Environment-Sensitive Epigenetics and the Heritability of Complex Diseases

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ABSTRACT Genome-wide association studies have thus far failed to explain the observed heritability of complex human diseases. This is referred to as the “missing heritability” problem. However, these analyses have usually neglected to consider a role for epigenetic variation, which has been associated with many human diseases. We extend models of epigenetic inheritance to investigate whether environment-sensitive epigenetic modifications of DNA might explain observed patterns of familial aggregation. We find that variation in epigenetic state and environmental state can result in highly heritable phenotypes through a combination of epigenetic and environmental inheritance. These two inheritance processes together can produce familial covariances significantly higher than those predicted by models of purely epigenetic inheritance and similar to those expected from genetic effects. The results suggest that epigenetic variation, inherited both directly and through shared environmental effects, may make a key contribution to the missing heritability.

The challenges of identifying the common or rare genes that contribute to the transmission of heritable human diseases and other complex phenotypes have been discussed for some time (Moran 1973; Layzer 1974; Feldman and Lewontin 1975; Kamin and Goldberger 2002). Large-scale single-nucleotide polymorphism (SNP) genotyping was hoped to reveal DNA variants that would explain much of the variance in complex phenotypes. So far, however, only a small amount of the heritable variation in most phenotypes can be explained by common genomic variants (Goldstein 2009). This problem is often referred to as the “missing heritability” problem. A potential explanation is that the observed heritability reflects not only Mendelian inheritance, but also inheritance of epigenetic or environmental states (Maher 2008; Eichler et al. 2010; Petronis 2010).

The term epigenetics has been defined in various ways (Waddington 1957; Bird 2007; Bossdorf et al. 2008). We consider as epigenetic any contribution to the phenotype through modification of the chromatin that does not involve a change in DNA sequence. Such modifications include methylation of cytosine nucleotides at CpG sites and histone protein modification. Such epigenetic modifications may be transmissible across generations or arise de novo each generation; the heritability of chromatin modifications is extremely variable among organisms (reviews of evidence in mammals in Jablonka and Lamb 1989; Rakyan et al. 2001; Rakyan and Beck 2006; Jablonka and Raz 2009; and in plants in Jablonka and Lamb 1989; Martienssen and Colot 2001; Henderson and Jacobsen 2007; Jablonka and Raz 2009). Particular epigenetic states are associated with a number of human diseases, including some cancers, Angelman’s syndrome, Prader–Willi syndrome, and Beckwith–Wiedemann syndrome (Egger et al. 2004; Jiang et al. 2004; Feinberg 2007; Hirst and Marra 2009), as well as psychiatric disorders such as schizophrenia, depression, and Rett syndrome (Abdolmaleky et al. 2005; Tsankova et al. 2007).

Culture and environment can also affect phenotypes and cause them to aggregate in families. The disease Kuru, endemic to the Fore tribe of Papua New Guinea, is transmitted through ingestion of a prion during a funeral ritual in which individuals consume dead relatives or close acquaintances (Gajdusek et al. 1966; Lindenbaum 2008). Despite this purely cultural transmission, the high disease correlation between relatives originally led researchers to believe
that Kuru was a genetic disorder (Harper 1977; Cavalli-Sforza and Feldman 1981).

Diseases and other phenotypes may also exhibit complex inheritance when epigenetic states are environment sensitive. In mice, a mother’s grooming and licking of an offspring can induce epigenetic changes in the offspring, causing a modified stress response when the offspring reach adulthood (Weaver et al. 2004; Meaney and Szyf 2005; Weaver et al. 2006). The mechanisms governing this system have been reviewed by Weaver (2007). Maternal diet in mice can affect offspring phenotype by increasing methylation rates (Wolff et al. 1998; Cooney et al. 2002; Waterland and Jirtle 2003, 2004; Cropley et al. 2006; Waterland et al. 2006; Lillycrop et al. 2007) or modifying histones (Lillycrop et al. 2007; Sandovici et al. 2011). Silencing the expression of a DNA methyltransferase, Dnmt3, in honeybees induces developmental changes similar to those induced by feeding larvae a diet of royal jelly; suggesting that the diet of honeybees controls rates of epigenetic modification, which ultimately regulates larval development (Kucharski et al. 2008; Elango et al. 2009). The epigenetic modifications are associated with patterns of alternative splicing (Lyko et al. 2010). Recently, evidence for environment-sensitive rates of methylation has been found in humans (Heijmans et al. 2008; Katari et al. 2009; Waterland et al. 2010). Other examples of environmental effects on epigenetic state are reviewed by Jirtle and Skinner (2007).

The dependence of phenotypic heritability on inheritable epigenetic or environmental factors has been subject to theoretical investigations. Slatkin (2009) showed that the epigenetic contribution to the resemblance among siblings for a disease depends on how likely the epigenetic states are to be induced or reset between generations. With little intergenerational memory, the state may contribute greatly to disease risk, but little to recurrence risk ratio between siblings. Only when the epiallele is likely to be retained across generations is it able to contribute significantly to recurrence risk ratio.

In the framework of cultural evolution, several models have addressed the role of a heritable environmental state on phenotypic resemblance between relatives. For a culturally transmitted phenotype, familial correlations depend strongly on the parameters governing transmission (Cavalli-Sforza and Feldman 1973, 1981; Feldman and Cavalli-Sforza 1979; Feldman et al. 1995, 2000; Otto et al. 1995). Similar to the results found by Slatkin (2009), these studies showed that more faithful transmission of a cultural trait led to higher correlations between relatives. Tal et al. (2010) echo these results, focusing on a statistical model of nongenetic heritable contributions to phenotypic variance and covariance between relatives. Both Feldman et al. (1995) and Tal et al. (2010) suggest that different ways of estimating heritability can produce very different estimates, because the familial correlations are functions not only of genetic relatedness, but also of the correlations in cultural, environmental, and epigenetic states. For example, sibling phenotypic correlation may be lower than parent–offspring correlation for some models of cultural transmission. Progress has been made toward a framework for understanding heritability when there is inheritance of nongenetic traits, but to date models remain very general with respect to the epigenetic processes of inheritance and the epigenetic effects on phenotype (Bonduriansky and Day 2009; Danchin and Wagner 2010; Danchin et al. 2011; Day and Bonduriansky 2011). Recent work by Day and Bonduriansky (2011) offers a general framework to explore many types of nongenetic inheritance and their interaction with genetic inheritance. Examining epigenetic inheritance as one form of nongenetic inheritance, Day and Bonduriansky (2011) present a model similar to that of Tal et al. (2010) and Slatkin (2009), demonstrating that the interaction of several forms of inheritance (there epigenetic and genetic) can lead to surprisingly complex evolutionary dynamics.

Little theoretical work has investigated the interaction between epigenetic and environmental effects on heritability when both epigenetic and environmental states are inheritable. Here we present a model in which the rates of epigenetic change depend on the environment experienced by the individual. Correlation between the environmental state of an individual and those of its parents will thus generate correlation between the epigenetic states of parents and offspring—modeled, for example, as no methylation (0) or methylation (1) of a cytosine at a particular autosomal CpG site (Figure 1). Therefore, a disease whose risk depends solely on nonheritable epigenetic states may have high heritability due to the effects of a heritable environment. Many epigenetic modifications are reset during gametogenesis and early development, a few are inherited, and, during the development of an individual, new modifications may occur. The heritability of a disease thus depends in general on the transmission of environmental states and epigenetic states and their interaction.

We assume that individuals may experience one of two distinct environmental states, which could reflect the presence or absence of a cultural interaction (such as maternal grooming of offspring), a particular diet, or even a geographical or social position. The environments allow population stratification such that individuals may preferentially find their partners in the environment where they develop. This is modeled by assortative mating with respect to environment, which is equivalent to a simple geographically structured population. An individual’s phenotype is envisioned as healthy or sick for a disease occurring in adulthood and is influenced by the environment and epigenotype of the individual.

Adult epigenotypes at the studied genomic site are determined by two processes: (1) the persistence of epigenetic states of their parents in zygotes and (2) the subsequent modification of these states during individual development (Figure 2). The transmission of disease risk, however, involves correlation between parents and offspring, and we therefore merge the two processes into one
describing the total apparent transmission of epigenetic state between generations. This process is governed by two rates of epimutation: change from state 0 in parent to state 1 in offspring \((m_{0 \rightarrow 1})\) and vice versa \((m_{1 \rightarrow 0})\). Although we frame our model in terms of disease risk as influenced by methylation, it may also be applied to other phenotypes and other epigenetic modifications, such as no acetylation (0) or acetylation (1) of a histone at a particular genomic site.

We do not include genetic contributions to disease risk, and we assume that the epigenetic variation in question is independent of any genetic variation in the population. While this is not always the case, many studies demonstrate that epigenetic variation may be independent of genetic variation (Cubas et al. 1999; Cervera et al. 2002; Riddle and Richards 2002; Keyte et al. 2006; Shindo et al. 2006; Vaught et al. 2007; Verhoeven et al. 2010; Herrera and Bazaga 2011). We also disregard the possibility of direct environmental influence on disease risk. Although we recognize that both genetic and direct environmental contributions are relevant in discussions of heritability, we choose to focus on the interaction between environmental and epigenetic inheritance.

We find that the heritability of a disease can vary greatly depending on rates of transmission of the epigenetic and environmental states and that environment-sensitive rates of epigenetic modification may produce very high heritabilities.

These results suggest that epigenetic inheritance may contribute significantly to the heritability of diseases, in particular where rates of epigenetic modification are environment dependent.

**Model**

We consider one autosomal epigenetic locus with two epigenetic alleles (0 and 1) in diploid individuals experiencing one of two distinct environmental states, labeled \(x\) and \(y\). We assume the population is infinite, with nonoverlapping generations, and monitor the life cycle from one adult generation to the next adult generation through the processes of reproduction, transmission of environmental state, and transmission and modification of epigenotype. The variables \(f_{ui,j}\) represent the proportion of adult individuals in the adult population that have epigenotype \(ij\) and live in environment \(u\) (with \(i, j \in \{0, 1\}, u \in \{x, y\}\)). We assume that the epigenetic development of a zygote does not depend on the parental origin of the alleles; that is, epigenotype 01 is identical to epigenotype 10, so \(f_{ui,01} = f_{ui,10}\). This is not typically the case for genomic imprinting, but may be a reasonable simplifying assumption for environment-sensitive epigenetics. The proportion of adults living in environmental state \(u\) is therefore \(f_u = f_{u,00} + 2f_{u,01} + f_{u,11}\). The frequency of epiallele 0 within environment \(u\) is \(p_{u,0} = (f_{u,00} + f_{u,01})/f_u\), and \(p_{u,1} = 1 - p_{u,0}\). The frequency of epiallele \(i\) in the entire population is \(p_i = f_{DPxi} + f_{DPyi}\).
Reproduction and transmission

Adults are assumed to mate assortatively with respect to environmental state, but randomly with respect to epigenotype. The degree of environmental assortative mating is represented by $m$, with a fraction $1-m$ of the population mating randomly and a fraction $m$ mating only with individuals in the same environmental state. The probability of a $u \times v$ mating ($M_{uv}$) is thus given by

$$M_{uv} = \left\{ \begin{array}{ll} \frac{(1-m)f_d^2}{f_d} + mf_u & \text{if } u = v \\ (1-m)f_d f_v & \text{if } u \neq v \end{array} \right. \quad (u,v \in \{x,y\}).$$

The parameter $m$ is equal to the correlation in environmental state between the two parents. The assumption of unaltered transmission of the epialleles to the offspring entails that a mating between an individual in environment $u$ and one in environment $v$ produces an offspring of epigenotype $ij$ with probability $\Omega_{uvij} = \frac{1}{2}(p_{ij}p_{xj} + p_{i}p_{x})$. The form of $\Omega_{uvij}$ reflects that it does not matter which allele was supplied by the parent in a particular environmental state.

The environmental state of an offspring depends on the environmental states of both its parents, independent of their sex. The proportion of offspring from an $x \times y$ mating that end up in environmental state $v \neq u$ is described by the parameter $e_{uv}$, while the remaining $1-e_{uv}$ stay in the parental environment. The proportion of offspring from an $x \times y$ mating that experience environmental state $x$ is $(1-e_x)(1-a) + e_xa$ and the proportion ending up in environmental state $y$ is $e_y(1-a) + (1-e_y)a$. The transmission of the environmental state is thus described by the parameters $e_x$, $e_y$, and $a$ (with $e_u \in [0, 0.5]$, $a \in [0, 1]$), where $1-e_u$ represents the fidelity of transmission of the parental environmental state $u$ ($u \in \{x, y\}$), and $1-a$ is a measure of the dominance of environment $x$ for offspring of $x \times y$ matings expressed as a bias toward the transmission patterns of an offspring from an $x \times x$ mating. No bias exists when $a = 0.5$, and the distribution of offspring environments mimics that from an $x \times x$ mating or a $y \times y$ mating when $a = 0$ or $a = 1$, respectively.

Immediately after environmental inheritance, the offspring are considered juveniles, and the proportion of individuals in the juvenile population that have epigenotype $ij$ and live in environmental state $u$ is denoted by $f_{u,ij}$,

$$f_{x,ij} = M_{xx}\Omega_{xx,ij}(1-e_x) + 2M_{xy}\Omega_{xy,ij}(1-e_x)(1-a) + e_ya) + M_{yy}\Omega_{yy,ij}e_y$$

$$f_{y,ij} = M_{xx}\Omega_{xx,ij}e_x + 2M_{xy}\Omega_{xy,ij}(e_x(1-a) + (1-e_y)a) + M_{yy}\Omega_{yy,ij}(1-e_y).$$

Epigenetic modification

Epigenetic modifications are simplified by assuming conservative inheritance of the parental epigenetic states and collecting their modifications into processes that occur during an individual’s maturation from juvenile to adult. During an individual’s maturation from juvenile to adult in environment $u$, the probability of change from epigenetic state 0 to state 1 of an allele is $\mu_{u,0,1}$, and $\mu_{u,1,0}$ is the probability of change from state 1 to state 0. The probabilities of an epiallele 0 or 1 remaining unchanged are $\mu_{u,0,0} = 1 - \mu_{u,0,1}$ and $\mu_{u,1,1} = 1 - \mu_{u,1,0}$, respectively. We use the term epimutation rates for $\mu_{u,0,1}$ and $\mu_{u,1,0}$, but stress that they describe the combined effects of reset parental states and de novo modifications occurring in the offspring. After epimutation the adult frequencies of the epigenotypes and environmental states in the next generation, denoted by $f_{u,ij}$, are given in terms of the juvenile offspring frequencies $\tilde{f}_{u,ij}$ as

$$\tilde{f}_{u,00} = \mu_{u,0,0}\tilde{f}_{u,00} + 2\mu_{u,0,-1}\mu_{u,1,-1}\tilde{f}_{u,01} + \mu_{u,1,0}\tilde{f}_{u,11}$$

$$\tilde{f}_{u,01} = \mu_{u,0,-1}\mu_{u,0,1}\tilde{f}_{u,00} + (\mu_{u,0,0}\mu_{u,1,1} + \mu_{u,0,-1}\mu_{u,1,0})\tilde{f}_{u,01} + \mu_{u,1,-1}\tilde{f}_{u,11}$$

$$\tilde{f}_{u,11} = \mu_{u,0,1}\tilde{f}_{u,01} + 2\mu_{u,0,-1}\mu_{u,1,-1}\tilde{f}_{u,01} + \mu_{u,1,0}\tilde{f}_{u,11}.$$  \hspace{1cm} (1)

Substitution of the expressions for $\tilde{f}_{u,ij}$ into these equations produces the full recursion system in the adult frequencies of epigenotypes and environmental states (given in the Appendix).

Disease risk

The probability that an adult individual with epigenotype $ij$ develops disease in environment $u$ is given as $\alpha_{u,ij}$. For the sake of clarity, we specify the effects of epigenotype as deviations from the disease risk $\alpha$ associated with epigenotype 00, and we disregard direct effects of the environment. In general, $\alpha \in [0, 1]$,

$$\alpha_{u,00} = \alpha; \quad \alpha_{u,01} = \alpha_{u,10} = \alpha + r\delta; \quad \alpha_{u,11} = \alpha + \delta,$$

with $u \in \{x, y\}$. The parameters $\delta$ and $r$ describe the effect of epigenetic state on disease risk, where $\delta \in [0, 1]$ represents the additive effect on disease risk of the epiallele 11 with the effect of epiallele 0 set to zero, and $r \in [0, 1]$ represents the degree of dominance of the epiallele with respect to the disease phenotype. The disease risks are additive when $r = \frac{1}{2}$.

Results

The proportion $f_{x}$ of individuals within environment $x$ always approaches a unique equilibrium $\hat{f}_{x}$ as the evolution progresses (proved in supporting information, File S1, section S1). Numerical iteration of the recursion equations, using the R programming language, allows us to monitor the evolution of the frequencies $f_{u,ij}$. Iterations using a grid of parameters and initial conditions suggest that, for any parameter values, the frequencies $f_{u,ij}$ will converge for all initial conditions to a unique equilibrium denoted by the frequencies $\hat{f}_{u,ij}$. We study the inheritance of the disease
when the population is at equilibrium and discuss it in terms of the estimated heritability for parent–offspring pairs.

Heritability

From the equilibrium values of the frequencies and the parameters of the model, the disease prevalence \( K \) in the population is

\[
K = \sum_u \sum_{ij} \alpha u_{ij} f_{u,ij},
\]

the population variance in the disease phenotype in the parental generation is \( V_D = K(1 - K) \), and the parent–offspring covariance in disease state is denoted by \( W_D \) (see Appendix). These generate an estimate of the narrow sense heritability of the disease, namely

\[
h^2 = \frac{2W_D}{V_D}
\]

(Falconer and Mackay 1996). An alternative measure of familial aggregation, recurrence risk ratio, is analyzed and discussed in File S1, section S5, Figure S2, and Figure S3.

We examine two simple cases with the disease risk parameters \( \alpha = 0.1, r = 0.5 \), and \( \delta = 0.4 \). These correspond to a relatively common disease and a high risk epiallele, although the qualitative results discussed also hold for a range of values of \( \alpha, r \), and \( \delta \). The environmental transmission is symmetric, with bias parameter \( \beta = 0.5 \) and \( e_y = e_x = e \). A bias \( \beta \) away from 0.5 or unequal values of \( e_x \) and \( e_y \) produce qualitatively similar results, with generally lower heritability as the bias or asymmetry increases. We examine three values of \( e \) and two values of environmental assortment \( m \) across a range of values for \( \mu_x,0 \rightarrow 1 \) and \( \mu_y,0 \rightarrow 1 \).

Case 1: Environmental and epigenetic transmission: Here half of the transmitted methylations are reset each generation, i.e., \( \mu_x,0 \rightarrow 0 = \mu_y,1 \rightarrow 0 = 0.5 \), and we explore a range of values for \( \mu_x,0 \rightarrow 1 \) and \( \mu_y,0 \rightarrow 1 \).

Figure 3 illustrates the heritability values resulting from this case. Each of the panels shows the variation of the estimated heritability of the disease phenotype with respect to variation in the epimutation rates \( \mu_x,0 \rightarrow 1 \) and \( \mu_y,0 \rightarrow 1 \), with the two columns of panels distinguishing \( m = 0 \) and 0.5, and the three rows distinguishing \( e = 0.01, 0.1 \), and 0.5. The colors in each panel represent the estimated heritability of the disease. The diagonal values (where \( \mu_x,0 \rightarrow 1 = \mu_y,0 \rightarrow 1 \)) within each panel correspond to the single-environment model of epigenetic change discussed by Slatkin (2009). We note that as long as there is any positive correlation between the environments of parents and offspring (that is, \( e < 0.5 \)), the highest heritability values are not along that diagonal, but occur when \( \mu_x,0 \rightarrow 1 \) is very high and \( \mu_y,0 \rightarrow 1 \) is very low or vice versa. The contours overlaid on these panels indicate curves of equal disease prevalence \( K \). Interestingly, except in the case where the environmental states of parents and offspring have no correlation \( (e = 0.5) \), each contour of equal prevalence achieves a minimum heritability value when \( \mu_x,0 \rightarrow 1 = \mu_y,0 \rightarrow 1 \) and a maximum when \( \mu_x,0 \rightarrow 1 \) and \( \mu_y,0 \rightarrow 1 \) are as different as possible. This demonstrates that the heritability patterns are not simply due to the effects of the parameters on disease prevalence. The absolute heritability values are not interesting, because these depend on the magnitudes of \( \alpha \) and \( \delta \), and the presented patterns are consistent across a range of values of \( \alpha \) and \( \delta \). Heritability values can be negative because parent–offspring correlations can be negative when parent and offspring are likely to have different epigenotypes at the dynamic equilibrium.

With assortative mating \( (m > 0) \), or very faithful transmission of environmental state from parents to offspring \( (e < 0.5) \), the magnitude of heritability is generally higher, especially when the epimutation rates are very different in the two environments. In the extreme case where \( m = 0 \) and \( e = 0.5 \), heritability is a function only of disease prevalence (Figure 3, bottom left).

Case 2: Environmental transmission but no epigenetic transmission: Here epigenetic modifications are not transmitted to offspring (Figure 1); i.e., the likelihood of an allele being in epigenetic state 0 or 1 in an offspring does not depend on its state in the parent. This corresponds to \( \mu_u,0 \rightarrow 1 = \mu_u,1 \rightarrow 1 \) (where \( u \in \{x, y\} \)). Because \( \mu_u,1 \rightarrow 0 + \mu_u,1 \rightarrow 1 = 1 \), this case is also equivalent to \( \mu_u,0 \rightarrow 1 = 1 - \mu_u,1 \rightarrow 0 \).

With these parameters the equilibrium can be found in a simple form (see File S1, section S2), giving the equilibrium parent–offspring disease covariance

\[
W_D = \delta^2 (\mu_x,0 \rightarrow 1 - \mu_y,0 \rightarrow 1)^2 \left[ 2r + (1 - 2r)(\mu_x,0 \rightarrow 1 + \mu_y,0 \rightarrow 1) \right]^2 \omega_e,
\]

where \( W_{\omega_e} \) is the covariance between the environmental state of a parent and its offspring. The prevalence is

\[
K = \bar{f} \delta (\mu_x,0 \rightarrow 1 - \mu_y,0 \rightarrow 1) \left[ 2r + (1 - 2r)(\mu_x,0 \rightarrow 1 + \mu_y,0 \rightarrow 1) \right] + \alpha + \delta \left( 2\mu_x,0 \rightarrow 1 + (1 - 2r)\mu_y,0 \rightarrow 1 \right),
\]

and the variance in disease phenotype is \( V_D = K(1 - K) \).

Figure 4 illustrates the variation in heritability in the same way as Figure 3. Again, the heritability of the disease is highest when \( \mu_x,0 \rightarrow 1 \) and \( \mu_y,0 \rightarrow 1 \) are very different (one is close to 0 and the other is close to 1). However, we do not see an increase in heritability in the region where \( \mu_x,0 \rightarrow 1 \) and \( \mu_y,0 \rightarrow 1 \) are both small. The reason is the antisymmetry assumption in epimutation rates, that is, when \( \mu_u,0 \rightarrow 1 \) is small, \( \mu_u,1 \rightarrow 0 \) is large (for \( u \in \{x, y\} \)), and low values of \( \mu_u,0 \rightarrow 1 \) do not correspond to faithful transmission of epigenetic state from parent to offspring. When \( e = 0.5 \), the parent–offspring covariance in environmental state is 0, resulting in a heritability of 0.

Comparing different values of the environmental transmission parameters, we see similar patterns to those of case.
1, with greater assortative mating and more faithful transmission producing higher heritability and a more pronounced pattern of increased heritability when the epimutation rates are very different between environments.

Comparing cases: A short discussion of the relationship between the two cases analyzed is presented in File S1, section S3, and Figure S1.

Comparing with a genetic locus

Our model disregards genetic contributions to phenotype. Similar disease parameters may, however, be used to compare the heritability contributed by a genetic locus to the heritability contributed by an epigenetic locus; i.e., the three genotypes 00, 01, and 11 carry the three risk parameters $\alpha_{00} = \alpha$, $\alpha_{01} = \alpha + r\delta$, and $\alpha_{11} = \alpha + \delta$. When $\alpha = 0.01$, $\delta = 0.5$, and $r = 0.5$, a high-risk allele at a frequency of $p_1 = 0.05$ yields a disease heritability of 0.176 (see File S1, section S4), with a prevalence of 0.035 in the population. The same disease parameters in the epigenetic model with $\mu_{x,1\rightarrow 0} = \mu_{y,1\rightarrow 0} = 0.5$ produce a heritability of 0.086 with the same prevalence, when $\epsilon = 0.1$, $m = 0$, and the methylation rates differ only slightly between environments ($\mu_{x,0\rightarrow 1} = 0$ and $\mu_{y,0\rightarrow 1} = 0.052$). For $\epsilon_x = 0.12$, $\epsilon_y = 0.01$, $m = 0.5$, $\mu_{x,0\rightarrow 1} = 0.5$, and $\mu_{y,0\rightarrow 1} = 0$, we obtain a heritability of 0.219 again with prevalence 0.035. In fact, with this prevalence we find heritabilities of magnitudes similar to those of the genetic case across a range of parameters. Epigenetic loci with environmentally sensitive methylation rates could therefore contribute to familial aggregation of a phenotype at levels at least as large as those of genetic loci.

Discussion

Our model and results offer several new perspectives on epigenetic contributions to heritability. When epigenetic states are correlated with environmental states, both of which can be heritable, a trait may show a high estimated heritability without highly faithful transmission of either the epigenetic or the environmental state. In fact, even in the case where the epigenetic state of a gene in a juvenile does not reflect the parental epigenetic state of that gene, the corresponding phenotype can be heritable through the effect of the environment on the epigenetic state of the gene. In that case our model presents a specific dynamic explanation of how a heritable environmental state is able to cause heritable epigenetic modifications of a phenotype. In practice, the risk factor due to environmental exposures may be hard to determine, so in cases where the environment

Figure 3 Dependence of heritability on epimutation rates and environmental inheritance for case 1 (environmental and epigenetic transmission). The colors in each panel indicate the heritability of the disease for that set of parameters. The environmental transmission is symmetric ($e_x = e_y = e$, $a = 0.5$), making each panel symmetric around the diagonal. The two columns distinguish the cases of random mating ($m = 0$) and moderate assortative mating ($m = 0.5$). The three rows correspond to high ($e = 0.01$), moderate ($e = 0.1$), and no fidelity of environmental transmission ($e = 0.5$). The horizontal axis in each panel indicates the value of $\mu_{x,0\rightarrow 1}$, and the vertical axis indicates the value of $\mu_{y,0\rightarrow 1}$. The contour curves represent constant disease prevalence values ($K$), with the bottom left contour indicating a prevalence of 0.15 and each progressive contour toward the top right corresponding to an increase in prevalence of 0.05. For all panels, the other parameter values are $\mu_{x,1\rightarrow 0} = \mu_{y,1\rightarrow 0} = 0.5$, $\alpha = 0.1$, $r = 0.5$, $\delta = 0.4$, and $a = 0.5$.

Figure 4 Dependence of heritability on epimutation rates and environmental inheritance for case 2 (environmental transmission but no epigenetic transmission). The results are presented in the same way as in Figure 3, and the fixed parameters are identical, except that now $\mu_{x,1\rightarrow 0} = 1 - \mu_{x,0\rightarrow 1}$ and $\mu_{y,1\rightarrow 0} = 1 - \mu_{y,0\rightarrow 1}$.
induces epigenetic modifications, association studies based on epigenetic variation may be a simpler way to assess the heritable risk. This raises a more fundamental problem in the study of epigenetic transmission, namely that it is difficult to separate inheritance of an epigenetic state from inheritance of an environmental exposure to which the epigenetic state is sensitive.

We assumed in our model that the disease caused by an individual’s epigenotype occurs after the life stage in which epigenetic modifications occur. A more realistic model should incorporate age structure, including the fetal state, and would have to model epimutation at each age class. The analysis of such a model would be considerably more complex, but we expect that the qualitative results would not differ.

The dynamics of our model might easily be modified to incorporate selection. If the fitnesses of the different epigenetic states depend on which environment the individual is in, then it is not clear exactly how selective effects would interact with environmental inheritance and epimutation. Some effort has gone into understanding how epimutation could be adaptive in environments that fluctuate temporally. Considering the rate of epimutation as a trait under genetic control, previous models of bet hedging and symmetric stochastic switching have suggested that the optimal rates of epimutation depend on the expected length of time an individual remains in each environment (Lachmann and Jablonka 1996; Russell and Leibler 2005; Wolf et al. 2005; King and Masel 2007; Salathe et al. 2009; Gaál et al. 2010; Liberman et al. 2011).

Our model can be seen as an extension of that of Slatkin (2009). Whenever the rates of epigenetic change and the disease risk do not depend on the environment, our model reduces to Slatkin’s single-environment model. He concluded that transmissible epigenetic effects are likely to be important to the heritability of disease phenotypes only when many epigenetic loci contribute to disease risk, the epialleles are highly penetrant, or the epigenetic states are unlikely to change between generations. With multiple inherited environments, these conditions are no longer necessary. For a fixed level of disease prevalence in the population, we show that the estimated heritability is highest when the two environments induce very different methylation rates (Figures 3 and 4). Also, the heritability can be significantly higher than that produced by an epigenetic process that is not environment sensitive. Slatkin’s multiplicative model of disease risk is a special case of our model. In particular, a background risk $b$ and an allele-specific risk increase factor of $1 + \rho$ (using the notation of Slatkin 2009) correspond in our model to the case $\alpha = b$, $\delta = b\rho(2 + \rho)$, and $\gamma = 1/(2 + \rho)$. Using a multiplicative disease model in our epigenetic model did not change the qualitative results, so we focused on the additive case ($\gamma = 0.5$).

The quantitative genetic model of Tal et al. (2010) also assumed no heritable environment, and epigenetic modifications that are reset with probability $\nu$ then have a certain probability of being reinduced. Although this model is framed in terms of a quantitative trait and does not explicitly incorporate discrete epigenetic states, if we imagine an environment as inducing the epigenetic state 1 in our model, then the parameter $\nu$ from Tal et al. (2010) would be equivalent to $\mu_{1 \rightarrow 0} + \mu_{0 \rightarrow 1}$. Their model would apply equally well to cultural traits or a heritable environmental state. From the covariances between different relatives they obtained, Tal et al. (2010) demonstrated how to estimate the epigenetic contribution to heritability as a function of various observed familial covariances—an approach reminiscent of that used by Feldman et al. (1995, 2000). However, by focusing only on one transmissible nongenetic contribution to phenotype and considering the inducing state as independent of the current epigenetic state, environmental effects on epigenetic state are not included in their model. Several other heuristic or statistical models have also been proposed for studying epigenetic contributions to heritability (Bonduriansky and Day 2009; Danchin and Wagner 2010; Day and Bonduriansky 2011).

By specifying an explicit dynamic model of epigenetic transmission, our model and that of Slatkin (2009) offer a bridge between dynamic processes and statistical estimates, enriching the understanding of epigenetic contributions to heritability. Our dynamical model has a most remarkable property in the case of environmental inheritance and environment-sensitive epigenetics, namely the possibility of the stable presence of a serious, heritable, early onset, and common disease in a population. Purely genetic transmission of such a disease would induce strong natural selection against the risk alleles, with decreasing disease incidence through time, unless this evolutionary effect were balanced—as in the case of the balance between the effects of malaria and sickle-cell anemia. The high disease mortality in a particular environment will of course have demographic repercussions, but these could easily be balanced by immigration into the high-risk environment—lung cancer in heavily smoking subcultures provides an illustration of this kind of effect. A new smoker could be considered a migrant into the smoking environment, and someone quitting smoking considered a migrant from the smoking to the nonsmoking environment.

Environment-sensitive effects on disease risk during early development have been indicated by investigations of environmental exposures during prenatal development. Birth cohorts prenatally exposed to famine show significant increases in schizophrenia risk in later life. Such effects can be traced to the Dutch Hunger Winter of 1944–1945 (Susser and Lin 1992; Susser et al. 1996) and the Chinese Famine of 1959–1961 (St. Clair et al. 2005). These studies did not include epigenetics, but environment-sensitive epigenetic factors have been proposed to play a key role in the development of schizophrenia (Tsankova et al. 2007; Rutten and Mill 2009).

Despite the many parameters in our model, they should be estimable from data. For example, Verhoeven et al.
(2010) tracked rates of methylation state change across generations in common dandelions for a variety of ecological treatments (corresponding to environments in our model). Their data allow estimation of our epimutation parameters $\mu_{a,i}$. The characteristics of methylation dynamics in plants are not good predictors of those in mammals, but similar investigations should be feasible. The environmental transmission parameters $a$ and $e$ are more troublesome, although longitudinal measurements of the environmental states of individuals and their offspring are possible. The estimation of the environmental risk parameters $\alpha_{a,i}$ would entail measurements of the disease phenotype as well as the environmental and epigenetic states of individuals.

Addressing the question of missing heritability, we have demonstrated that very high correlations between the phenotypes of relatives can occur even in the absence of any contribution from genetic variation to the variation in phenotype. The estimated additive genetic variance of a phenotype showing familial aggregation because of a combination of genetic, epigenetic, and environmental effects will only partly be accounted for by all the SNPs that are associated with the phenotype. We do not attempt to calculate heritability estimates that control for environmental or epigenetic effects in our analysis. In the presence of nongenetic modes of inheritance, the classical narrow sense heritability is not the most useful measure for understanding how phenotypes aggregate or how populations will respond to selection. Instead, a measure that incorporates variation from all modes of inheritance will offer more explanatory power (Danchin and Wagner 2010; Danchin et al. 2011).

The results of our analysis suggest that epigenetic factors could play an important role in the statistics of complex diseases and other phenotypes, with epigenetic contributions to familial covariances potentially having magnitudes comparable to those of genetic contributions. Progress of investigations into epigenetic disease etiology will rely on the development of observational methodology and more inclusive models that take account of specific epigenetic phenomena and their interactions with environments.

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Appendix

The Full Frequency Recursions

\[
\begin{align*}
\dot{f}_{x,ij} &= \left[\left(1 - m + m/f_x\right)(1 - e_x)\right] \left\{ \left( f_{x,00} + f_{x,01} \right)^2 \mu_{x,0 \to j} \mu_{x,0 \to j} + \left( f_{x,00} + f_{x,01} \right) \left( f_{x,01} + f_{x,11} \right) \left( \mu_{x,0 \to j} \mu_{x,1 \to j} + \mu_{x,1 \to j} \mu_{x,0 \to j} \right) \\
&\quad + \left( f_{x,01} + f_{x,11} \right)^2 \mu_{x,1 \to j} \mu_{x,1 \to j} \right\} \\
&\quad + \left( 2 \left[ 1 - \left(1 - e_x \right) \left(1 - a \right) + e_x a \right] \right) \times \left\{ \left( f_{x,00} + f_{x,01} \right) \left( f_{y,00} + f_{y,01} \right) \mu_{x,0 \to j} \mu_{x,0 \to j} + \left( f_{x,00} + f_{x,01} \right) \left( f_{y,01} + f_{y,11} \right) \right\} \times \left\{ \left( f_{x,01} + f_{x,11} \right) \left( f_{y,01} + f_{y,01} \right) \mu_{x,1 \to j} \mu_{x,1 \to j} + \left( f_{x,01} + f_{x,11} \right) \left( f_{y,01} + f_{y,11} \right) \right\} \\
&\quad + \left( 2 \left[ 1 - \left(1 - e_x \right) \left(1 - a \right) + e_x a \right] \right) \times \left\{ \left( f_{y,00} + f_{y,01} \right)^2 \mu_{x,0 \to j} \mu_{x,0 \to j} \right\} \\
&\quad + \left( f_{y,00} + f_{y,01} \right) \left( f_{y,01} + f_{y,11} \right) \mu_{x,0 \to j} \mu_{x,1 \to j} + \left( f_{y,01} + f_{y,11} \right)^2 \mu_{x,1 \to j} \mu_{x,1 \to j} \right\} \\
\dot{f}_{y,ij} &= \left[\left(1 - m + m/f_x\right)e_y\right] \left( f_{y,00} + f_{y,01} \right)^2 \mu_{y,0 \to j} \mu_{y,0 \to j} \\
&\quad + \left( f_{y,00} + f_{y,01} \right) \left( f_{y,01} + f_{y,11} \right) \left( \mu_{y,0 \to j} \mu_{y,1 \to j} + \mu_{y,1 \to j} \mu_{y,0 \to j} \right) \\
&\quad + \left( f_{y,01} + f_{y,11} \right)^2 \mu_{y,1 \to j} \mu_{y,1 \to j} \right\} \\
&\quad + \left( 2 \left[ 1 - \left(1 - e_y \right) \left(1 - a \right) + e_y a \right] \right) \times \left\{ \left( f_{y,00} + f_{y,01} \right) \left( f_{y,00} + f_{y,01} \right) \mu_{y,0 \to j} \mu_{y,0 \to j} + \left( f_{y,00} + f_{y,01} \right) \left( f_{y,01} + f_{y,11} \right) \\
&\quad + \left( f_{y,01} + f_{y,11} \right) \left( f_{y,00} + f_{y,11} \right) \left( \mu_{y,0 \to j} \mu_{y,1 \to j} + \mu_{y,1 \to j} \mu_{y,0 \to j} \right) \\
&\quad + \left( f_{y,01} + f_{y,11} \right)^2 \mu_{y,1 \to j} \mu_{y,1 \to j} \right\} \times \left\{ \left( f_{y,00} + f_{y,01} \right)^2 \mu_{y,0 \to j} \mu_{y,0 \to j} \right\} \\
&\quad + \left( f_{y,00} + f_{y,01} \right) \left( f_{y,01} + f_{y,11} \right) \mu_{y,0 \to j} \mu_{y,1 \to j} + \left( f_{y,01} + f_{y,11} \right)^2 \mu_{y,1 \to j} \mu_{y,1 \to j} \right\} \\
&\quad + \left( f_{y,00} + f_{y,01} \right) \left( f_{y,01} + f_{y,11} \right) \mu_{y,0 \to j} \mu_{y,0 \to j} + \left( f_{y,01} + f_{y,11} \right)^2 \mu_{y,1 \to j} \mu_{y,1 \to j} \right].
\end{align*}
\]

Parent–Offspring Covariance

Here we derive a formula for the parent–offspring covariance for arbitrary values of all parameters. The disease risk of an individual in environment $u$ with epigenotype $ij$ is $\alpha_{u,i,j} \in [0,1]$. Assuming equilibrium, the covariance is straightforward but cumbersome to compute from our recursions. We compute the parent–offspring covariance in disease, $W_{\text{D}}$, by summing over all possible ways that parent and offspring can both be diseased and then subtracting off the square of the disease prevalence $K$. 

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Before we write out the full equation for covariance, we define a few quantities to make notation simpler. We define \( Z_{uv,i} \) as the probability that a focal parent in environment \( u \) produces a juvenile offspring in environment \( v \), and that offspring receives an epiallele in state \( i \) from the nonfocal parent:

\[
Z_{x,0} = \hat{p}_{x,0} [(1 - m) \hat{f}_x + m(1 - e_x) + \hat{p}_{y,0} (1 - m) \hat{f}_y] ((1 - e_x)(1 - a) + e_y a) \\
Z_{x,1} = \hat{p}_{x,1} [(1 - m) \hat{f}_x + m(1 - e_x) + \hat{p}_{y,1} (1 - m) \hat{f}_y] ((1 - e_x)(1 - a) + e_y a) \\
Z_{y,0} = \hat{p}_{x,0} [(1 - m) \hat{f}_x + m e_x + \hat{p}_{y,0} (1 - m) \hat{f}_y] (e_x(1 - a) + (1 - e_y) a) \\
Z_{y,1} = \hat{p}_{x,1} [(1 - m) \hat{f}_x + m e_x + \hat{p}_{y,1} (1 - m) \hat{f}_y] (e_x(1 - a) + (1 - e_y) a) \\
Z_{xy,0} = \hat{p}_{x,0} [(1 - m) \hat{f}_x + m e_x + \hat{p}_{y,0} (1 - m) \hat{f}_y] (e_x(1 - a) + e_y a) \\
Z_{xy,1} = \hat{p}_{x,1} [(1 - m) \hat{f}_x + m e_x + \hat{p}_{y,1} (1 - m) \hat{f}_y] (e_x(1 - a) + e_y a) \\
Z_{yy,0} = \hat{p}_{x,0} [(1 - m) \hat{f}_x + (1 - e_x)(1 - a) + e_y a) + \hat{p}_{y,0} (1 - m) \hat{f}_y + m] (1 - e_y) \\
Z_{yy,1} = \hat{p}_{x,1} [(1 - m) \hat{f}_x + (1 - e_x)(1 - a) + e_y a) + \hat{p}_{y,1} (1 - m) \hat{f}_y + m] (1 - e_y).
\]

The quantities \( \hat{p}_{u,i} \) are the equilibrium frequencies of allele \( i \) within environment \( u \). So the terms \( \hat{p}_{u,i} \) in the preceding equations represent the probabilities that the mate of the focal parent is contributing an \( i \) allele. The bracketed terms represent the probabilities of the environmental classes of matings, conditioned on the focal parent's environment. The purpose of defining \( Z_{uv,i} \) is to aid in representing the quantity \( Z_{uvijkl} \), which is the probability of a focal parent in environment \( u \) with epigenotype \( ij \) producing an offspring in environment \( v \) with adult epigenotype \( kl \). We can define \( Z_{uvijkl} \) in terms of the values \( Z_{uv,i} \) as

\[
Z_{uvijkl} = Z_{uv,0} \left( \frac{\mu_{v,i-k} + \mu_{v,j-k}}{2} \right) \frac{\mu_{v,0-l}}{2} + \frac{\mu_{v,i-l} + \mu_{v,j-l}}{2} \frac{\mu_{v,0-k}}{2} \\
+ Z_{uv,1} \left( \frac{\mu_{v,i-k} + \mu_{v,j-k}}{2} \right) \frac{\mu_{v,1-l}}{2} + \frac{\mu_{v,i-l} + \mu_{v,j-l}}{2} \frac{\mu_{v,1-k}}{2} \\
= Z_{uv,0} \left( \frac{\mu_{v,i-k} + \mu_{v,j-k}}{4} \right) \frac{\mu_{v,0-l}}{4} + \frac{\mu_{v,i-l} + \mu_{v,j-l}}{4} \frac{\mu_{v,0-k}}{4} \\
+ Z_{uv,1} \left( \frac{\mu_{v,i-k} + \mu_{v,j-k}}{4} \right) \frac{\mu_{v,1-l}}{4} + \frac{\mu_{v,i-l} + \mu_{v,j-l}}{4} \frac{\mu_{v,1-k}}{4}.
\]

This equation separates out matings by whether the nonfocal parent contributes allele 0 or 1. Each product of the epimutation rates corresponds to a particular combination of epialleles received from the two parents.

It is now simple to write the covariance between the adult phenotype of a focal parent and the adult phenotype of an offspring using \( Z_{uvijkl} \), because \( Z_{uvijkl} \) is the probability of a focal parent producing an adult offspring in environment \( v \) with epigenotype \( kl \), conditioned on the environmental state and epigenotype of the focal parent. Expressed in terms of these variables, the equilibrium covariance in a disease phenotype is

\[
W_{D} = \left( \sum_{u} \sum_{ij} \alpha_{u,ij} f_{u,ij} \sum_{v} \sum_{kl} \alpha_{v,kl} Z_{uvijkl} \right) - K^2,
\]

where \( \alpha_{u,ij} \) are the disease risks of an adult individual in environment \( u \) with epigenotype \( ij \), as explained in the Disease risk section. Our final equation for \( W_{D} \) is therefore simply the sum over the frequencies of all parent–offspring combinations weighted by their disease risks, minus the prevalence squared.
Environment-Sensitive Epigenetics and the Heritability of Complex Diseases

Robert E. Furrow, Freddy B. Christiansen, and Marcus W. Feldman
S1. Convergence of \( f_x \). The general recursion for \( f_x \), the proportion of individuals in environment \( x \), between generations is

\[
f'_x = \tilde{f}_{x,00} + 2\tilde{f}_{x,01} + \tilde{f}_{x,11}
\]

That is,

\[
f'_x = M_{xx} \Omega_{xx,00} (1 - e_x) + 2M_{xy} \Omega_{xy,00} ((1 - e_x)(1 - a) + e_y a) + M_{yy} \Omega_{yy,00} e_y \\
+ 2 [M_{xx} \Omega_{xx,01} (1 - e_x) + 2M_{xy} \Omega_{xy,01} ((1 - e_x)(1 - a) + e_y a) + M_{yy} \Omega_{yy,01} e_y] \\
+ M_{xx} \Omega_{xx,11} (1 - e_x) + 2M_{xy} \Omega_{xy,11} ((1 - e_x)(1 - a) + e_y a) + M_{yy} \Omega_{yy,11} e_y.
\]

Because \( \Omega_{uv,00} + 2\Omega_{uv,01} + \Omega_{uv,11} = 1 \) (since all offspring from a \( u \)-by-\( v \) mating must have some epigenotype), our recursion system simplifies to

\[
f'_x = (1 - e_x) [(1 - m) f_x^2 + m f_x] + 2[1 - e_x - a(1 - e_x - e_y)] [(1 - m) f_x f_y] \\
+ e_y [(1 - m) f_y^2 + m f_y] \\
f'_x = ((1 - e_x)(1 - m) - 2[1 - e_x - a(1 - e_x - e_y)](1 - m) + e_y(1 - m)) f_x^2 \\
+ ((1 - e_x - e_y)(2 - m - 2a + 2am)) f_x + e_y(1 - m + m) \\
f'_x = -(1 - e_x - e_y)(1 - m)(1 - 2a)f_x^2 \\
+ (1 - e_x - e_y)((1 - m)(1 - 2a) + 1)f_x + e_y.
\]

This recursion system always results in convergence of \( f_x \) to a unique fixed point in \((0,1)\), whenever \( e_x, e_y \in (0, .5) \). To see this, we first recast our recursion as \( f'_x = H(f_x) \),
where
\[ H(\xi) = -(1 - e_x - e_y)(1 - m)(1 - 2a)\xi^2 + (1 - e_x - e_y)((1 - m)(1 - 2a) + 1)\xi + e_y. \]

Noting that \( H(0) = e_y \) and \( H(1) = 1 - e_x \), we see that there must be exactly one value \( \hat{f}_x \) such that \( \hat{f}_x = H(\hat{f}_x) \), because \( H(\xi) - \xi \) is a quadratic function that must cross zero exactly once for \( \xi \in (0, 1) \). Hence the fixed point is unique within \( (0, 1) \). To investigate convergence we consider the derivative \( \dot{H} \) of the function \( H \), with respect to \( \xi \).

\[
\dot{H}(\xi) = -2(1 - e_x - e_y)(1 - m)(1 - 2a)\xi + (1 - e_x - e_y)((1 - m)(1 - 2a) + 1)
\]
\[
= (1 - e_x - e_y) + (1 - 2\xi)(1 - e_x - e_y)(1 - m)(1 - 2a)
\]
\[
\dot{H}(0) = (1 - e_x - e_y) + (1 - e_x - e_y)(1 - m)(1 - 2a)
\]
\[
\dot{H}(1) = (1 - e_x - e_y) - (1 - e_x - e_y)(1 - m)(1 - 2a).
\]

Because \( e_x, e_y \in (0, 0.5) \), we see that \( \dot{H}(\xi) \in (0, 2) \) for \( \xi \in [0, 1] \). Recalling that \( H(0) > 0 \) and \( H(1) < 1 \), we note that \( H \) is monotonically increasing and \( H(\xi) > \xi \) for \( \xi < \hat{f}_x \), \( H(\xi) < \xi \) for \( \xi > \hat{f}_x \). This implies that there is global, non-oscillating convergence to the fixed point \( \hat{f}_x \) from any starting value \( f_x \in [0, 1] \).

In the special cases \( a = \frac{1}{2} \) or \( m = 1 \), the recursion for \( f_x \) reduces to
\[ f'_x = (1 - e_x - e_y)f_x + e_y. \]

We note that
\[ f'_x - \frac{e_y}{e_x + e_y} = (1 - e_x - e_y)\left(f_x - \frac{e_y}{e_x + e_y}\right), \]
therefore \( f_x \) converges geometrically fast to \( \frac{e_y}{e_x + e_y} \), except in the degenerate case where \( e_x = e_y = 0 \).
S2. Covariance for Case 2: Environmental transmission but no epigenetic transmission. Unlike the general case, when there is no faithful epigenetic transmission between generations we can calculate the parent offspring covariance in disease risk in a simple closed form. We begin by finding the parent-offspring covariance in environmental state ($W_E$) at equilibrium. We specify the indicator variables $L_p$ and $L_o$, where $L_p$ is 1 when the parent is in environment $x$, and 0 otherwise, and $L_o$ is 1 when the offspring of that parent is in environment $x$, and 0 otherwise.

$$W_E = Cov(L_p, L_o) = E[L_pL_o] - E[L_p]E[L_o] = E[L_pL_o] - \hat{f}_x^2,$$

because $E[L_p] = E[L_o] = \hat{f}_x$ at equilibrium, and $L_p = 1$ for all $x$-by-$x$ matings and half of the $x$-by-$y$ matings (when the focal parent is the parent in $x$). From this, we evaluate $W_E$ as

$$W_E = \text{Prob(both parents in } x \text{ and offspring in } x) - \frac{1}{2} \text{Prob(parents in different environments and offspring in } x) - \hat{f}_x^2$$

$$= [(1 - m)\hat{f}_x^2 + m\hat{f}_x](1 - e_x) + \frac{1}{2} * 2[(1 - m)\hat{f}_x\hat{f}_y][(1 - e_x)(1 - a) + e_ya] - \hat{f}_x^2$$

$$= [(1 - m)\hat{f}_x^2 + m\hat{f}_x](1 - e_x) + [(1 - m)\hat{f}_x(1 - \hat{f}_x)][(1 - e_x)(1 - a) + e_ya] - \hat{f}_x^2.$$

In this case $\mu_{u,0\rightarrow 1} = \mu_{u,1\rightarrow 1}, \alpha_{u,00} = \alpha, \alpha_{u,01} = \alpha + r\delta, \text{ and } \alpha_{u,11} = \alpha + \delta$, for $u \in \{x, y\}$. We define $G_{u,ij}$ to be indicator variables that are 1 when a parent in environment $u$ has genotype $ij$ and 0 otherwise. $G_{u,ij}'$ are the analogous variables for the offspring at adulthood. Defining $D_{ij}$ as an indicator variable that is 1 when a parent with epigenotype $ij$ contracts the disease and 0 otherwise (and $D_{ij}'$ the analogous variable for an adult offspring), we have the disease state of a random parent in the population represented by

$$L_p(G_{x,00}D_{00} + 2G_{x,01}D_{01} + G_{x,11}D_{11}) + (1 - L_p)(G_{y,00}D_{00} + 2G_{y,01}D_{01} + G_{y,11}D_{11}).$$
Similarly, the disease state at adulthood of a random offspring is

\[
L_o(G'_{x,00}D'_{00} + 2G'_{x,01}D'_{01} + G'_{x,11}D'_{11}) + (1 - L_o)(G'_{y,00}D'_{00} + 2G'_{y,01}D'_{01} + G'_{y,11}D'_{11}).
\]

We note that for any random variable \( C \) independent of \( A, B, \) and \( AB, \) the relation \( Cov(CA, B) = E[C]Cov(A, B) \) always holds. Using the independence properties of the indicator variables defined above, the parent-offspring covariance simplifies to

\[
W_D = [\alpha((1 - \mu_{x,0-1})^2 - (1 - \mu_{y,0-1})^2) + 2(\alpha + r\delta)(\mu_{x,0-1}(1 - \mu_{x,0-1}) - \mu_{y,0-1}(1 - \mu_{y,0-1}))
+ (\alpha + \delta)(\mu_{x,0-1} - \mu_{y,0-1})]^2 W_E
= [\delta(2r(\mu_{x,0-1} - \mu_{y,0-1}) + (1 - 2r)(\mu_{x,0-1}^2 - \mu_{y,0-1}^2))]^2 W_E
= \delta^2(\mu_{x,0-1} - \mu_{y,0-1})^2[2r + (1 - 2r)(\mu_{x,0-1} + \mu_{y,0-1})]^2 W_E.
\]

The disease prevalence \( K \) in the adult population is

\[
K = E[L_p(G_{x,00}D_{00} + 2G_{x,01}D_{01} + G_{x,11}D_{11}) + (1 - L_p)(G_{y,00}D_{00} + 2G_{y,01}D_{01} + G_{y,11}D_{11})]
= \hat{f}_x(\delta(\mu_{x,0-1} - \mu_{y,0-1})[2r + (1 - 2r)(\mu_{x,0-1} + \mu_{y,0-1})]) + (\alpha + \delta(2r\mu_{y,0-1}(1 - \mu_{y,0-1}) + \mu_{y,0-1}^2)
= \hat{f}_x(\delta(\mu_{x,0-1} - \mu_{y,0-1})[2r + (1 - 2r)(\mu_{x,0-1} + \mu_{y,0-1})]) + (\alpha + \delta(2r\mu_{y,0-1}(1 - 2r)\mu_{y,0-1}^2)).
\]

**S3. Comparing heritability between Case 1 and Case 2.** To understand how the two cases relate to each other, we plot estimated heritability for parameters that range linearly from those used in Case 1 to those of Case 2. Each curve in Figure S1 plots the estimated heritability on the vertical axis with respect to the parameter \( c \in [0, 1] \) on the horizontal axis. The parameter \( c \) determines whether patterns of epigenetic reset are similar to Case 1 or Case 2, where epimutation rates are related by the equation \( \mu_{u,1-0} = 0.5 + c(0.5 - \mu_{u,0-1}). \) If \( c = 0 \), then \( \mu_{u,1-0} = 0.5 \) and we are in Case 1. If \( c = 1 \), then \( \mu_{u,1-0} = 1 - \mu_{u,0-1} \) and we are in Case 2. We see that if \( \mu_{x,0-1} \) is very different from \( \mu_{y,0-1} \), then the case without direct epigenetic transmission (Case 2) results in much
higher heritability estimates. But if the rates of epimutation are similar in both environments, then epigenetic transmission is more important to familial covariance and Case 1 results in higher heritability estimates. The disease parameters used are again $\alpha = 0.1$, $r = 0.5$, $\delta = 0.4$, and we assume $\mu_{y,0\rightarrow1} = 0.1$, $e = 0.1$, $a = 0.5$, and $m = 0.5$.

**S4. Covariance for a genetic locus.** Here we derive the parent-offspring covariance as if our locus were genetic, for the sake of comparison. Because rates of mutation per nucleotide are vanishingly small in humans, we assume no mutation between parent and offspring. In that case, we simply have Mendelian inheritance and no environmental effects. We have three genotypes: 00, 01, and 11, and three risk parameters $\alpha_{00} = \alpha$, $\alpha_{01} = \alpha + r\delta$, and $\alpha_{11} = \alpha + \delta$. To calculate the covariance in disease state ($W_D$), we will use $\text{Cov}(A, B) = E[AB] - E[A]E[B]$. But $E[A] = E[B] = K = p_0^2\alpha_{00} + 2p_0p_1\alpha_{01} + p_1^2\alpha_{11}$, so we must simply calculate $E[AB]$. For this we assume that the population is in Hardy-Weinberg equilibrium, and that the frequencies of the alleles 0 and 1 are $p_0$ and $p_1$, respectively ($p_0 + p_1 = 1$). In this case, our covariance is

$$W_D = \alpha_{00}p_0^2\left(\alpha_{00}p_0 + \alpha_{01}p_1\right) + \alpha_{01}2p_0p_1\left(\frac{\alpha_{00}p_0 + \alpha_{01}p_1}{2} + \frac{\alpha_{01}p_0 + \alpha_{11}p_1}{2}\right)$$

$$+ \alpha_{11}p_1^2\left(\alpha_{01}p_0 + \alpha_{11}p_1\right) - K^2.$$

Using this, our expression for the heritability, $h^2 = \frac{2W_D}{V_D}$, is exactly the narrow sense heritability, defined as the fraction of phenotypic variance attributable to additive genetic variance.

**S5. Recurrence Risk Ratio.** An alternative way to describe familial aggregation of a disease uses the recurrence risk ratio, which for an individual B, related to individual A, is

$$\lambda = \frac{E[AB]}{KE[A]}.$$

This ratio expresses how likely a relative (B) of a diseased proband (A) is to become diseased relative to a random individual in the population. At equilibrium, $E[A] = K$ for
any individual, and $E[AB] = \text{Cov}(A, B) + K^2$. Computing the recurrence risk ratio of an offspring (B) with respect to its affected parent (A), $\text{Cov}(A, B) = W_D = h^2 V_D/2 = h^2 K(1 - K)/2$, so we can relate $\lambda$ to our heritability estimate $h^2$ using the formula

$$\lambda = \frac{h^2 (1 - K)}{2K} + 1.$$  

Case 1: Environmental and epigenetic transmission. Comparing our heritability estimate with the recurrence risk ratio, we find similar results. Figure S2 shows side-by-side panels of estimated heritability and the log of the recurrence risk ratio for identical parameter values. However, it is worth noting that because the relationship between estimated heritability and recurrence risk ratio depends on the prevalence, the patterns are not identical. In Figure S3 we focus on the particular instance of Case 1 where $\mu_{y,0\rightarrow1} = 0.05$ ($e = 0.1$, $m = 0.5$, $\alpha = 0.1$, $\delta = 0.4$, $r = 0.5$, $\mu_{x,1\rightarrow0} = \mu_{y,1\rightarrow0} = 0.5$), and we see that the recurrence risk ratio is maximized for an intermediate value of $\mu_{x,0\rightarrow1}$, whereas heritability is maximized when $\mu_{x,0\rightarrow1}$ is as large as possible.

Similar to the results for heritability, increasing assortative mating ($m$), or fidelity of transmission of environmental state ($1 - e$), produce higher recurrence risk ratios with higher magnitude and a more pronounced increase in $\lambda$ when the epimutation rates are very different between environments.

Case 2: Environmental transmission but no epigenetic transmission. Results for recurrence risk ratio are similar to those for heritability.
FIGURE S1  Comparing heritability estimates between Case 1 and Case 2. The horizontal axis is the value of a parameter $c$, such that $\mu_{u,1 \to 0} = 0.5 + c(0.5 - \mu_{u,0 \to 1})$ for $u \in \{x,y\}$. The vertical axis is the estimated heritability for that set of parameters. Each curve plotted corresponds to a different value of $\mu_{x,0 \to 1}$, with $\mu_{y,0 \to 1} = 0.1$ throughout. For all curves, the other parameters are $\alpha = 0.1$, $r = 0.5$, $\delta = 0.4$, $e = 0.1$, $a = 0.5$, and $m = 0.5$. 
**FIGURE S2** Dependence of heritability and log recurrence risk ratio on epimutation rates for Case 1 ($\mu_{x,1 \to 0} = \mu_{y,1 \to 0} = 0.5$). The colors in the top panel indicate heritability, and in the bottom panel indicate the natural log of recurrence risk, ln($\lambda$). The horizontal axis in each panel indicates the value of $\mu_{x,0 \to 1}$, and the vertical axis indicates the value of $\mu_{y,0 \to 1}$. The contour curves represent constant disease prevalence values ($K$), with the lower left contour indicating a prevalence of 0.15, and each progressive contour toward the upper right corresponding to an increase in prevalence of 0.05. For both of these panels, the other parameter values are $\mu_{x,1 \to 0} = \mu_{y,1 \to 0} = 0.5$, $\alpha = 0$, $r = 0.5$, $\delta = 1$, $m = 0.5$, $e = 0.1$, and $a = 0.5$. 
**Figure S3** Dependence of heritability and log recurrence risk ratio on $\mu_{x,0\rightarrow 1}$, the epimutation rate in environment $x$, for Case 1 ($\mu_{x,1\rightarrow 0} = \mu_{y,1\rightarrow 0} = 0.5$). The horizontal axis is the value of $\mu_{x,0\rightarrow 1}$, and the vertical axis is either $\ln(\lambda)$ or heritability in the left panel, and prevalence (K) in the right panel. For both panels, the other parameter values are $\mu_{y,0\rightarrow 1} = 0.05$, $\mu_{x,1\rightarrow 0} = \mu_{y,1\rightarrow 0} = 0.5$, $\alpha = 0$, $r = 0.5$, $\delta = 1$, $m = 0.5$, $e = 0.1$, and $a = 0.5$. 