	.001	Additive	.691
FEV_1/FVC	D1S2644	227	44	.0075	.006	Additive	.987
Eosinophilia	D2S1790	296	106	.0040	.004	Additive	.777
LDL	D19S918	148	70	.0013	.001	Recessive	.287
HDL	D20S901	266	26	.0037	.002	Recessive	.953
Triglycerides	D11S2000[c]	221	101	.00071	<.001	Additive	.178
Lp(a)	D6S305[c]	228	166	7.9×10^{-11}	<.001	Additive	<.001
Insulin	D19S591[c]	100	10	.00091	.001	Recessive	.448
BMI	D14S1426[c]	137	126	.00019	<.001	Additive	.109
Percent fat	D14S1426[c]	137	126	.00037	<.001	Additive	.234
FFM	D3S1766[c]	220	79	.0014	.002	Recessive	.629
WHR	D18S1371[c]	141	116	.00075	.002	Recessive	.342
Adult height	D10S219	76	101	.0012	.001	Additive	.486
SBP	D11S1993[c]	236	54	.0016	.002	Additive	.544
DBP	D11S1993[c]	242	43	.0015	.002	Additive	.496
Cortisol	D11S1981[c]	146	21	7.6×10^{-5}	<.001	Additive	.033
Creatinine	D12S366	195	133	.0020	.001	Additive	.621
Kallikrein	D8S373[c]	221	164	.0023	.003	Additive	.720
Serotonin	D15S153	208	62	.00046	.001	Additive	.146

NOTE.—Traits with genomewide $P < .05$ are underlined.

[a] Bonferroni-adjusted values.

[b] Based on 1,000 simulations.

[c] Framework marker.

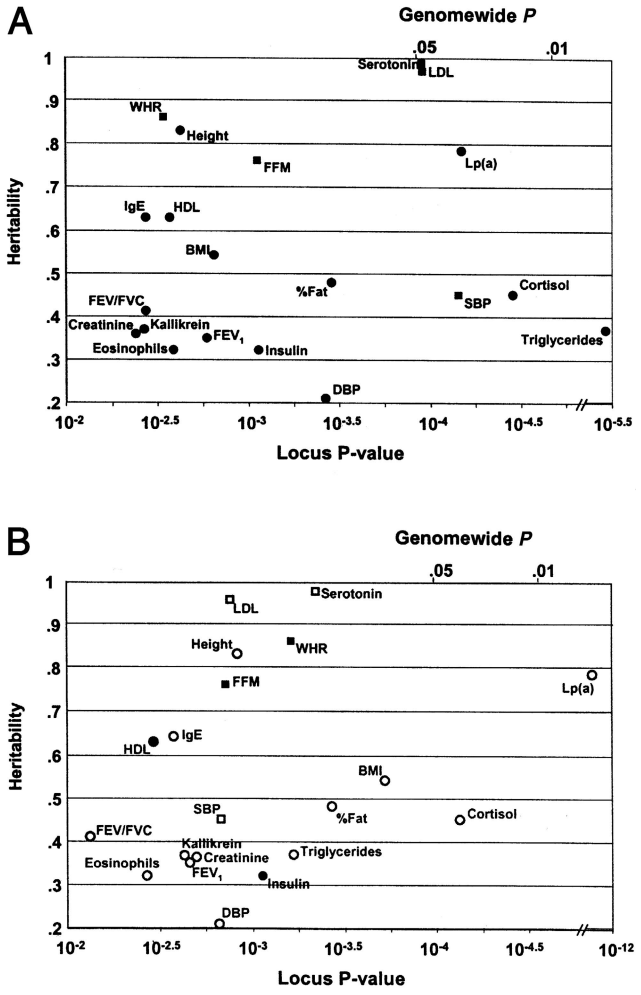

Figure 1 Relationship between heritability and the significance of the strongest association on genomewide screens for 20 QTLs. Square symbols represent traits with dominance variances (i.e., $H^2 > h^2$); circles represent traits with additive variance only (i.e., $H^2 = h^2$). Locus-specific *P* values are shown on the bottom axis, and approximate genomewide *P* values are shown on the top axis. *A,* Results of genomewide association mapping by use of the ASHBD method. *B,* Results of genomewide association mapping by use of the general two-allele model. Blackened symbols represent loci for which the best-fitting model is approximately recessive, and unblackened symbols represent loci for which the best-fitting model is approximately additive.

marker and Lp(a) is a result of the close proximity of these two loci. Had we sampled only a locus that was 7 cM away (D6S1277) from this known major locus for Lp(a), we would have observed a locus-specific *P* value of .004 and a corresponding genomewide *P* value >.70. Thus, the placement of genetic markers can have a major impact on the ability to detect association with additive alleles, and this observation suggests that fairly dense maps (<<5 cM) may be required to detect these loci, even in a young founder population. This could account for the relatively weak signals observed for some of the traits that did not reach a genomewide threshold of 10%. The placement of additional markers around the loci with the best linkage signals for some of these traits may yield additional significant loci. On the other hand, it is questionable whether adding more markers will detect QTLs for height, IgE, or HDL that would reach genomewide significance in this population. In fact, most of the >200 nonframework markers in this sample are in genomic regions that have been linked to, or associated with, asthma or the associated phenotype, IgE (Ober et al. 2000). Yet, despite relatively dense maps on chromosomes 5q, 6p, 12q, and 11q and in candidate genes related to IgE levels (such as the *IL4, IL13, IL4RA, FCREB1,* and *IFNG* loci) (Ober and Moffatt 2000), no strong signals were observed for this phenotype among the Hutterites.

A second important feature of the present study is that it was population based, with nearly complete ascertainment of all members of the population. Subjects were unselected with respect to disease or to any of the phenotypes studied. This allows us to obtain unbiased estimates of the components of variance but may limit the ability to generalize from our results to samples collected using different ascertainment schemes. In particular, our study design will allow us to detect genes that influence normal variation in these quantitative traits but not necessarily loci that contribute to disease. For example, IgE levels in the Hutterites are lower than those reported for families ascertained on the basis of asthma or atopy (Wjst et al. 1999; Xu et al. 2000; Lester et al. 2001), even among Hutterites with asthma (Ober et al. 2000). The contribution of individual genes, as well as the power to detect linkage to loci that influence high IgE levels, may be better among families ascertained through asthmatic or atopic individuals than in the Hutterites (for examples, see Xu et al. 2000 and Mathias et al. 2001). On the other hand, it is difficult to correct for ascertainment bias in such highly selected samples, although correction for ascertainment is critical for estimating QTL effect size (Commuzzie and Williams 1999; Blangero et al. 2001).

Characterizing variation in specific genes that influences susceptibility to common diseases could have a significant public health impact. The ability to identify individuals at risk for particular diseases would allow for both lifestyle and pharmaceutical interventions that could possibly delay disease onset and/or ameliorate the clinical course. A first step in dissecting the genetics of common diseases is to better understand the underlying genetic models and the relative role of specific genes in disease etiology. Founder populations, such as the Hutterites, with reduced environmental variance may offer unique advantages, not only for identifying disease genes (Lander and Schork 1994; Kruglyak 1999; Wright

et al. 1999) but also for providing insights into the genetic architecture of common human diseases.

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Electronic-Database Information

The URL for data in this article is as follows:

Mammalian Genotyping Service, http://www.research.marshfieldclinic.org/genetics/ (for genome screen)

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