

Heritability Estimation of Sex-Specific Effects on Human Quantitative Traits

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Recent studies have suggested that sex-specific genetic architecture could be because of the effects of autosomal genes that are differentially expressed in males and females. Yet, few studies have explored the effects of X-linked genes on sex-specific genetic architecture. In this study, we extended the variance component, maximum likelihood method to evaluate the relative contributions of sex-specific effects on both autosomes and the X chromosome to estimates of heritability of 20 quantitative human phenotypes in the Hutterites. Seventeen of these traits were previously analyzed in this population under a model that did not include X chromosomal effects; three traits are analyzed for the first time (age at menarche, percent fat and fat-free mass [FFM]). Seven traits (systolic blood pressure (SBP), adult height, fasting insulin, triglycerides, lipoprotein (a) [Lp(a)], serotonin, and age at menarche) showed significant X-linked effects; three of these (SBP, adult height, and triglycerides) showed X-linked effects only in males. Four traits (Lp(a), low-density lipoprotein cholesterol, ratio of percent predicted forced expiratory volume at 1 s/forced vital capacity, and FFM) showed significant sex-environment interactions, and two traits (high-density lipoprotein cholesterol and FFM) showed significant sex-specific autosomal effects. Our analyses demonstrate that sex-specific genetic effects may not only be common in human quantitative traits, but also that the X chromosome both plays a large role in these effects and has a variable influence between the sexes. *Genet. Epidemiol.* 31:338–347, 2007. © 2007 Wiley-Liss, Inc.

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INTRODUCTION

Many anthropometric, physiologic, and behavioral traits are sexually dimorphic in humans, and many common diseases have significant sex-specific prevalences, ages of onset, or both [Chen et al., 2003; Stromberg and Martensson, 2003; Woods et al., 2003; Lawlor et al., 2004; Madeb and Messing, 2004; Patel et al., 2004; Ren and Ceylan-Isik, 2004]. We recently reported [Weiss et al., 2006] significant sex-specific genetic architecture in a survey of 17 quantitative traits in the Hutterites, a founder population of European descent. In that study, estimates of heritability in single sex samples revealed significant interactions with sex for five traits (low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol [HDL-c], systolic blood pressure [SBP],

fasting insulin, and adult height) [Weiss et al., 2006]. We suggested that the sex-specific genetic architecture of these traits could be because of autosomal genes that are differentially expressed in males and females, or to X-linked genes. Here, we quantify the relative contributions of sex-specific effects on both autosomes and the X chromosome to overall estimates of heritability of 20 quantitative human phenotypes.

Heritability measures the proportion of phenotypic variance attributable to genetic variance. Typically, two heritabilities are estimated, narrow sense heritability (h^2) and broad sense heritability (H^2). Narrow heritability gives the proportion of additive variance in the phenotypic variance, whereas broad heritability measures the proportion of all genetic variance in the phenotypic variance (i.e. including additive, dominance and

epistatic effects). Heritability estimates in humans generally assume equal genetic variances in both sexes [e.g., Abney et al., 2000, 2001; Moskau et al., 2005]. To determine sex-specific heritabilities, some studies have been performed in single-sex samples [Biino et al., 2005; Kurina et al., 2005; Weiss et al., 2005a]. On the other hand, analyzing the entire sample under a unified model that allows for possible sex-specific effects provides a more formal model-selection approach to determine whether there is statistical evidence for particular effects (e.g., sex-specific autosomal or X-linked) in the data. Additionally, it is possible to estimate the correlation between relatives of opposite sexes, which is not possible in single-sex samples. Although heritability estimates, including X-linked effects, were recently implemented in the software SOLAR (sequential oligogenic linkage analysis routines (Southwest Foundation for Biomedical Research)) [Kent et al., 2005a,b], most current genetic studies ignore X-linked effects and few have examined sex \times environment interactions. However, there are likely many human traits that are influenced by sex-specific autosomal or X-linked genes. Accurate estimation of the sex-specific components of heritability for common traits would allow us to assess the relative degree to which traits are determined by sex-specific genes, including X-linked genes.

SUBJECTS AND METHODS

To determine whether there are significant sex interactions on either autosomes or the X chromosome, we evaluated sex interactions in the estimation of heritability for 20 quantitative traits in the Hutterites, including the 17 traits reported previously [Weiss et al., 2006]. The Hutterites are a young founder population who live on communal farms in the northern United States and western Canada. The Hutterites of South Dakota have been the subjects of our studies of complex trait mapping for many years [Abney et al., 2000, 2002; Ober et al., 2001, 2000; Kurina et al., 2005; Newman et al., 2003; Weiss et al., 2005a, 2004]. Details of the population and sampling strategy have been described previously [Ober et al., 2001]. The 806 Hutterites who participated in our studies are related to each other in a known 13-generation pedigree consisting of 1,623 individuals. Each individual is related to every other through multiple lines of descent from 62 founders. The limited number of Hutterite founders, extensive

linkage disequilibrium, communal lifestyle, and known genealogy provide significant advantages for mapping complex trait genes.

In this study, we use a variance component, maximum likelihood method to estimate sex-specific autosomal, X chromosomal and environmental effects for the 20 quantitative traits. Our analysis includes variance components for modeling of autosomal genetic effects in inbred pedigrees [Abney et al., 2000] and X chromosomal effects, including both dosage and no dosage compensation [Kent et al., 2005a]. We also clarify the definition of heritability in the presence of sex-specific effects, X chromosomal effects, and inbreeding as well as the definition of the elements of the X chromosomal covariance matrix when inbreeding is present. We include measurements of lipids (LDL-c, HDL-c, triglycerides, lipoprotein (a) [Lp(a)]), blood pressure (diastolic blood pressure [DBP] and SBP), lung function (percent predicted forced expiratory volume at 1 second [%FEV₁], ratio of FEV₁/forced vital capacity [FEV₁/FVC]), immune-related measures (eosinophilia, total serum immunoglobulin E [IgE], lymphocyte count, percent lymphocytes per white blood cell [% lymphocyte]), anthropometric measurements (body mass index, percent body fat, fat-free mass [FFM], and adult height), a sex-specific trait (age at menarche), as well as whole blood serotonin, fasting insulin, and serum cortisol. Nineteen of these phenotypes have been described previously [Ober et al., 2001; Newman et al., 2003; Kurina et al., 2005; Weiss et al., 2005b]. Age at menarche, determined retrospectively by questionnaire, is defined as the age, in years, at which menstruation first occurred. For 17 of the 20 traits, differences in heritabilities between males and females had been examined in this population under a model that includes neither X effects nor sex-specific environmental effects [Weiss et al., 2006], whereas three are new in this study (age at menarche, percent fat and FFM). Two traits (IgE and eosinophilia) had individuals removed (40 and 14, respectively) relative to a previous analysis [Ober et al., 2001] because these individuals were taking allergy medication at the time of the sampling.

There has been little effort to elucidate the contribution of the X chromosome on quantitative traits until recently. Wiener et al. [2003] extended the Haseman-Elston method to do linkage analysis on the X chromosome for sib pairs. The software package SOLAR [Almasy and Blangero, 1998] is capable of doing single-point quantitative

trait mapping on the X chromosome. Lange and Sobel [2006] extended the theory of mapping X-linked QTL to multivariate traits and implemented the model in the software Mendel. Ekström proposed a method for computing multi-point identity-by-descent (IBD) on the X chromosome [Ekström, 2004]. There, the X chromosomal effects were assumed to be different in males and females. An alternative view is taken by Kent et al. [2005a,b], in which the effects of a QTL allele are assumed to be the same in both sexes, but with an allowance for a possible X inactivation effect. This permits analysis under a simpler model because under the assumption of either complete X inactivation (dosage compensation) or a complete absence of inactivation (no dosage compensation), the number of parameters needed to describe the variance owing to X-linked effects can be reduced from three to one. Partial inactivation can be allowed by using two parameters (see the Appendix). Because our interest is not only effects due to the X chromosome but also effects that differ between the sexes (i.e. sex interaction), we allow for three possibilities (dosage compensation, no dosage compensation, and X chromosomal sex interaction effects). Additionally we do not restrict our analyses of sex-specific effects to the X chromosome, but also allow for the possible presence of such sex interactions on the autosomes or in the environmental effects.

We assume a standard multivariate normal distribution for the trait and, if we partition the trait vector such that females come before males (i.e. $y^t = (y_f^t \ y_m^t)$), then the covariance matrix is

$$\begin{aligned} \Omega = & \begin{pmatrix} 2\Phi_f\sigma_{a,f}^2 & 2\Phi_{fm}\sigma_{a,fm} \\ 2\Phi_{fm}\sigma_{a,fm} & 2\Phi_m\sigma_{a,m}^2 \end{pmatrix} + \begin{pmatrix} \Delta_f\sigma_{d,f}^2 & \Delta_{fm}\sigma_{d,fm} \\ \Delta_{fm}\sigma_{d,fm} & \Delta_m\sigma_{d,m}^2 \end{pmatrix} \\ & + \begin{pmatrix} S_f\sigma_{s,f}^2 & S_{fm}\sigma_{s,fm} \\ S_{fm}\sigma_{s,fm} & S_m\sigma_{s,m}^2 \end{pmatrix} \\ & + \begin{pmatrix} 2\Psi_f\sigma_{X,f}^2 & \sqrt{2}\Psi_{fm}\sigma_{X,fm} \\ \sqrt{2}\Psi_{fm}\sigma_{X,fm} & \Psi_m\sigma_{X,m}^2 \end{pmatrix} \\ & + \begin{pmatrix} \Lambda_f\sigma_{Xd,f}^2 & 0 \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} I_{n_f}\sigma_{e,f}^2 & 0 \\ 0 & I_{n_m}\sigma_{e,m}^2 \end{pmatrix}. \quad (1) \end{aligned}$$

Here, Φ , Δ , Ψ , Λ , and I are the kinship coefficient, Jacquard's Δ_7 ([Jacquard, 1974]; also defined in the Appendix), X-chromosomal kinship coefficient, X-chromosomal version of Δ_7 and identity matrices, respectively. The matrix S and variance component σ_s^2 correspond to the $(\Delta_1 + \Delta_2 - f_A f_B)SS_{\mu_n}$ term in Abney et al. [2000]. This

component only exists in the presence of inbreeding and is included here because one trait (HDL-c) showed a significant nonzero value for the variance component. In all of the above terms the subscripts f , fm and m indicate quantities for female-female, female-male, and male-male pairs, respectively. The values n_f and n_m are the number of females and males in the sample. The scalar quantities $\sigma_{z,f}^2$, $\sigma_{z,m}^2$, and $\sigma_{z,fm}$ are the variances and covariance associated with effect z . In the above covariance equation we have used the convention where $\sqrt{2}$ is placed in front of Ψ_{fm} . Although not strictly necessary, this allows us to interpret $\sigma_{X,fm}$ as a true covariance (see the Appendix). In the Appendix we define the elements of each of the matrices allowing for the possibility of inbreeding and derive model dependent constraints on the variance parameters.

The above equation for the covariance matrix contains 15 freely varying parameters, albeit some of which are constrained. For any particular data set, many of these parameters will be zero or equal to one another, either because the effect they are parameterizing is zero or because there is insufficient power to detect the effect in the data. Hence, we used maximum likelihood to estimate parameters and undertook model selection to determine which of the parameters to include in the final model. We proceeded by starting with an environmental effects only model and adding, in turn, variance components for additive, dominance, and X-linked effects. When estimating X-linked effects, models both with and without dosage compensation were evaluated (see the Appendix for the constraints on the X-linked variance components these models imply). We ignore the X-linked dominance effects in females (i.e. $\sigma_{Xd,f}^2$ was set to 0) in all the models tested. In each step of the model selection process, estimates, and standard errors at previously included variance components were examined. If an estimate was less than approximately two standard errors, we evaluated a model where that component was constrained to be zero. This procedure allows us to find an optimal model without overfitting. The significant genetic effects were chosen on the basis of the likelihood ratio test for nested models (see Kent et al. [2005a] for a discussion about the degrees of freedom in the resulting χ^2 statistic), or using both AIC [Akaike, 1974] and BIC [Schwarz, 1978] for non-nested models. In the data sets considered here, the best fitting model was usually clear, but in cases where there existed ambiguity (e.g., AIC and BIC

selected different models) we list all relevant models.

Once a model was selected, we then tested for the presence of a sex effect in each of the model's variance components. We used the likelihood ratio test to compare the model with no sex-specific effects, $\sigma_{z,f}^2 = \sigma_{z,m}^2 = \sigma_{z,fm}^2 > 0$ (for an X-linked effect the equivalent constraint under the selected model of dosage compensation is used), and the model with sex interaction, where both of $\sigma_{z,f}^2$ and $\sigma_{z,m}^2$ are freely varying and $|\sigma_{z,fm}| \leq \sqrt{\sigma_{z,f}^2 \sigma_{z,m}^2}$. In the sex interaction model we also consider cases where one of the sex-specific variances is zero.

From the parameter estimates we determine heritability and its standard error. When there are no sex-specific effects, the narrow heritability $h^2 = \sigma_a^2 / \sigma_t^2$ relates the fraction of the total variance attributable to additive effects. Here, we define σ_t^2 as the total residual variance (i.e. after removing the effects of covariates, such as age and sex). The broad heritability $H^2 = \sigma_g^2 / \sigma_t^2$ measures the fraction of variance because of all genetic effects, including additive, dominance, and epistatic effects. In the presence of sex-specific and X chromosomal effects, we define the population-wide narrow heritability as $h^2 = h_A^2 + h_X^2$ where h_A^2 is the narrow heritability of the autosomes,

$$h_A^2 = \frac{(n_f/n)(1 + \bar{F}_f)\sigma_{a,f}^2 + (n_m/n)(1 + \bar{F}_m)\sigma_{a,m}^2}{\sigma_t^2} \quad (2)$$

and h_X^2 is the narrow heritability because of the X chromosome,

$$h_X^2 = \frac{(n_f/n)(1 + \bar{F}_{X,f})\sigma_{X,f}^2 + (n_m/n)\sigma_{X,m}^2}{\sigma_t^2} \quad (3)$$

and we have for the total variance,

$$\begin{aligned} \sigma_t^2 = & \frac{n_f}{n}(1 + \bar{F}_f)\sigma_{a,f}^2 + \frac{n_m}{n}(1 + \bar{F}_m)\sigma_{a,m}^2 + \frac{n_f}{n}(1 - \bar{F}_f)\sigma_{d,f}^2 \\ & + \frac{n_m}{n}(1 - \bar{F}_m)\sigma_{d,m}^2 + \frac{n_f}{n}[\bar{F}_f(1 - \bar{F}_f) - \sigma_{F_f}^2]\sigma_{s,f}^2 \\ & + \frac{n_m}{n}[\bar{F}_m(1 - \bar{F}_m) - \sigma_{F_m}^2]\sigma_{s,m}^2 \\ & + \frac{n_f}{n}(1 + \bar{F}_{X,f})\sigma_{X,f}^2 + \frac{n_m}{n}\sigma_{X,m}^2 + \frac{n_f}{n}\sigma_{e,f}^2 + \frac{n_m}{n}\sigma_{e,m}^2, \end{aligned} \quad (4)$$

where n is the total sample size (i.e. $n = n_f + n_m$), \bar{F}_f and \bar{F}_m are the average inbreeding coefficients in females and males and $\bar{F}_{X,f}$ is the average X chromosomal inbreeding coefficient in females. $\sigma_{F_f}^2$ and $\sigma_{F_m}^2$ are the variances of the inbreeding

coefficient in the female and male populations, respectively. Furthermore, we have assumed in equation (4) that there is no inbreeding depression. If inbreeding depression is, in fact, present or additional inbreeding dominance components are nonzero, then equation (4) would have to be amended as described in Abney et al. [2000]. The population-wide broad heritability is

$$H^2 = 1 - \frac{(n_f/n)\sigma_{e,f}^2 + (n_m/n)\sigma_{e,m}^2}{\sigma_t^2}. \quad (5)$$

We can also define female and male specific heritabilities. For females, for instance, the numerator and denominator of equation (2) would only include the variances in the female population. The narrow heritability in females would then be

$$h_f^2 = h_{A,f}^2 + h_{X,f}^2 = \frac{(1 + \bar{F}_f)\sigma_{a,f}^2 + (1 + \bar{F}_{X,f})\sigma_{X,f}^2}{(1 + \bar{F}_f)\sigma_{a,f}^2 + (1 + \bar{F}_{X,f})\sigma_{X,f}^2 + \sigma_{e,f}^2} \quad (6)$$

and similarly for broad heritability. The equivalent relations hold for the narrow and broad heritability in males, where the female variances are replaced with the male variances.

RESULTS

We applied the above method to the 20 phenotypes. To adhere to the distributional assumption of our method, 13 of the 20 phenotypes were transformed. The sample sizes, sex ratio, transformation, and covariates used for each phenotype are shown in Table I. For IgE and eosinophilia, we excluded individuals on allergy medication in this study. As a result, sample sizes and estimates of heritability for these traits differ slightly from those reported previously [Ober et al., 2001] but are unchanged from Weiss et al. [2006]. The best fitting model for each trait was chosen by the model selection described above. Because age at menarche is a sex-specific trait, only models with autosomal or X-linked effects in females were tested. The estimates of the population-wide heritabilities for the 20 phenotypes are shown in Table II. The estimates of heritability in the males and females for the 10 phenotypes showing significant sex effects are shown in Table III.

Seven of the 20 traits showed significant X chromosome effects. These include three of the traits with significant sex interactions identified in our previous study in single sex samples (SBP,

TABLE I. Sample sizes, transformation and covariates of phenotypes

Phenotype	Sample size (female:male)	Transformation	Covariates
LDL-c	288 (182:106)	—	Age
HDL-c	484 (246:238)	Cube root	Age, sex
Triglycerides	484 (246:238)	LN	Age, sex
Lp(a)	374 (193:181)	LN	Age, sex
DBP	623 (333:290)	Square root	Age, age ² , sex
SBP	623 (333:290)	LN	Age, sex
%FEV ₁	654 (341:313)	—	Age, age ²
FEV ₁ /FVC	654 (341:313)	—	Age, sex
Eosinophilia	561 (289:272)	LNLN	Sex
IgE	682 (373:309)	LN	Age, sex
Lymphocyte count	569 (293:276)	LN	Age
% Lymphocyte	570 (294:276)	—	Age, sex
BMI	666 (354:312)	LNLN	Age, age ² , age ³ , sex
Percent fat	663 (354:309)	—	Age, age ³ , sex
Fat free mass	664 (353:311)	Square root	Ln(age), sex, height ²
Adult height	516 (278:238)	—	Age, sex
Age at menarche	269 (269:0)	—	Birth year
Serotonin	567 (300:267)	LN	Age, sex
Fasting insulin	497 (273:224)	LNLN	Age
Cortisol	504 (265:239)	LN	Sex

LN, natural logarithm.

adult height, and insulin) [Weiss et al., 2006], as well as triglycerides, Lp(a), serotonin and age at menarche (Table II). Three of these traits (SBP, adult height, and triglycerides) showed X-chromosomal effects exclusively in the males, with X-linked heritabilities ranging from 0.17 (adult height) to 0.34 (triglycerides). Of the other four traits showing X chromosomal effects, two (serotonin and insulin) were best modeled with dosage compensation. In fact, two models fit about equally well for insulin—one with autosomal additive and environmental variances only and one with environmental and autosomal dominance variances, as well as an X-linked variance with dosage compensation. The AIC was lower in the X-linked model, but BIC was lower in the autosomal model. Therefore, we listed both models in Table II. On the other hand, the X-linked effects were best modeled with no dosage compensation for Lp(a). Finally, the genetic effects were restricted exclusively to the X chromosome for age at menarche, a female-specific trait.

Four traits, LDL-c, HDL-c, FEV₁/FVC, and FFM showed evidence for non X-chromosomal sex effects. Two genetic models fit about equally well

for FFM—one with sex-specific autosomal additive variances and the other with sex-specific environmental variances. The sex-specific autosomal model had an autosomal additive male-female correlation of 0.999, suggesting that, overall, the genes acting in the two sexes are the same but have different magnitudes. The AIC was lower in the sex-specific autosomal additive model, whereas BIC was lower in the sex-environment interaction model. Therefore, we listed the heritability estimates for both models (Table II). The remaining nine traits did not show significant evidence for sex-specific effects, consistent with our earlier study [Weiss et al., 2006].

Of the five traits in our previous study [Weiss et al., 2006] that showed evidence of sex interaction, only HDL-c has the same genetic model as before. Of the other four traits, SBP, adult height, and insulin now show evidence for X chromosomal effects while the fourth (LDL-c) shows a sex-environment interaction effect. Therefore, the heritability estimates for these traits differ from those reported previously [Weiss et al., 2006]. For SBP, the autosomal narrow heritability remained at zero, whereas the broad heritability changed from 0.66 (SE 0.11) to 0.48 (SE 0.15), although the difference is within the 95% confidence intervals of the estimates. For adult height, the overall narrow heritability is unchanged, but now includes an X-linked component in males. The overall narrow heritability increased from 0.16 (SE 0.08) to 0.33 (SE 0.08) for fasting insulin and from 0.23 (SE 0.10) to 0.35 (SE 0.13) for LDL-c, whereas the broad heritability dropped from 0.82 (SE 0.16) to 0.71 (SE 0.17) for fasting insulin and from 1 (SE 0.15) to 0.69 (SE 0.31) for LDL-c. Again, these differences are within the 95% confidence intervals of the estimates.

DISCUSSION

Heritability estimation is usually a first step in genetic studies, because it provides an estimate of how much phenotypic variation is attributable to genetic effects. In general, one might expect that a more accurate polygenic model, which includes significant sex-specific and X-chromosomal variances, might improve the power in later linkage and association studies where an oligogenic model with a polygenic background is often assumed. Recent work [Kent et al., 2005a; Lange and Sobel, 2006], however, suggest that gains in power may be small. Nevertheless, we believe that

TABLE II. Heritability estimates and the best genetic models for 20 phenotypes

Phenotype	Significant variance components	Autosomal additive effect h_A^2 (SE)	X-linked additive effect h_X^2 (SE)	Total genetic effect H^2 (SE)
Traits with significant X chromosome effects				
SBP	D, X_M , E	0	0.16 (.05)	0.48 (.15)
Adult height	A, X_M , E	0.81 (.06)	0.09 (.03)	0.90 (.06)
Fasting insulin ^a	D, X_{DC} , E	0	0.33 (.08)	0.71 (.17)
	A, E	0.36 (.09)	0	0.36 (.09)
Triglycerides	A, X_M , E	0.39 (.08)	0.20 (.05)	0.59 (.09)
Lp(a)	A, X_{noDC} , E_M	0.40 (.09)	0.47 (.08)	0.88 (.04)
Serotonin	A, D, X_{DC}	0.26 (.11)	0.39 (.09)	1.00 (.13)
Age at menarche	X_F , E_F	0	0.46 (.11)	0.46 (.11)
Traits with significant non-X chromosome sex effects				
LDL-c	A, D, E_F	0.35 (.13)	0	0.69 (.31)
HDL-c ^b	A, S_M , E	0.54 (.08)	0	0.78 (.07)
FEV ₁ /FVC ^b	A, E_F , E_M	0.42 (.08)	0	0.42 (.08)
FFM ^a	A_F , A_{FM} , A_M , D, E	0.47 (.08)	0	0.79 (.14)
	A, D, E_F , E_M	0.42 (.09)	0	0.79 (.14)
Traits with no significant sex effects				
DBP ^b	A, E	0.20 (.07)	0	0.20 (.07)
% FEV ₁ ^b	A, E	0.35 (.08)	0	0.35 (.08)
Eosinophilia ^b	A, E	0.43 (.08)	0	0.43 (.08)
IgE ^b	A, D, E	0.53 (.10)	0	0.85 (.15)
Lymphocyte count ^b	A, D, E	0.33 (.11)	0	0.90 (.18)
% Lymphocyte ^b	A, E	0.28 (.08)	0	0.28 (.08)
BMI ^b	A, E	0.54 (.08)	0	0.54 (.08)
Percent fat	A, E	0.48 (.08)	0	0.48 (.08)
Cortisol ^b	A, E	0.54 (.09)	0	0.54 (.09)

Note: A = additive; D = dominance; S_M = male-specific inbreeding; A_F , A_M , A_{FM} = autosomal additive in females only, in males only and the covariance between two sexes, respectively; X_M = male-specific X-linked; X_F = female-specific X-linked additive; X_{DC} = X-linked additive with dosage compensation; X_{noDC} = X-linked additive with no dosage compensation; E = environmental variance; E_F and E_M are the environmental variances in females only and in males only, respectively. h_A^2 is heritability due to autosomal additive effects; h_X^2 is heritability due to X-linked additive effects; H^2 is the heritability due to autosomal additive, dominance and X-linked effects.

^aTwo models statistically equivalent; see text for details.

^bHeritability estimates unchanged from previous report [Weiss et al., 2006].

TABLE III. Sex specific heritability estimates for 10 traits with sex effects^a

Phenotype	Male-specific heritability ^b			Female-specific heritability ^b		
	$h_{A,m}^2$ (SE)	$h_{X,m}^2$ (SE)	H_m^2 (SE)	$h_{A,f}^2$ (SE)	$h_{X,f}^2$ (SE)	H_f^2 (SE)
SBP	0	0.29 (.08)	0.56 (.13)	0	0	0.38 (.17)
Adult height	0.74 (.06)	0.17 (.05)	0.91 (.06)	0.89 (.07)	0	0.89 (.07)
Fasting insulin	0	0.40 (.07)	0.74 (.18)	0	0.26 (.07)	0.68 (.19)
Triglycerides	0.32 (.07)	0.34 (.07)	0.66 (.09)	0.49 (.11)	0	0.49 (.11)
Lp(a)	0.42 (.09)	0.32 (.07)	0.74 (.06)	0.39 (.09)	0.61 (.09)	1.00 (.03)
Serotonin	0.23 (.11)	0.46 (.09)	1.00 (.13)	0.29 (.12)	0.31 (.08)	1.00 (.15)
LDL-c	0.50 (.18)	0	1.00 (.31)	0.29 (.11)	0	0.59 (.19)
HDL-c	0.54 (.08)	0	0.78 (.07)	0.71 (.09)	0	0.71 (.09)
FEV ₁ /FVC	0.39 (.07)	0	0.39 (.07)	0.46 (.09)	0	0.46 (.09)
Fat free mass ^c	0.56 (.08)	0	0.83 (.11)	0.35 (.09)	0	0.75 (.16)
	0.37 (.08)	0	0.70 (.13)	0.48 (.10)	0	0.90 (.16)

Note: ^aOne female-specific trait—age at menarche—is not listed here.

^b $h_{A,m}^2$ and $h_{A,f}^2$ are the autosomal narrow heritability for males and females, respectively. $h_{X,m}^2$ and $h_{X,f}^2$ are the X-linked narrow heritability for males and females, respectively. H_m^2 and H_f^2 are the broad heritability for males and females, respectively.

^cTwo models statistically equivalent. The upper model is autosomal sex-specific additive model, whereas the lower one is the sex-environment interaction model.

a better understanding of how the X-chromosome and sex-specific effects influence quantitative traits to be of fundamental interest.

It is worth noting that agreement of the estimates of broad heritability between the current and previous [Weiss et al., 2006] studies tends to be high. In seven of the traits from our previous study the primary difference lies in how the total genetic variance is apportioned. Now, we find the X chromosome often contributing a substantial portion of the variance, frequently with a sex-specific effect. This is not to suggest that earlier estimates of the narrow heritability were invalid, rather it demonstrates that improved modeling of the phenotype results in more refined heritability estimates.

It is striking that 11 out of the 20 quantitative traits included in this study, many of which are associated with common human diseases, have significant sex interaction effects. Given that only 4% of genes are located on the X chromosome [Ross et al., 2005], one might expect that the fraction of QTLs on the X chromosome should be low compared with the autosomes. Surprisingly, we find that about one-third of our phenotypes have a large proportion of the genetic effects located on the X chromosome. In fact, for some phenotypes, the X-linked genes may even contribute more than the autosomal genes. For example, the X-linked effects account for more than 50% of the total phenotypic variation in Lp(a), despite the fact that the major structural locus for Lp(a) resides on an autosome [Boerwinkle et al., 1992]; and our single sex-specific trait (age at menarche) had genetic effects only on the X-chromosome. It is also notable that three traits (SBP, adult height, and triglycerides) showed X-linked effects only in males, whereas no traits (except age at menarche) showed X-linked effects only in females. This is consistent with the assertion that the human X chromosome is enriched for male-specific genes [Lercher et al., 2003]. Indeed, our findings suggest that not only is a sex-specific genetic architecture likely to be common in human quantitative traits, but also that this may often be due to the genetic effects of the X chromosome.

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APPENDIX

The covariance between relatives due to an X linked locus has been derived previously [Bohidar, 1964; James, 1973; Bulmer, 1985; Grossman and Eisen, 1989]. Below, we define the variance parameters and the relationship coefficients associated with them. These definitions explicitly allow for, and clarify, the effects of inbreeding. We then derive the constraints on the parameters for different models of dosage compensation and reconcile two common parameterizations that have led to confusion on the issue.

First, we define the possible identity states between two individuals for both an autosomal and an X chromosomal loci. For a pair of individuals, A and B, in an inbred population, there are 15 possible identity states at an autosomal locus [Lynch and Walsh, 1998]. These same identity states are present for a female-female pair at an X chromosomal locus. A female-male pair at an X chromosomal locus, however, have possible identity states as shown in Figure 1. A line between two alleles indicates that those alleles are identical by descent, whereas the absence of a line indicates they are not. A male-male pair, A and B, simply have probability $P_1 = \Pr(A\text{'s allele is IBD with B's allele})$. For any pair of individuals

i and j , then, the ij th element in each matrix in Equation (1) is

$$[\Phi]_{ij} = \phi_{ij} = \Delta_1 + \frac{1}{2}(\Delta_3 + \Delta_5 + \Delta_7) + \frac{1}{4}\Delta_8,$$

$$[\Delta]_{ij} = \Delta_7,$$

$$[S]_{ij} = \Delta_1 + \Delta_2 - F_i F_j,$$

$$[\Psi]_{ij} = \psi_{ij}$$

$$= \begin{cases} \Delta_{1,X} + \frac{1}{2}(\Delta_{3,X} + \Delta_{5,X} + \Delta_{7,X}) + \frac{1}{4}\Delta_{8,X} & \text{for a female – female pair} \\ \Delta_1 + \frac{1}{2}\Delta_3 & \text{for a female – male pair} \\ P_1 & \text{for a male – male pair} \end{cases}$$

$$[\Lambda]_{ij} = \Delta_{7,X},$$

where F_i is the inbreeding coefficient of person i , ϕ_{ij} is the kinship coefficient for pair ij , and $\Delta_{k,X}$ is the k th condensed identity coefficient for the X chromosome, which will, in general, be different than the corresponding value for the autosomes. Note that the ij th component of Ψ is the X chromosomal version of the kinship coefficient and may be computed using a similar algorithm to the one used for an autosomal locus [Lange et al., 1976].

We now turn to the definitions of the variance parameters $\sigma_{z,ij}^2$ under the presence of sex-specific

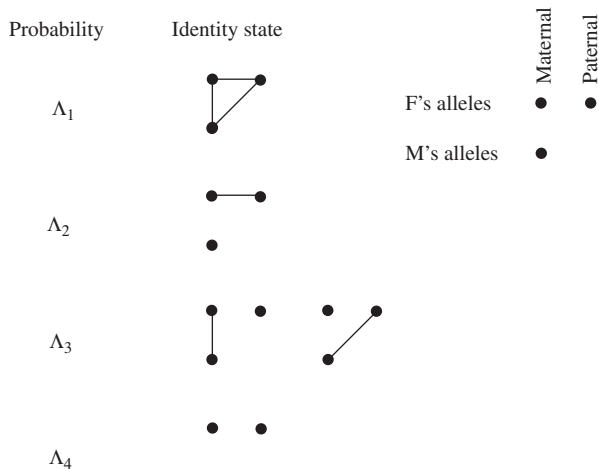


Fig. 1. Five possible identity states for a female F and male M at an X chromosomal locus, grouped according to their four condensed identity states.

effects. We define the effect of an autosomal QTL in females as $g_{kl} = \alpha_k + \alpha_l + \delta_{kl}$ for genotype (k, l) , whereas for males it is $g_{kl} = \beta_k + \beta_l + \epsilon_{kl}$. At an X-linked locus the effect in females takes the same form while in males it becomes $g_k = \beta_k$. Furthermore, $E(\alpha) = E(\beta) = 0$ for both autosomal and X-linked loci.

Covariance in female-female pairs at an autosomal and X-linked locus: The covariance in female-female pairs takes the same form at both autosomal and X-linked loci and is, for individuals i and j

$$\text{Cov}(g^i, g^j) = 2\phi_{ij}\sigma_{a,f}^2 + \Delta_7\sigma_{d,f}^2.$$

Hence, $\sigma_{a,f}^2 = 2E(\alpha^2) = E[(\sqrt{2}\alpha)^2]$ and similarly for an X-linked locus.

Covariance in male-male pairs at an autosomal locus: The covariance in male-male pairs at an autosomal locus takes the same form as in female-female pairs, but with β and ϵ replacing α and δ , respectively.

Covariance in female-male pairs at an autosomal locus: The covariance between males and females is similar in form to those for same sex pairs,

$$\text{Cov}(g^i, g^j) = 2\phi_{ij}\sigma_{a,fm} + \Delta_7\sigma_{d,fm}$$

but now $\sigma_{a,fm} = 2E(\alpha\beta)$.

Covariance in male-male pairs at an X-linked locus: Males only have one allele at an X-linked locus, leading to the following for the covariance,

$$\text{Cov}(g^i, g^j) = \Psi_{ij}E(\beta^2) = \Psi_{ij}\sigma_{X,m}^2.$$

Here, $\sigma_{X,m}^2 = E(\beta^2)$.

Covariance in female-male pairs at an X linked locus: The fact that the definition of $\sigma_{X,m}^2$ differs from $\sigma_{a,m}^2$ by a factor of two, leads to slightly different formula than in the autosomal case,

$$\text{Cov}(g^i, g^j) = \sqrt{2}\Psi_{ij}\sigma_{X,fm},$$

where $\sigma_{X,fm} = E(\sqrt{2}\alpha\beta)$. The scaling of this covariance is the one chosen by [Bulmer, 1985] and Kent et al. [2005a] and has the advantage of obeying the typical covariance constraint, $|\sigma_{X,fm}| \leq \sqrt{\sigma_{X,f}^2\sigma_{X,m}^2}$. Another scaling commonly seen is where $\text{Cov}(g^i, g^j) = 2\Psi_{ij}\tilde{\sigma}_{X,fm}$. This parameterization is also valid in that it gives the same maximum likelihood estimates of heritability and the other variance parameters, but now the appropriate constraint is $|\tilde{\sigma}_{X,fm}| \leq \sqrt{(\sigma_{X,f}^2\sigma_{X,m}^2/2)}$.

Depending on the model for a particular trait, different constraints may be imposed on the variance component parameters.

No sex-specific additive effect at autosomal loci: When the effect at a QTL is independent of the sex of the individual, the sex-specific additive effects are equal, $\alpha_k = \beta_k$ for all the alleles k , in which case $E(\alpha^2) = E(\beta^2) = E(\alpha\beta)$ and,

$$\sigma_{a,f}^2 = \sigma_{a,m}^2 = \sigma_{a,fm}.$$

No sex-specific dominance effect at autosomal loci: This case is identical to the autosomal additive case, but now $\delta_{kl} = \epsilon_{kl}$ for all alleles k and l . Hence,

$$\sigma_{d,f}^2 = \sigma_{d,m}^2 = \sigma_{d,fm}.$$

No sex-specific effect at X-linked loci with X inactivation: We take the effects of QTL alleles at an X-linked locus to be the same in males and females, but assume there to be dosage compensation under the mechanism of a random X chromosome being inactivated in each cell of the female. In this case it is reasonable to use a model where $\alpha_k = (1/2)\beta_k$ for all alleles k . Then, $E(\beta^2) = 4E(\alpha^2)$ and $E(\sqrt{2}\alpha\beta) = 2\sqrt{2}E(\alpha^2)$. This results in constraints,

$$\sigma_{X,m}^2 = 2\sigma_{X,f}^2,$$

$$\sigma_{X,fm} = \sqrt{2}\sigma_{X,f}.$$

No sex-specific effect at X-linked loci with no X inactivation: Again, we take the effects of QTL alleles at an X-linked locus to be the same in males and females but assume no dosage compensation (i.e. the complete absence of X inactivation). Then

$\alpha_k = \beta_k$ for all alleles k . This leads to $E(\beta^2) = E(\alpha^2)$ and $E(\sqrt{2}\alpha\beta) = \sqrt{2}E(\alpha^2)$, giving constraints,

$$\begin{aligned}\sigma_{X,m}^2 &= \frac{1}{2} \sigma_{X,f}^2, \\ \sigma_{X,fm} &= \frac{1}{\sqrt{2}} \sigma_{X,f}^2.\end{aligned}$$

No sex-specific effect at X-linked loci with variable X inactivation: It is possible to generalize the previous two cases to one where there is a variable amount of X inactivation (Kent et al.

2005a). In this case $\alpha_k = (1 + \lambda)\beta_k/2$ for all alleles k . This leads to the following constraints,

$$\begin{aligned}\sigma_{X,m}^2 &= \frac{2}{(1 + \lambda)^2} \sigma_{X,f}^2, \\ \sigma_{X,fm} &= \frac{\sqrt{2}}{1 + \lambda} \sigma_{X,f}^2,\end{aligned}$$

where $0 \leq \lambda \leq 1$. Dosage compensation is equivalent to $\lambda = 0$, whereas no dosage compensation is equivalent to $\lambda = 1$.