

## Report

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# Broad and Narrow Heritabilities of Quantitative Traits in a Founder Population

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Estimation of the components of variance for a quantitative trait allows one to evaluate both the degree to which genetics influences the trait and the trait's underlying genetic architecture. For particular traits, the estimates also may have implications for discriminating between potential models of selection and for choosing an appropriate model for linkage analysis. Using a recently developed method, we estimate the additive and dominance components of variance—or, equivalently, the narrow and broad sense heritabilities—of several traits in the Hutterites, a founder population with extensive genealogical records. As a result of inbreeding and because Hutterite individuals are typically related through multiple lines of descent, we expect that power to detect dominance variance will be increased relative to that in outbred studies. Furthermore, the communal lifestyle of the Hutterites allows us to evaluate the genetic influences in a relatively homogeneous environment. Four phenotypes had a significant dominance variance, resulting in a relatively high broad heritability. We estimated the narrow and broad heritabilities as being, respectively, .36 and .96 for LDL, .51 and 1.0 for serotonin levels, and .45 and .76 for fat free mass (FFM). There was no significant additive component for systolic blood pressure (SBP), resulting in a narrow heritability of 0 and a broad heritability of .45. There were several traits for which we found no significant dominance component, resulting in equal broad and narrow heritability estimates. These traits and their heritabilities are as follows: HDL, .63; triglycerides, .37; diastolic blood pressure, .21; immunoglobulin E, .63; lipoprotein(a), .77; and body-mass index, .54. The large difference between broad and narrow heritabilities for LDL, serotonin, FFM, and SBP are indicative of strong dominance effects in these phenotypes. To our knowledge, this is the first study to report an estimate of heritability for serotonin and to detect a dominance variance for LDL, FFM, and SBP.

The variation that exists in a quantitative trait can be divided into genetic and nongenetic, or environmental, components, and the genetic component can be further subdivided into additive, dominance, and epistatic variances. In principle, one can include components of variance for gene  $\times$  environment interactions and shared environmental (e.g., household) effects as well. In humans, estimation of the entirety of the epistatic and gene  $\times$  environment components of variance of a trait is difficult, although contributions to some of these variance components (e.g., additive-additive epistasis), for individual pairs of loci, have been estimated from genotype data (Cloninger et al. 1998; Blangero et al. 2000). Here,

we focus on estimation of the additive, dominance, and environmental variances from phenotype data. We expect that, in a population such as the Hutterites, the ability to clearly separate the additive and dominance variance components will be greater than what ordinarily is possible in analyses of outbred populations, because every pair of individuals in the Hutterites has a nonzero probability of sharing two alleles identical by descent (IBD). In a randomly mating population, the additive variance of a trait is the variance due to the mean genotypic effects of individual alleles at quantitative-trait loci (QTLs) across the genome. The narrow heritability ( $h^2$ ), defined as the ratio of a trait's additive variance to its total variance, is a measure of the predictability of offspring trait values that is based on parental trait values. Note that the additive variance, or the narrow heritability, gives only limited information about the genetic model for QTLs influencing the trait. A low or zero additive variance places a constraint on the magnitudes of additive effects of QTLs; however, a

Received January 17, 2001; accepted for publication February 28, 2001; electronically published April 10, 2001.

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0002-9297/2001/6805-0027\$02.00

high additive variance does not necessarily indicate that there are any QTLs that follow a strictly additive model. It is, in fact, possible to have a high additive variance even when all loci follow a dominant model. Most important, when the influence of genetics on a trait is considered, the additive variance, although usually the major factor, is not always the best measure. It is possible, for instance, to have a trait that is heavily influenced by genetics but that, nevertheless, has a relatively low additive variance (and, hence, narrow heritability). This can be caused, for example, when selection has been acting on the trait (Fisher 1958; Crnokrak and Roff 1995; Charlesworth and Hughes 2000).

Because the additive variance does not always give an adequate assessment of the influence of genetics on a trait, it is important that we consider the dominance variance—and, hence, the broad heritability ( $H^2$ )—of our traits. Unlike the additive variance, which measures the variance due to mean effects of single alleles, the dominance variance of a trait measures the variance due to the interaction effect of the two alleles that constitute the genotype at a locus, summed over the genome. Note that this is distinct from the interaction that may occur between genotypes at separate loci (i.e., epistasis). Furthermore, a nonzero dominance variance is indicative of dominance effects in one or more loci. Methods for estimation of dominance variance in humans have been widely available for many years (Lange et al. 1976; Spence et al. 1977), and, indeed, more recent methods for QTL variance-component linkage mapping (Amos 1994; Almasy and Blangero 1998) also allow estimation of dominance variance. Nevertheless, one typically assumes that the additive effects are the primary contributors to the trait, and most previous studies of heritability in humans have ignored dominance effects. Although our investigations indicate that this assumption is generally true (see our results for HDL, triglycerides, diastolic blood pressure [DBP], immunoglobulin E [IgE], body-mass index [BMI], and lipoprotein(a) [Lp(a)]), there may be traits for which the additive effects are not the major cause of genetic variation. We choose to focus on estimation of dominance variance, because the unusual pedigree structure of the Hutterites allows information on all pairs of relatives to contribute to the estimation of dominance variance. We expect the information inherent in the Hutterite pedigree to lead to a more accurate estimation of the dominance component than has been found in outbred populations. In turn, an accurate estimate of dominance variance will provide an assessment of the degree to which traits are determined by genetic factors and an appropriate model for linkage analysis. Furthermore, for traits that have undergone selection, it is possible to evaluate different models based on, in part, the ratio of additive variance to dominance variance (Charlesworth and Hughes 2000). Because we

are using an inbred pedigree, it is possible that up to four dominance-variance components contribute to the overall genetic variance, with three of these being unique to the case of an inbred pedigree (Harris 1964; Jacquard 1974; Cockerham and Weir 1984; Abney et al. 2000). We estimated these three additional dominance components, and, in all cases, they were not significantly different from zero.

Analyses were performed on phenotypes collected from the Hutterites, a religious sect that originated in the Tyrolean Alps during the 1500s. Between the mid 1700s and mid 1800s, while in Russia, the population grew in size from ~120 to >1,000 members (Hostetler 1974). In the 1870s, ~900 of these members migrated to what is now South Dakota, and roughly half settled on three communal farms. The population has since expanded dramatically, with >35,000 Hutterites living in >350 communal farms (called “colonies”) in the northern United States and western Canada. The Hutterites’ communal lifestyle ensures that all members are exposed to a relatively uniform environment. Genealogical records trace all extant Hutterites to <90 ancestors who lived between the early 1700s and early 1800s (Martin 1970). The relationships among these ancestors are unknown, but some of them may have been related. The three original South Dakota colonies have given rise to the three major subdivisions of the modern Hutterite population, the Schmiedeleut (S-leut), the Dariusleut, and the Leherleut. Members of each subdivision have remained reproductively isolated from the other two subdivisions since 1910 (Bleibtreu 1964). The subjects of our study, the S-leut Hutterites of South Dakota, are descendants of 64 Hutterite ancestors (Ober et al. 1997). Information on the relationships among members of our sample is in the form of a 13-generation, 12,903-member genealogy. We focus on an 806-person subset that consists of all individuals of age >5 years in nine colonies, drawn from three of the four lineages of the S-leut (Mange 1964). For this 806-person subset, we have a 13-generation pedigree consisting of 1,623 individuals. Except for IgE, for which the sampling was done over 3 years, the phenotypes were collected over a span of ~6 mo. Hence, because their effects are confounded in this study, the age covariate is considered equivalent to year of birth.

We analyzed several cholesterol (HDL, LDL, and triglycerides) and blood pressure (systolic blood pressure [SBP] and DBP) measurements as well as IgE, serotonin, Lp(a), BMI, and fat free mass (FFM), using a variance-component, maximum-likelihood method (Abney et al. 2000). In this method, we model the phenotype as a multivariate normal with mean  $\mathbf{X}\beta$  and covariance  $\Omega$ , where  $\mathbf{X}$  is the matrix of covariates and  $\beta$  is the vector of fixed effects. The matrix  $\Omega$  is a function of the variance components and is given by  $\Omega = 2\Phi V_a + \Delta_7 V_d + \mathbf{I} V_e$ , where  $\Phi$

**Table 1**  
Number of Individuals, Transformation, and Covariates of Phenotypes

Phenotype	No. of Individuals	Transformation	Covariate(s)
HDL	521	Cube root	Age, sex
LDL	483	Cube root	Age
Triglycerides	521	log	Age, sex
SBP	681	log	Age, sex
DBP	680	Square root	Age, (age) <sup>2</sup> , sex
IgE	722	log	Age, sex
Serotonin	567	log	Age, sex
Lp(a)	394	log	Age, sex
BMI	666	log(log)	Age, (age) <sup>2</sup> , (age) <sup>3</sup> , sex
FFM	664	Square root	log(age), (height) <sup>2</sup> , sex

is the kinship coefficient matrix;  $\Delta_7$  is the matrix whose  $i,j$ th element is the probability that individuals  $i$  and  $j$  share two alleles IBD and neither  $i$  nor  $j$  is autozygous;  $\mathbf{I}$  is the identity matrix; and  $V_a$ ,  $V_d$ , and  $V_e$  are the additive, dominance, and environmental variances, respectively. Although phenotypes are not necessarily multivariate normal, they may often be transformed so that, when regressed against covariates, their residuals become approximately normally distributed. The variance is then  $V_t = (1 + f)V_a + (1 - f)V_d + V_e$ , where  $f$  is the average inbreeding coefficient of the population. The narrow and broad heritabilities are defined as  $h^2 = (1 + f)V_a/V_t$  and  $H^2 = 1 - V_e/V_t$ , respectively. In some cases, it may be of interest to use the phenotype's population variance,  $V_p$ , in place of its residual variance,  $V_t$ .

The Hutterite pedigree structure is such that every individual in the study sample is related to every other individual, through multiple lines of descent. In general, then, every Hutterite pair is capable of sharing two alleles IBD. In outbred populations, this is usually possible only for sibling pairs, although one may occasionally

find other, more-complex relationships (e.g., double first-cousins) in which sharing two alleles IBD is possible. The ramifications for estimation of dominance variance are significant. The ability to detect and accurately estimate the dominance variance depends on the size and informativeness of the sample for which  $\Delta_7$  is nonzero and on the capacity to separate out any confounding factors. Because essentially every Hutterite pair has nonzero  $\Delta_7$ , for a study consisting of 500 individuals there are 125,250 pairs contributing to the estimation of dominance variance, although the majority have a  $\Delta_7$  value much lower than that for full sibs. (In our set of 806 Hutterites, the mean is .0044 and the range is  $9.3 \times 10^{-5}$ –.271, with 16,713 pairs having  $\Delta_7 > .01$  and with 1,601 pairs having  $\Delta_7 > .24$  [Abney et al. 2000], whereas for outbred full sibs  $\Delta_7$  is .25.) The ability to remove confounding factors from dominance-variance estimation is a result of having (essentially) a continuous distribution of  $\Delta_7$  values in the Hutterites, making it unlikely that another factor could mimic dominance variance. If one is using an outbred population in which only full sibs contribute to  $\Delta_7$ , environmental variances resulting from some models of shared environmental effect may, on the basis of phenotype data, be indistinguishable from dominance variance. Nevertheless, it is certainly possible to estimate dominance variance in outbred populations, although we expect inbred populations such as the Hutterites to be advantageous in this regard.

In order to adhere to the distributional assumptions of our method, phenotypes were transformed so that, when they were regressed against covariates, their residuals were approximately normally distributed. The transformation and covariates used for each phenotype are shown in table 1, and trait means and variances are shown in table 2. We considered models that had, in addition to an envi-

**Table 2**  
Trait Means and Variances

PHENOTYPE	UNTRANSFORMED <sup>a</sup>		TRANSFORMED <sup>b</sup>		
	$\mu_{un}$	$V_{un}$	$\mu_{tr}$	$V_p$	$V_t$
HDL (mg/dl)	47.9	196	3.60	.123	.114
LDL (mg/dl)	129	1,521	5.01	.244	.194
Triglycerides (mg/dl)	139	8,840	4.75	.367	.293
SBP (mmHg)	124	256	4.81	.017	.012
DBP (mmHg)	80	100	8.94	.335	.245
IgE (IU/ml)	97.6	64,500	3.19	2.74	2.64
Serotonin (ng/ml)	191	6,240	5.18	.152	.139
Lp(a) (mg/dl)	2.90	13.6	.52	1.153	1.024
BMI (kg/m <sup>2</sup> )	24.5	37.2	1.15	$6.3 \times 10^{-3}$	$2.5 \times 10^{-3}$
FFM (kg)	45.0	177	6.63	1.02	.30

<sup>a</sup>  $\mu_{un}$  = Mean of phenotype prior to transformation;  $V_{un}$  = Variance of phenotype prior to transformation.

<sup>b</sup>  $\mu_{tr}$  = Mean of phenotype after transformation;  $V_p$  = variance of transformed phenotype prior to regression;  $V_t$  = residual variance of transformed phenotype.

**Table 3**  
**Heritability Estimates for Phenotypes, under Various Models**

Phenotype (Variance Components) <sup>a</sup>	<i>h</i> <sup>2</sup> (SE)	<i>H</i> <sup>2</sup> (SE)	log-Likelihood <sup>b</sup>	BIC
<i>HDL (E and A)</i>	.63 (.08)	.63 (.08)	356.0	-680.8
<i>LDL (E, A, and D)</i>	.36 (.13)	.96 (.20)	186.4	-341.9
LDL (E and A)	.50 (.09)	.50 (.09)	182.0	-339.2
<i>Triglycerides (E and A)</i>	.37 (.08)	.37 (.08)	76.4	-121.6
<i>SBP (E and D)</i>	0 <sup>c</sup>	.45 (.15)	1,169.5	-2,306.4
SBP (E and A)	.15 (.06)	.15 (.06)	1,168.0	-2,303.4
<i>DBP (E and A)</i>	.21 (.06)	.21 (.06)	-141.9	-244.6
<i>IgE (E and A)</i>	.63 (.07)	.63 (.07)	-636.2	1,305.3
<i>Serotonin (E, A, and D)</i>	.51 (.11)	1.0 (.25)	334.3	-630.6
Serotonin (E and A)	.63 (.08)	.63 (.08)	330.1	-628.43
<i>Lp(a) (E and A)</i>	.77 (.08)	.77 (.08)	-149.4	328.6
<i>BMI (E and A)</i>	.54 (.07)	.54 (.07)	1,709.5	-3,373.5
<i>FFM (E, A, and D)</i>	.45 (.10)	.76 (.15)	358.7	-672.0
FFM (E and A)	.50 (.07)	.50 (.07)	356.5	-674.0

NOTE.—The best-fitting models are in boldface italic type.

<sup>a</sup> E = environmental; A = additive; D = dominance.

<sup>b</sup> Without the constant term.

<sup>c</sup> With D in the model, *h*<sup>2</sup> for SBP was estimated to be <.10 at 95% confidence.

ronmental variance component, only additive variance, only dominance variance, and both additive- and dominance-variance components. For each trait, we compared all models by the Bayesian information criterion (BIC) (Schwartz 1978). In addition, for nested pairs of models, we used the likelihood-ratio  $\chi^2$  test to determine which components were significant. The results of the analyses are shown in table 3, with the most-favored model displayed in boldface italic type. For FFM, two models—one with additive and environmental variance and the other with additive, dominance, and environmental variance—were nearly equivalent, according to BIC. The second of these models is in boldface italic type because the dominance-variance component was deemed significant according to the  $\chi^2$  likelihood-ratio test ( $P = .036$ ). For HDL, triglycerides, DBP, IgE, Lp(a), and BMI, the best model included only the additive and environmental variances, and, hence, the narrow-heritability and broad-heritability estimates are equal. The heritability results for HDL, triglycerides (Brenn 1994; Mitchell 1996; Perusse et al. 1997; Edwards et al. 1999), DBP (Cheng et al. 1998; An et al. 1999; Rotimi et al. 1999), IgE (Bazaraal et al. 1974; Hopp et al. 1984, 1990), Lp(a) (Rainwater et al. 1997), and BMI (Borecki et al. 1998; Cheng et al. 1998) are in approximate agreement with the results in previous studies, as are the untransformed trait means and variances (table 2).

A significant dominance component, resulting in differing values for broad and narrow heritability, was found in LDL, FFM, SBP, and serotonin. Except for serotonin, for which we are unaware of any other published studies, the untransformed trait means and SDs are in approximate agreement with those for other populations. For LDL, if we were to assume that only en-

vironmental and additive genetic variance contribute, we would obtain a narrow heritability of .50 (table 3), a value consistent with previous measurements of .40–.50 (Mitchell et al. 1996; Perusse et al. 1997). When dominance variance is included in the model, however, we obtain a lower narrow heritability, of .35. In spite of the moderate narrow heritability, there is a high dominance-variance component resulting in a broad heritability of .96, indicating that, in the Hutterites, almost all of the variation in the trait is genetically based. This is, perhaps, not surprising, given the uniform diet and lifestyle among Hutterite individuals. As with LDL, when the heritability of FFM is evaluated under the model without dominance variance, we obtain a value of .50 (table 3). A previous study of FFM found a heritability of .65 (Rice et al. 1997). With dominance variance included, we obtain lower narrow and higher broad heritabilities—.45 and .76, respectively.

The results for SBP and serotonin also are surprising. When SBP is analyzed under the model without dominance variance, we obtain a narrow heritability of .15—a value somewhat lower than the values of .18–.54 reported elsewhere (Brenn 1994; Mitchell et al. 1996; Cheng et al. 1998; An et al. 1999; Rotimi et al. 1999). However, the most-favored model includes only dominance and environmental variances—no additive variance—which results in a narrow heritability of 0 and a broad heritability of .45. This should be interpreted to mean not that there is no additive variance but, rather, that the additive variance is low and does not reach statistical significance. We can place an upper bound of .10 on the narrow heritability, at 95% confidence. For serotonin level, when we estimate the heritability under the model without dominance variance, we obtain a

value of .63. When we include dominance variance, the estimate for narrow heritability becomes .51 whereas that for broad heritability is 1.0, suggesting that, after adjustment for covariates (table 1), the variation in whole-blood-serotonin levels in the Hutterites is largely genetically based. We are unaware of any previous estimates of the heritability of blood-serotonin level.

To our knowledge, these are the first estimates of dominance variance reported for LDL, FFM, serotonin, and SBP. We also note that, for these traits, use of a model that does not include dominance variance can give a misleading view of how important genetic effects are to the observed trait variability. One should be aware, however, that the standard errors of the estimates increase when additional variance components are included—and that, in some cases (e.g., serotonin level), they can be quite large. It also is possible that, if a substantial portion of the true phenotypic variance is due to effects that we did not model (e.g., epistasis), then this may result in both the additive and dominance variances being upwardly biased. On the basis of our previous study (Abney et al. 2000), however, we believe that this bias will be small, since the majority of this unmodeled variance will be attributed to random residual (i.e., environmental) variance. Our analysis, which relies on only phenotype data and pedigree information, suggests that QTL-mapping methods that take advantage of the nonadditivity of a trait may prove effective when a significant dominance variance is detected. The extent to which this is true will almost certainly be dependent on the population under study, and we anticipate that populations such as the Hutterites will prove advantageous in this respect. It is possible that the significant dominance components detected are specific to the Hutterites. For instance, they could be a consequence of the population history of the Hutterites (e.g., founder effect). More generally, heritabilities can vary depending on factors such as allele frequencies and various environmental effects. However, our estimated heritabilities, based on a model without dominance variance, are consistent with results in other populations, and we suspect that our additional results concerning dominance variance of these traits will be generally applicable to other populations as well.

## Acknowledgments

We thank Nancy Cox for her valuable discussions and thoughtful input and Joseph November for his helpful computer work. This research was supported by a National Science Foundation GIG Postdoctoral Fellowship (to M.A.), National Institutes of Health grants HG01645 (to M.S.M.) and HL49596 (to C.O.), and a grant from Hoffman–La Roche (to C.O.).

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