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2 **Supplementary Information for**
3 **Genetic nurturing, missing heritability, and causal analysis in genetic statistics**

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7 **This PDF file includes:**

8 Supplementary text

9 Fig. S1

10 SI References

11 **Supporting Information Text**

12 **Supplementary Information A:**

13 **Equilibrium of the model with cultural transmission**

The linear recursion [4] can be rewritten in matrix form:

$$\begin{pmatrix} x_1^{n+1} \\ x_2^{n+1} \\ x_3^{n+1} \end{pmatrix} = \begin{pmatrix} 2e_1p & 2e_1q & 0 \\ e_2p & e_2 & e_2q \\ 0 & 2e_3p & 2e_3q \end{pmatrix} \begin{pmatrix} x_1^n \\ x_2^n \\ x_3^n \end{pmatrix} + \begin{pmatrix} c_1 \\ c_2 \\ c_3 \end{pmatrix} = \mathbf{B}\mathbf{x} + \mathbf{c}. \quad [\text{A1}]$$

14 The eigenvalues of \mathbf{B} , the roots of the characteristic polynomial of matrix \mathbf{B} , are roots of

$$\begin{vmatrix} 2e_1p - \lambda & 2e_1q & 0 \\ e_2p & e_2 - \lambda & e_2q \\ 0 & 2e_3p & 2e_3q - \lambda \end{vmatrix} = 0, \quad [\text{A2}]$$

16 which reduces to

$$\lambda[\lambda^2 - (2e_1p + e_2 + 2e_3q)\lambda + 2e_1e_2p^2 + 2e_2e_3q^2 + 4e_1e_3pq] = 0. \quad [\text{A3}]$$

18 These roots are $\lambda = 0$ and the roots of $f(\lambda) = 0$, where

$$f(\lambda) = \lambda^2 - (2e_1p + e_2 + 2e_3q)\lambda + 2e_1e_2p^2 + 2e_2e_3q^2 + 4e_1e_3pq. \quad [\text{A4}]$$

Since

$$\begin{aligned} \Delta &= (2e_1p + 2e_3q + e_2)^2 - 4(2e_1e_2p^2 + 2e_2e_3q^2 + 4e_1e_3pq) \\ &= p(2e_1p - 2e_3q + e_2)^2 + q(-2e_1p + 2e_3q + e_2)^2 \geq 0; \\ \lambda_1 + \lambda_2 &= 2e_1p + 2e_3q + e_2 \in (-2, 2); \\ \lambda_1\lambda_2 &= 2e_1e_2p^2 + 2e_2e_3q^2 + 4e_1e_3pq \in (-1, 1). \end{aligned} \quad [\text{A5}]$$

This implies

$$\begin{aligned} \lambda_1 &\in (-1, 1); \\ \lambda_2 &\in (-1, 1). \end{aligned} \quad [\text{A6}]$$

We conclude that the system will converge to the equilibrium point, which is given by

$$\begin{aligned} x_1 &= 2e_1px_1 + 2e_1qx_2 + c_1; \\ x_2 &= e_2px_1 + e_2x_2 + e_2qx_3 + c_2; \\ x_3 &= 2e_3qx_3 + 2e_3px_2 + c_3. \end{aligned} \quad [\text{A7}]$$

This can be rewritten as

$$\begin{aligned} (1 - 2e_1p)x_1 - 2e_1qx_2 &= c_1; \\ -e_2px_1 + (1 - e_2)x_2 - e_2qx_3 &= c_2; \\ (1 - 2e_3q)x_3 - 2e_3px_2 &= c_3. \end{aligned} \quad [\text{A8}]$$

We can then solve these equations to get

$$\begin{aligned} x_1 &= \frac{B_1}{A}; \\ x_2 &= \frac{B_2}{A}; \\ x_3 &= \frac{B_3}{A}; \end{aligned} \quad [\text{A9}]$$

$$\begin{aligned} A &= 1 - e_2 - 2e_1p - 2e_3q + 2e_1e_2p^2 + 2e_2e_3q^2 + 4e_1e_3pq; \\ B_1 &= (1 - e_2 - 2e_3q + 2e_2e_3q^2)c_1 + 2e_1q(1 - 2e_3q)c_2 + 2e_1e_2q^2c_3; \\ B_2 &= e_2p(1 - 2e_3q)c_1 + (1 - 2e_3q)(1 - 2e_1p)c_2 + e_2q(1 - 2e_1p)c_3; \\ B_3 &= 2e_3e_2p^2c_1 + 2e_3p(1 - 2e_1p)c_2 + (1 - e_2 - 2e_1p + 2e_1e_2p^2)c_3. \end{aligned}$$

20 **Supplementary Information B:**

21 **Calculation of covariance and regression coefficients in model with cultural transmission**

22 Denote $\bar{x} = E(X_{ch}) = E(X_p) = E(X_m)$, it is easy to see

$$\begin{aligned}
 Cov(X_{ch}, N_{pa}^n) &= E(X_{ch}N_{pa}^n) - E(X_{ch})E(N_{pa}^n) \\
 &= P(X_{ch} = 1, N_{pa}^n = 1) + 2P(X_{ch} = 1, N_{pa}^n = 2) - E(X_{ch})E(N_{pa}^n) \\
 &= 1 - P(X_{ch}N_{pa}^n = 0) - P(X_{ch} = 1, N_{pa}^n = 2) + 2P(X_{ch} = 1, N_{pa}^n = 2) - 2\bar{x}q \\
 &= 1 + P(X_{ch} = 0, N_{pa}^n = 0) + P(X_{ch} = 1, N_{pa}^n = 2) - P(X_{ch} = 0) - P(N_{pa}^n = 0) - 2\bar{x}q
 \end{aligned} \tag{B1}$$

$$P(X_{ch} = 0, N_{pa}^n = 0) = p^4(1 - c_1 - 2e_1x_1) + 2p^3q[1 - c_2 - e_2(x_1 + x_2)] + p^2q^2(1 - c_3 - 2e_3x_2); \tag{B2.a}$$

$$P(X_{ch} = 1, N_{pa}^n = 2) = p^2q^2(c_1 + 2e_1x_2) + 2pq^3[c_2 + e_2(x_2 + x_3)] + q^4(c_3 + 2e_3x_3); \tag{B2.b}$$

$$P(X_{ch} = 0) = 1 - \bar{x}; \tag{B2.c}$$

$$P(N_{pa}^n = 0) = p^2; \tag{B2.d}$$

$$\bar{x} = p^2x_1 + 2pqx_2 + q^2x_3. \tag{B2.e}$$

Thus, we have

$$\begin{aligned}
 Cov(X_{ch}, N_{pa}^n) &= 1 + P(X_{ch} = 0, N_{pa}^n = 0) + P(X_{ch} = 1, N_{pa}^n = 2) - P(X_{ch} = 0) - P(N_{pa}^n = 0) - 2\bar{x}q \\
 &= 1 + p^4(1 - c_1 - 2e_1x_1) + 2p^3q[1 - c_2 - e_2(x_1 + x_2)] + p^2q^2(1 - c_3 - 2e_3x_2) \\
 &\quad + p^2q^2(c_1 + 2e_1x_2) + 2pq^3[c_2 + e_2(x_2 + x_3)] + q^4(c_3 + 2e_3x_3) - (1 - \bar{x}) - p^2 - 2\bar{x}q \\
 &= \bar{x}(1 - 2q) + p^2(q^2 - p^2)c_1 + 2pq(q^2 - p^2)c_2 + q^2(q^2 - p^2)c_3 \\
 &\quad - 2p^3x_1(pe_1 + qe_2) + 2pqx_2[q(pe_1 + qe_2) - p(pe_2 + qe_3)] + 2q^3x_3(pe_2 + qe_3) \\
 &= (p - q)(\bar{x} - \bar{c}) - 2p^3x_1(pe_1 + qe_2) + 2pqx_2[q(pe_1 + qe_2) - p(pe_2 + qe_3)] + 2q^3x_3(pe_2 + qe_3).
 \end{aligned} \tag{B3}$$

From [11] we can further simplify to obtain

$$\begin{aligned}
 Cov(X_{ch}, N_{pa}^n) &= -2p^2q(pe_1 + qe_2)x_1 + 2pqx_2[p(pe_1 + qe_2) - q(pe_2 + qe_3)] + 2q^2p(pe_2 + qe_3)x_3 \\
 &= 2pq[p(pe_1 + qe_2)(x_2 - x_1) + q(pe_2 + qe_3)(x_3 - x_2)].
 \end{aligned} \tag{B4}$$

Then we get

$$\beta_1 = \frac{Cov(X_{ch}, N_{pa}^t)}{Var(N_{pa}^t)} = p(x_2 - x_1) + q(x_3 - x_2); \tag{B5.a}$$

$$\beta_2 = \frac{Cov(X_{ch}, N_{pa}^n)}{Var(N_{pa}^n)} = p(pe_1 + qe_2)(x_2 - x_1) + q(pe_2 + qe_3)(x_3 - x_2). \tag{B5.b}$$

23 **Supplementary Information C:**

24 **Covariance decomposition**

The parent-offspring phenotype covariance is given by

$$\begin{aligned}
Cov(X_{ch}, X_p + X_m) &= E[X_{ch}(X_p + X_m)] - E(X_{ch}) E(X_p + X_m) \\
&= P(X_{ch} = 1, X_p + X_m = 1) + 2P(X_{ch} = 1, X_p + X_m = 2) - 2\bar{x}^2 \\
&= 1 - P(X_{ch}(X_p + X_m) = 0) + P(X_{ch} = 1, X_p + X_m = 2) - 2\bar{x}^2 \\
&= 1 - P(X_{ch} = 0) - P(X_p = 0, X_m = 0) + P(X_{ch} = 0, X_p = 0, X_m = 0) \\
&\quad + P(X_{ch} = 1, X_p = 1, X_m = 1) - 2\bar{x}^2,
\end{aligned} \tag{C1}$$

25 where

$$P(X_p = 0, X_m = 0) = P(X_p = 0)P(X_m = 0) = (1 - \bar{x})^2, \tag{C2.a}$$

$$\begin{aligned}
P(X_{ch} = 0, X_p = 0, X_m = 0) &= p^2(1 - c_1)[p(1 - x_1) + q(1 - x_2)]^2 \\
&\quad + 2pq[p(1 - x_1) + q(1 - x_2)][p(1 - x_2) + q(1 - x_3)] \\
&\quad + q^2(1 - c_3)[p(1 - x_2) + q(1 - x_3)]^2 \\
&= (1 - \bar{x})^2 - \left\{ p^2 c_1 [1 - (px_1 + qx_2)]^2 + 2pq c_2 [1 - (px_1 + qx_2)][1 - (px_2 + qx_3)] \right. \\
&\quad \left. + q^2 c_3 [1 - (px_2 + qx_3)]^2 \right\}
\end{aligned} \tag{C2.b}$$

and

$$\begin{aligned}
P(X_{ch} = 1, X_p = 1, X_m = 1) &= p^2(c_1 + 2e_1)(px_1 + qx_2)^2 + 2pq(c_2 + 2e_2)(px_1 + qx_2)(px_2 + qx_3) \\
&\quad + q^2(c_3 + 2e_3)(px_2 + qx_3)^2.
\end{aligned} \tag{C2.c}$$

Hence

$$\begin{aligned}
Cov(X_{ch}, X_p + X_m) &= \bar{x} - 2\bar{x}^2 - (p^2 c_1 + 2pq c_2 + q^2 c_3) + 2p(px_1 + qx_2)(pc_1 + qc_2) + 2q(px_2 + qx_3)(pc_2 + qc_3) \\
&\quad + 2p^2 e_1 (px_1 + qx_2)^2 + 4pq e_2 (px_1 + qx_2)(px_2 + qx_3) + 2q^2 e_3 (px_2 + qx_3)^2 \\
&= \Delta_1 + \Delta_2,
\end{aligned} \tag{C3}$$

where

$$\begin{aligned}
\Delta_1 &= 2p(px_1 + qx_2)^2 + 2q(px_2 + qx_3)^2 - 2\bar{x}^2 \\
&= 2 \left\{ p(px_1 + qx_2)^2 + q(px_2 + qx_3)^2 - [p(px_1 + qx_2) + q(px_2 + qx_3)]^2 \right\} \\
&= 2pq(px_1 + qx_2 - px_2 - qx_3)^2 \\
&= 2pq(px_1 + qx_2 - px_2 - qx_3)^2 \\
&= 2pq\beta_1^2,
\end{aligned} \tag{C4.a}$$

and

$$\begin{aligned}
\Delta_2 &= \bar{x} - \bar{c} - 2p(px_1 + qx_2)[p(x_1 - c_1) + q(x_2 - c_2)] - 2q(px_2 + qx_3)[p(x_2 - c_2) + q(x_3 - c_3)] \\
&\quad + 2p^2 e_1 (px_1 + qx_2)^2 + 4pq e_2 (px_1 + qx_2)(px_2 + qx_3) + 2q^2 e_3 (px_2 + qx_3)^2
\end{aligned} \tag{C4.b}$$

26 Again we use the equilibrium condition [11], which gives

$$\begin{aligned}
\Delta_2 &= \bar{x} - \bar{c} - 2p(px_1 + qx_2)[p(x_1 - c_1) + q(x_2 - c_2)] - 2q(px_2 + qx_3)[p(x_2 - c_2) + q(x_3 - c_3)] \\
&\quad + 2p^2 e_1 (px_1 + qx_2)^2 + 4pq e_2 (px_1 + qx_2)(px_2 + qx_3) + 2q^2 e_3 (px_2 + qx_3)^2 \\
&= e_1 [2p^2 (px_1 + qx_2) - 4p^2 (px_1 + qx_2)^2 + 2p^2 (px_1 + qx_2)^2] \\
&\quad + e_2 [2pq(px_1 + x_2 + qx_3) - 2pq(px_1 + x_2 + qx_3)^2 + 4pq(px_1 + qx_2)(px_2 + qx_3)] \\
&\quad + e_3 [2q^2 (px_2 + qx_3) - 4q^2 (px_2 + qx_3)^2 + 2q^2 (px_2 + qx_3)^2] \\
&= 2p^2 (px_1 + qx_2) [1 - (px_1 + qx_2)] e_1 \\
&\quad + 2pq \left\{ (px_1 + qx_2) [1 - (px_1 + qx_2)] + (px_2 + qx_3) [1 - (px_2 + qx_3)] \right\} e_2 \\
&\quad + 2q^2 (px_2 + qx_3) [1 - (px_2 + qx_3)] e_3 \\
&= 2p(pe_1 + qe_2)(px_1 + qx_2) [1 - (px_1 + qx_2)] + 2q(pe_2 + qe_3)(px_2 + qx_3) [1 - (px_2 + qx_3)].
\end{aligned} \tag{C5}$$

27 Supplementary Information D: Analysis of Missing Heritability

From equations (16) and (17), the parent-offspring phenotype covariance can be decomposed in the following way

$$\begin{aligned} Cov(X_{ch}, X_p + X_m) &= \Delta_1 + \Delta_2; \\ \Delta_1 &= 2pq(j_1 - j_2)^2; \\ \Delta_2 &= 2p(pe_1 + qe_2)j_1(1 - j_1) + 2q(pe_2 + qe_3)j_2(1 - j_2), \end{aligned} \quad [D1]$$

28 where $j_1 = px_1 + qx_2$, $j_2 = px_2 + qx_3$.

29 There is missing heritability when $\Delta_2 \gg \Delta_1$. Here we carry out a quantitative analysis of a simple case and derive some
30 conditions when there is missing heritability.

31 Before doing the analysis, we make some preparations. Using the equilibrium condition ([4], also supplementary equation
32 [A9]), we have

$$j_1 = px_1 + qx_2 = \frac{pB_1 + qB_2}{A} = \frac{p(1 - e_2p - 2e_3q)c_1 + q(1 - 2e_3q)c_2 + q^2e_2c_3}{A}; \quad [D2]$$

$$j_2 = px_2 + qx_3 = \frac{pB_2 + qB_3}{A} = \frac{p^2e_2c_1 + p(1 - 2e_1p)c_2 + q(1 - e_2q - 2e_1p)c_3}{A}, \quad [D3]$$

where

$$\begin{aligned} B_1 &= (1 - e_2 - 2e_3q + 2e_2e_3q^2)c_1 + 2e_1q(1 - 2e_3q)c_2 + 2e_1e_2q^2c_3; \\ B_2 &= e_2p(1 - 2e_3q)c_1 + (1 - 2e_3q)(1 - 2e_1p)c_2 + e_2q(1 - 2e_1p)c_3; \\ B_3 &= 2e_3e_2p^2c_1 + 2e_3p(1 - 2e_1p)c_2 + (1 - e_2 - 2e_1p + 2e_1e_2p^2)c_3; \\ A &= 1 - e_2 - 2e_1p - 2e_3q + 2e_1e_2p^2 + 2e_2e_3q^2 + 4e_1e_3pq. \end{aligned} \quad [D4]$$

33 Now consider the simple case, where $c_i = c + \delta c_i$; $e_i = e + \delta e_i$, with $i = 1, 2, 3$ and $c \gg \delta c_i$; $e \gg \delta e_i$. In this case, we have

$$\begin{aligned} j_1 &= \frac{c}{1 - 2e} + O_1(\delta c, \delta e) \\ j_2 &= \frac{c}{1 - 2e} + O_2(\delta c, \delta e). \end{aligned} \quad [D5]$$

Neglecting higher order terms and writing $\kappa = \frac{c}{1 - 2e}$, the criterion $\Delta_2 \gg \Delta_1$ becomes

$$\Delta_2 \approx 2e\kappa(1 - \kappa) \gg pqO(\delta c^2, \delta e^2) \approx \Delta_1. \quad [D6]$$

34 Now we assume k is of intermediate size (e.g., of the order of p or q). Then, a sufficient condition for $\Delta_2 \gg \Delta_1$ will be:
35 $e \gg O(\delta c^2, \delta e^2)$, and since we already know that $e \gg O(\delta e)$, which implies: $e \gg O(\delta e^2)$, the condition reduces to $e \gg O(\delta c^2)$.

36 This means that the magnitude of cultural effect (e) is greater than that of the variance of genetic effects (δc^2).

The following is a numerical example of this sufficient condition. Assume

$$c = 0.5; \quad e = 0.05; \quad p = 0.8; \quad q = 0.2; \quad (\delta_1, \delta_2, \delta_3) = (0.0322, 0.0223, 0.0542); \quad (\epsilon_1, \epsilon_2, \epsilon_3) = (0.0036, 0.0018, 0.0044).$$

37 Here δ 's are sampled from a uniform distribution of $(0, 0.05)$, ϵ 's are sampled from a uniform distribution on $(0, 0.005)$. Thus,
38 in this case, $e = O(\delta c) = 0.05$, which means that $e \gg O(\delta c^2)$ is satisfied, and $\frac{\Delta_1}{\Delta_1 + \Delta_2} \sim 10^{-4} \ll 1$.

39 In the main paper, we examine the case where $(c_1, c_2, c_3) = (c, c + d, c + 2d)$; $(e_1, e_2, e_3) = (e, e, e)$. From equation [9.a], it is
40 easy to see $\Delta_1 = \frac{2pqd^2}{(1-e)^2}$, and now we calculate $Cov(X_{ch}, X_p + X_m)$.

Replacing the c 's and e 's in equation [11.b] with $(c, c + d, c + 2d)$ and (e, e, e) , and $px_1 + qx_2$ and $px_2 + qx_3$ with j_1 and j_2 ,
we have

$$\Delta_2 = 2e[pj_1(1 - j_1) + qj_2(1 - j_2)]. \quad [D7]$$

41 From (8.a) we know $j_2 = j_1 + \beta_1$. Thus

$$\Delta_2 = 2e[pj_1(1 - j_1) + qj_2(1 - j_2)] = 2e[(j_1 + q\beta_1) - (j_1 + q\beta_1)^2 - pq\beta_1^2], \quad [D8]$$

42 which means

$$\begin{aligned} Cov(X_{ch}, X_p + X_m) &= \Delta_1 + \Delta_2 = 2pq\beta_1^2 + 2e[(j_1 + q\beta_1) - (j_1 + q\beta_1)^2 - pq\beta_1^2] \\ &= 2pq(1 - e)\beta_1^2 + 2e(j_1 + q\beta_1) - 2e(j_1 + q\beta_1)^2. \end{aligned} \quad [D9]$$

43 Now replace β_1 and j_1 with their corresponding expressions and we obtain

$$Cov(X_{ch}, X_p + X_m) = \frac{2pqd^2}{1 - e} + \frac{2e[c(1 - e) + qd]}{(1 - e)(1 - 2e)} - \frac{2e[c(1 - e) + qd]^2}{(1 - e)^2(1 - 2e)^2}, \quad [D10]$$

44 which depends on both d and e . (Dividing this covariance by the total variance does not change the results, since the total
45 variance equals $\frac{c_1+2qd}{1-2e}(1 - \frac{c_1+2qd}{1-2e})$.)

46 Since this case is relatively simple, it is possible to make corrections for Δ_1 . However, when e 's are different, even analogous
47 corrections are impossible and neither Δ_1 nor $Cov(X_{ch}, X_p + X_m)$ have a clear interpretation.

48 Although cultural transmission can contribute to missing heritability, absence of missing heritability does not necessarily
49 mean that cultural transmission is weak or non-existent. There exists parameter regions where cultural transmission is relative
50 strong but the two heritability estimates are roughly the same. Here we give an example: assume $(c_1, c_2, c_3) = (0.001, 0.05, 0.95)$,
51 $(e_1, e_2, e_3) = (0.02, 0.02, 0.02)$; $p = 0.9$; $q = 0.1$ In this case, cultural transmission is much more important than genetic factors
52 for 81% of people whose genotype is A_1A_1 ; equal in importance for 18% of people whose genotype is A_1A_2 ; and relatively
53 unimportant for 1% of people whose genotype is A_2A_2 . Thus, although in this case cultural transmission is very important for
54 most people in the population, $\frac{\Delta_1}{\Delta_1+\Delta_2} \approx 85\%$., which means that there is almost no missing heritability.

Supplementary Information E: On Kong et al.'s Analysis of 'Direct Effect'

In the main text, we illustrate how Kong et al.'s analysis of direct effect works for discrete trait when parents' phenotypes have the same effect on different children's genotypes. Here we provide a similar analysis for continuous traits and point out some issues in Kong et al.'s calculation.

In the Supplementary Information of Kong et al.'s paper "Effects of genetic nurture on phenotypic correlation between relatives" (ref. [S1]), they propose the following model

$$X_{ch} = (\delta + \eta)(a_m + a_p) + \eta(a_{NT_m} + a_{NT_p}) + \epsilon, \quad [E1]$$

where a_p, a_m represent the number transmitted paternal and maternal alleles and a_{NT_m}, a_{NT_p} represent the number non-transmitted maternal and paternal alleles (for a reference allele). ϵ is the sum of the intercept and the residual. $\delta + \eta$ and η are the regression coefficients and δ is what they call 'direct effect', while η represents the genetic nurturing effect.

For consistency, we transform their notation into the notation in our main text, where we have for the child's phenotype

$$X_{ch} = \beta_1(a_m + a_p) + \beta_2(a_{NT_m} + a_{NT_p}) + \delta, \quad [E2]$$

and for the mother's phenotype

$$X_m = \beta_1(a_{mp} + a_{mm}) + \beta_2(a_{mNT_m} + a_{mNT_p}) + \delta_m. \quad [E3]$$

Here a_{mp} and a_{mm} represent the number of transmitted alleles from mother's father and mother's mother, respectively, while a_{mNT_m} and a_{mNT_p} represent the number of non-transmitted alleles from mother's mother and mother's father, respectively, while δ, δ_m , and δ_p (below) are the sums of the intercepts and the residuals.

Since both (a_{mp}, a_{mm}) and (a_m, a_p) refer to the mother's genotype, we have

$$a_{mp} + a_{mm} = a_m + a_{NT_m}. \quad [E4]$$

Thus, for the mother,

$$X_m = \beta_1(a_m + a_{NT_m}) + \beta_2(a_{mNT_m} + a_{mNT_p}) + \delta_m. \quad [E5]$$

Similarly for the father we have

$$X_p = \beta_1(a_p + a_{NT_p}) + \beta_2(a_{pNT_p} + a_{pNT_m}) + \delta_p. \quad [E6]$$

Now consider a simple linear mechanistic model for a continuous trait, $X_{ch} = \alpha_1(a_m + a_p) + \alpha_2(X_m + X_p) + \epsilon$, where ϵ represents random effects. (For a more complex model, see ref [9] of the main paper.)

In this case, Kong et al.'s analysis holds and from path analysis we can see

$$\alpha_1 + \alpha_2\beta_1 = \beta_1; \quad \alpha_2\beta_1 = \beta_2. \quad [E7]$$

This implies

$$\beta_1 = \frac{\alpha_1}{1 - \alpha_2} \text{ and } \beta_2 = \frac{\alpha_1\alpha_2}{1 - \alpha_2}. \quad [E8]$$

It is easy to see that $\beta_1 - \beta_2 = \alpha_1$, which is exactly the direct genetic effect in the mechanistic model. This analysis can be extended to cases where the relationship between X_{ch} and (a_m, a_p) is not linear, but it fails when the relationship between X_{ch} and (X_m, X_p) is not linear. A simple example has α_2 different for different genotypes (gene-environment interaction in the norm of reaction, see ref. (9)). As in the discrete model, this is because the influence of genetic nurturing on the equilibrium frequency cannot be neglected when parents' phenotypes have different effects on different children's genotypes.

Another issue raised by Kong et al.'s model concerns the calculation of parent-offspring covariance and covariance between relatives; they assume that ϵ 's and a 's are independent of each other (S1). However, as we will show, this assumption of independence can be problematic even in linear cases. In order to show why this is unreasonable, we first calculate the covariance between mother and offspring without this assumption and then explain the consequences of the assumption.

From the regressions E2 and E5,

$$Cov(\delta, a_m) = Cov(\delta, a_{NT_m}) = Cov(\delta_m, a_m) = Cov(\delta_m, a_{NT_m}) = 0 \quad [E9]$$

Because of random mating, all the a 's are independent of each other. Also

$$Cov(\delta_m, a_p) = Cov(\delta_m, a_{NT_p}) = 0. \quad [E10]$$

We can then calculate the mother-offspring covariance as

$$Cov(X_{ch}, X_m) = \beta_1^2 Var(a_m) + \beta_1\beta_2 Var(a_{NT_m}) + Cov(\delta, \gamma_m), \quad [E11]$$

where

$$\gamma_m = \beta_2(a_{mNT_m} + a_{mNT_p}) + \delta_m. \quad [E12]$$

Since $Var(a_m) = Var(a_{NT_m}) = pq$, we have

$$Cov(X_{ch}, X_m) = (\beta_1^2 + \beta_1\beta_2)pq + Cov(\delta, \gamma_m), \quad [E13]$$

98 which holds without any assumption of independence. Then, if we add the assumption of independence of δ 's and a 's, we have
 99 $Cov(\delta, \gamma_m) = 0$, and hence

$$100 \quad Cov(X_{ch}, X_m) = (\beta_1^2 + \beta_1\beta_2)pq. \quad [E14]$$

101 This is the formula Kong et al. used in their calculation. However, this assumption (and simplification) basically entails
 102 that genetic nurturing is very weak. To show this for continuous traits, consider a mechanistic model for genetic nurturing:
 103 $X_{ch} = f(a_m, a_p, X_m, X_p, \epsilon)$, where ϵ represents random effects in the model (if the model is deterministic, then there is no ϵ
 104 term).

105 We then have the same regression expressions [E2] and [E5], $X_{ch} = \beta_1(a_m + a_p) + \beta_2(a_{NT_m} + a_{NT_p}) + \delta$ and $X_m =$
 106 $\beta_1(a_m + a_{NT_m}) + \gamma_m$, which imply

$$107 \quad \beta_1(a_m + a_p) + \beta_2(a_{NT_m} + a_{NT_p}) + \delta = f(a_m, a_p, \beta_1(a_m + a_{NT_m}) + \gamma_m, X_p, \epsilon). \quad [E15]$$

108 Thus

$$109 \quad \delta = f(a_m, a_p, \beta_1(a_m + a_{NT_m}) + \gamma_m, X_p, \epsilon) - [\beta_1(a_m + a_p) + \beta_2(a_{NT_m} + a_{NT_p})]. \quad [E16]$$

110 Using the fact that γ_m is independent of $a_m; a_p; a_{NT_m}; a_{NT_p}$, we have

$$111 \quad Cov(\delta, \gamma_m) = Cov(\gamma_m, f(a_m, a_p, \beta_1(a_m + a_{NT_m}) + \gamma_m, X_p, \epsilon)). \quad [E17]$$

Here γ_m is independent of all the terms in the f function except the γ_m term. For continuous traits, we use the Taylor expansion

$$112 \quad Cov(\delta, \gamma_m) = \frac{\partial f}{\partial X_m} Var(\gamma_m) + \frac{1}{2} \frac{\partial^2 f}{\partial X_m^2} Cov(\gamma_m, \gamma_m^2) + \dots \quad [E18]$$

112 For the first term, we know that

$$113 \quad Var(\gamma_m) = 2\beta_2^2 pq + Var(\delta) = 2\beta_2^2 pq + Var(\delta). \quad [E19]$$

114 The assumption that we can neglect $Cov(\delta, \gamma_m)$ can be represented by

$$115 \quad Cov(\delta, \gamma_m) \ll (\beta_1^2 + \beta_1\beta_2)pq \quad [E20]$$

116 If we assume that $Cov(\delta, \gamma_m) \sim \frac{\partial f}{\partial X_m} Var(\gamma_m)$, then [E20] implies

$$117 \quad \frac{\partial f}{\partial X_m} [2\beta_2^2 pq + Var(\delta)] \ll (\beta_1^2 + \beta_1\beta_2)pq. \quad [E21]$$

118 However, since $Var(\delta)$ depends on the form of f , this inequality will not automatically hold unless $\frac{\partial f}{\partial X_m}$ is very small, which
 119 requires weak genetic nurturing.

120 A special case of a continuous trait is the linear model. Again assume $X_{ch} = \alpha_1(a_m + a_p) + \alpha_2(X_m + X_p) + \epsilon$; from path
 121 analysis we have $\alpha_2(\gamma_m + \gamma_p) + \epsilon = \delta$ (see eq. [E2]). Together with [E19] this implies

$$122 \quad 4\alpha_2^2\beta_2^2 pq + 2\alpha_2^2 Var(\delta) + Var(\epsilon) = Var(\delta), \quad [E22]$$

123 which means $Var(\delta) = \frac{4\alpha_2^2\beta_2^2 pq + Var(\epsilon)}{1 - 2\alpha_2^2}$.

124 For the inequality $\frac{\partial f}{\partial X_m} [2\beta_2^2 pq + Var(\delta)] \ll (\beta_1^2 + \beta_1\beta_2)pq$, notice that $\frac{\partial f}{\partial X_m} = \alpha_2$. Then

$$125 \quad \alpha_2 [2\beta_2^2 pq + Var(\epsilon)] \ll (1 - 2\alpha_2^2)(\beta_1^2 + \beta_1\beta_2)pq. \quad [E23]$$

126 Use [E8] and replace β_1, β_2 with α_1, α_2 to obtain

$$127 \quad (1 - \alpha_2)^2 \alpha_2 Var(\epsilon) + 2\alpha_1^2 \alpha_2^3 pq \ll \alpha_1^2 (1 - 2\alpha_2^2) (1 + \alpha_2) pq. \quad [E24]$$

128 This inequality depends on the relative magnitude of $\alpha_1, \alpha_2, Var(\epsilon)$ and pq and thus will not automatically hold. To be more
 129 specific, the condition will only hold when $Var(\epsilon)$ is very small and α_2 is not too big.

130 We now turn to the discrete case, which is difficult to analyze directly in general. However, we already have a special case,
 131 which is the model in the main paper, where from [10],

$$132 \quad Cov(X_{ch}, X_m) = \frac{\Delta_1 + \Delta_2}{2} = (\beta_1^2 + \beta_1\beta_2)pq + \frac{\Delta_2}{2} - \beta_1\beta_2 pq. \quad [E25]$$

Thus

$$133 \quad Cov(\delta, \gamma_m) = \frac{\Delta_2}{2} - \beta_1\beta_2 pq, \quad [E26]$$

and inequality [E20] becomes

$$134 \quad \frac{\Delta_2}{2} - \beta_1\beta_2 pq \ll (\beta_1^2 + \beta_1\beta_2)pq. \quad [E27]$$

133 or

134

$$\Delta_2 \ll (2\beta_1^2 + 4\beta_1\beta_2)pq. \tag{E28}$$

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However, this can be problematic even in the simplest case. Assume $c_1 = c_2 = c_3 = c$ and $e_1 = e_2 = e_3 = e$. In this case, both β_1 and β_2 are 0, but $\Delta_2 > 0$. We have also seen that in the cases of ‘missing heritability’, $\Delta_2 \gg \Delta_1$ (or more explicitly $\Delta_2 \gg 2\beta_1^2 pq$), which makes it very unlikely that $\Delta_2 \ll (2\beta_1^2 + 4\beta_1\beta_2)pq$ (one way to make the assumption reasonable is to make the c ’s different enough and set the e ’s to be small, but this again assumes weak genetic nurturing).

In general, the assumption in [E20] cannot be automatically satisfied in both discrete and continuous cases. We have to make additional assumptions about the strength of genetic nurturing and the form of the function f in eq. [E15], including the randomness of the transmission process, assumptions that can be violated in many cases.

Supplementary Information F: Covariance and regression coefficient in the population subdivision model

Here we calculate the covariance among $N_p^t, N_m^t, N_p^n, N_m^n$ and X_{ch} and then compute the regression coefficients.

To simplify the calculation, we use the law of total covariance, which states that for random variables Y_1, Y_2, Z in the same probability space, $Cov(Y_1, Y_2) = E(Cov(Y_1, Y_2|Z)) + Cov(E(Y_1|Z), E(Y_2|Z))$. Let I be the indicator function for subpopulation with $I = i$ when the individual (and thus its parents) is in population i . Then, for the law of total covariance, set $Z = I$, $Y_1 = N_A^a, Y_2 = N_B^b$, where N_A^a and N_B^b are two different elements from the set $\{N_p^t, N_m^t, N_p^n, N_m^n\}$. Within each subpopulation, $N_p^t, N_m^t, N_p^n, N_m^n$ are mutually independent; thus $E(Cov(N_A^a, N_B^b|I)) = 0$, and

$$Cov(N_A^a, N_B^b) = Cov(E(N_A^a|I), E(N_B^b|I)). \quad [F1]$$

Since for $i = 1, 2, \dots, k$,

$$E[E(N_A^a|I)] = E[E(N_B^b|I)] = E(N_A^a) = E(N_B^b) = q; \quad E(N_A^a|I = i) = E(N_B^b|I = i) = qi; \quad P(I = i) = \alpha_i,$$

we have

$$\begin{aligned} Cov(N_A^a, N_B^b) &= Cov(E(N_A^a|I), E(N_B^b|I)) \\ &= \sum_{i=1}^k \alpha_i q_i^2 - q^2 = w - q^2 = pq - v. \end{aligned} \quad [F2]$$

(This calculation can also be made using Wright's F_{st} and heterozygosity, where the correlation between N_A^a and N_B^b can be written in another form from which the covariance can be calculated.)

In order to compute the regression coefficients, we also need to calculate $Cov(X_{ch}, N_m^t)$ and $Cov(X_{ch}, N_m^n)$. $Cov(X_{ch}, N_m^t)$ and $Cov(X_{ch}, N_m^n)$ can then be automatically found by symmetry. Similarly to [14], we again use the law of total covariance to obtain

$$Cov(X_{ch}, N_m^n) = E(Cov(X_{ch}, N_m^n|I)) + Cov(E(X_{ch}|I), E(N_m^n|I)). \quad [F3]$$

Since X_{ch} and N_m^n are independent within each subpopulation, we again have $E(Cov(X_{ch}, N_m^n|I)) = 0$ and $Cov(X_{ch}, N_m^n) = Cov(E(X_{ch}|I), E(N_m^n|I))$.

Now set $x_i = c_1 p_i^2 + 2c_2 p_i q_i + c_3 q_i^2$, and $x = \sum_{i=1}^k \alpha_i x_i$, which represent, respectively, the frequency of bar in each subpopulation and the meta-population. We have $Cov(X_{ch}, N_m^n) = Cov(E(X_{ch}|I), E(N_m^n|I)) = \sum_{i=1}^k \alpha_i q_i x_i - qx$, which we denote by K_1 . As in [16], $Cov(X_{ch}, N_m^t)$ can be decomposed as

$$Cov(X_{ch}, N_m^t) = E(Cov(X_{ch}, N_m^t|I)) + Cov(E(X_{ch}|I), E(N_m^t|I)). \quad [F4]$$

Then, since $Cov(E(X_{ch}|I), E(N_m^t|I)) = Cov(E(X_{ch}|I), E(N_m^n|I)) = \sum_{i=1}^k \alpha_i q_i x_i - qx$, all we need is $E(Cov(X_{ch}, N_m^t|I))$, as in the cultural transmission model; this is equal to $\sum_{i=1}^k \alpha_i p_i q_i [p_i(c_2 - c_1) + q_i(c_3 - c_2)]$, which we denote by K_2 .

Now we produce all the expressions needed to calculate β_1 and β_2 . From multivariate regression analysis, β_1 and β_2 are given by equations [F5]

$$\begin{aligned} Cov(X_{ch}, N_m^t) &= \beta_1 [Var(N_m^t) + Cov(N_m^t, N_p^t)] + \beta_2 [Cov(N_m^t, N_m^n) + Cov(N_m^t, N_p^n)]; \\ Cov(X_{ch}, N_m^n) &= \beta_1 [Cov(N_m^n, N_m^t) + Cov(N_m^n, N_p^t)] + \beta_2 [Var(N_m^n) + Cov(N_m^n, N_p^n)]. \end{aligned} \quad [F5]$$

Replace the covariances with the expressions above and since $Var(N_m^t) = Var(N_m^n) = pq$ we obtain

$$\begin{aligned} K_1 + K_2 &= \beta_1 (2pq - v) + \beta_2 (2pq - 2v); \\ K_1 &= \beta_1 (2pq - 2v) + \beta_2 (2pq - v), \end{aligned} \quad [F6]$$

and therefore

$$\begin{aligned} \beta_1 &= \frac{K_1 v + K_2 (2pq - v)}{(4pq - 3v)v}; \\ \beta_2 &= \frac{K_1 v - K_2 (2pq - 2v)}{(4pq - 3v)v}; \\ \beta_1 - \beta_2 &= \frac{K_2}{v}. \end{aligned} \quad [F7]$$

169 **Supplementary Information G: Recursion analysis of the assortative mating system**

170 Here we show that there is a unique fixed point which is globally stable for this assortative mating system.

171

From main text, the recursion for Q^n is

$$Q^{n+1} = (1-r)pq + \frac{(P^n c_1 + Q^n c_2)(R^n c_3 + Q^n c_2)}{[P^n c_1 + 2Q^n c_2 + R^n c_3]^2} (rP^n c_1 + 2rQ^n c_2 + rR^n c_3) \\ + \frac{[P^n(1-c_1) + Q^n(1-c_2)][R^n(1-c_3) + Q^n(1-c_2)]}{[P^n(1-c_1) + 2Q^n(1-c_2) + R^n(1-c_3)]^2} [rP^n(1-c_1) + 2rQ^n(1-c_2) + rR^n(1-c_3)]. \quad [G1]$$

Using $P^n + Q^n = p$; $R^n + Q^n = q$, the recursion can be reduced to

$$Q^{n+1} = (1-r)pq + \frac{r[Q^n(c_2 - c_1) + pc_1][Q^n(c_2 - c_3) + qc_3]}{Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3} + \frac{r[-Q^n(c_2 - c_1) + p(1 - c_1)][-Q^n(c_2 - c_3) + q(1 - c_3)]}{-Q^n(2c_2 - c_1 - c_3) + p(1 - c_1) + q(1 - c_3)}. \quad [G2]$$

172 To simplify this expression, assume $f(Q^n, c_1, c_2, c_3) = \frac{r[Q^n(c_2 - c_1) + pc_1][Q^n(c_2 - c_3) + qc_3]}{Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3}$.

173 Then

$$174 \quad Q^{n+1} = (1-r)pq + r[f(Q^n, c_1, c_2, c_3) + f(Q^n, 1 - c_1, 1 - c_2, 1 - c_3)]. \quad [G3]$$

Now we decompose $f(Q^n, c_1, c_2, c_3)$

$$f(Q^n, c_1, c_2, c_3) = \frac{[Q^n(c_2 - c_1) + pc_1][Q^n(c_2 - c_3) + qc_3]}{Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3} \\ = \frac{(c_2 - c_1)(c_2 - c_3)(Q^n)^2 + [pc_1(c_2 - c_3) + qc_3(c_2 - c_1)]Q^n + pqc_1c_3}{Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3} \\ = \frac{(c_2 - c_1)(c_2 - c_3)}{2c_2 - c_1 - c_3} Q^n + \frac{[pc_1(c_2 - c_3) + qc_3(c_2 - c_1) - \frac{(c_2 - c_1)(c_2 - c_3)(pc_1 + qc_3)}{2c_2 - c_1 - c_3}]Q^n + pqc_1c_3}{Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3} \quad [G4] \\ = \frac{(c_2 - c_1)(c_2 - c_3)}{2c_2 - c_1 - c_3} Q^n + \frac{\frac{pc_1(c_2 - c_3)^2 + qc_3(c_2 - c_1)^2}{2c_2 - c_1 - c_3} Q^n + pqc_1c_3}{Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3} \\ = \frac{(c_2 - c_1)(c_2 - c_3)}{2c_2 - c_1 - c_3} Q^n + \frac{pc_1(c_2 - c_3)^2 + qc_3(c_2 - c_1)^2}{(2c_2 - c_1 - c_3)^2} + \frac{pqc_1c_3 - \frac{[pc_1(c_2 - c_3)^2 + qc_3(c_2 - c_1)^2](pc_1 + qc_3)}{(2c_2 - c_1 - c_3)^2}}{Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3}.$$

175 Replacing (c_1, c_2, c_3) by $(1 - c_1, 1 - c_2, 1 - c_3)$, we get a similar expression for $f(Q^n, 1 - c_1, 1 - c_2, 1 - c_3)$. We then sum all
176 the terms and get

$$Q^{n+1} = (1-r)pq + r[f(Q^n, c_1, c_2, c_3) + f(Q^n, 1 - c_1, 1 - c_2, 1 - c_3)] \\ = (1-r)pq + r\left[\frac{p(c_2 - c_3)^2 + q(c_2 - c_1)^2}{(2c_2 - c_1 - c_3)^2} + \frac{A}{g(Q^n)} + \frac{B}{1 - g(Q^n)}\right], \quad [G5]$$

177 where

$$A = pqc_1c_3 - \frac{[pc_1(c_2 - c_3)^2 + qc_3(c_2 - c_1)^2](pc_1 + qc_3)}{(2c_2 - c_1 - c_3)^2} = \frac{-[pc_1(c_2 - c_3) - qc_3(c_2 - c_1)]^2}{(2c_2 - c_1 - c_3)^2}; \\ B = \frac{-[p(1 - c_1)(c_2 - c_3) - q(1 - c_3)(c_2 - c_1)]^2}{(2c_2 - c_1 - c_3)^2}; \\ g(Q^n) = Q^n(2c_2 - c_1 - c_3) + pc_1 + qc_3.$$

178 Write $\frac{dQ^{n+1}}{dQ^n} = h(Q^n)$, $M = g(Q^n)$, $a = pc_1(c_2 - c_3) - qc_3(c_2 - c_1)$, $b = p(1 - c_1)(c_2 - c_3) - q(1 - c_3)(c_2 - c_1)$, and assume
179 $p \geq q$. We now prove that $|h(x)| \leq r < 1$ for $x \in [0, q]$.

180

181 From the expression for Q^{n+1} , we get

$$h(x) = \frac{r[a - (a + b)g(x)][a - (a - b)g(x)]}{(2c_2 - c_1 - c_3)g(x)^2[1 - g(x)]^2}. \quad [G6]$$

Since $a - (a + b)g(x) = (2c_2 - c_1 - c_3)\{pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x\}$, we get

$$h(x) = \frac{r\{pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x\}[a - (a - b)g(x)]}{g(x)^2[1 - g(x)]^2}. \quad [G7]$$

182 We now prove $|a| \leq g(x); |b| \leq 1 - g(x)$ for $x \in [0, q]$.

183
184 Due to the symmetry between a and $-b$, $g(x)$ and $1 - g(x)$, and since $g(x)$ is a linear function of x , we only need to prove
185 $|a| \leq g(0)$ and $|a| \leq g(q)$.

186 The first inequality is obvious since

$$\begin{aligned} |a| &= |pc_1(c_2 - c_3) - qc_3(c_2 - c_1)| \\ &\leq pc_1|(c_2 - c_3)| + qc_3|(c_2 - c_1)| \\ &\leq pc_1 + q_3 = g(0). \end{aligned} \tag{G8}$$

187 We now prove $|a| \leq g(q)$. When $c_2 - c_1 > 0$, we have

$$\begin{aligned} g(q) &= 2c_2q + (p - q)c_1 = c_1 + 2(c_2 - c_1)q; \\ |a| &= |pc_1(c_2 - c_3) - qc_3(c_2 - c_1)| \leq c_1|p(c_2 - c_3)| + c_3(c_2 - c_1)q. \end{aligned} \tag{G9}$$

188 Comparing the coefficients of c_1 and $c_2 - c_1$ in $g(q)$ and $|a|$, we see $|a| \leq g(q)$.

189 When $c_2 - c_1 \leq 0$, we have

$$\begin{aligned} a &= pc_1(c_2 - c_3) - qc_3(c_2 - c_1) \\ &= pc_1c_2 - (p - q)c_1c_3 - qc_2c_3 \\ &\leq pc_1c_2 \\ &\leq pc_2 \\ &= qc_2 + (p - q)c_2 \\ &\leq 2qc_2 + (p - q)c_1 = g(q); \\ -a &= -[pc_1(c_2 - c_3) - qc_3(c_2 - c_1)] \\ &= -pc_1c_2 + (p - q)c_1c_3 + qc_2c_3 \\ &\leq qc_2 + (p - q)c_1 \\ &\leq 2qc_2 + (p - q)c_1 = g(q). \end{aligned} \tag{G10}$$

190 Thus, $|a| \leq g(q)$. Now we have proved $|a| \leq g(x); |b| \leq 1 - g(x)$. Notice that:

$$\begin{aligned} |a - (a - b)g(x)| &= |a[1 - g(x)] + bg(x)| \\ &\leq |a|[1 - g(x)] + |b|g(x) \\ &\leq 2g(x)[1 - g(x)]. \end{aligned} \tag{G11}$$

191 We have

$$\begin{aligned} |h(x)| &= \left| \frac{r\{pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x\}[a - (a - b)g(x)]}{g(x)^2[1 - g(x)]^2} \right| \\ &\leq \left| \frac{2\{pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x\}}{g(x)[1 - g(x)]} \right| r. \end{aligned} \tag{G12}$$

We now prove that

$$\left| \frac{2\{pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x\}}{g(x)[1 - g(x)]} \right| \leq 1. \tag{G13}$$

192 This is equivalent to proving

$$2|pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x| \leq g(x)[1 - g(x)]. \tag{G14}$$

194 The right hand of this inequality is a quadratic function opening downward, and the left hand side is a linear function.
195 Thus we only need to prove the inequality at $x = 0$ and $x = q$.

196

When $x = 0$,

$$2|pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)] \times 0 = 2pq|c_1 - c_3|;$$

$$\begin{aligned} g(0)[1 - g(0)] &= [pc_1 + qc_3][p(1 - c_1) + q(1 - c_3)] \\ &= p^2c_1(1 - c_1) + q^2c_3(1 - c_3) + 2pq(c_1 + c_3 - 2c_1c_3) \\ &\geq 2pq[c_1 + c_3 - 2\min(c_1, c_3)] \\ &= 2pq|c_1 - c_3|. \end{aligned} \tag{G15}$$

When $x = q$,

$$2|pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]q = 2q(p - q)|c_1 - c_2|;$$

$$\begin{aligned} g(q)[1 - g(q)] &= [2c_2q + (p - q)c_1][2(1 - c_2)q + (p - q)(1 - c_1)] \\ &= (p - q)^2c_1(1 - c_1) + 4c_2(1 - c_2)q^2 + 2q(p - q)[c_1(1 - c_2) + c_2(1 - c_1)] \\ &\geq 2q(p - q)(c_1 + c_2 - 2c_1c_2) \\ &\geq 2q(p - q)[c_1 + c_2 - 2\min(c_1, c_2)] \\ &= 2q(p - q)|c_1 - c_2|. \end{aligned} \tag{G16}$$

Hence we have proved

$$\frac{2\{pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x\}}{g(x)[1 - g(x)]} \leq 1. \tag{G17}$$

Thus

$$\begin{aligned} |h(x)| &\leq \left| \frac{2\{pq(c_1 - c_3) - [p(c_2 - c_3) - q(c_2 - c_1)]x\}}{g(x)[1 - g(x)]} \right|^r \\ &\leq r \in (0, 1). \end{aligned} \tag{G19}$$

197 We now prove that there is a unique fixed point in $(0, q)$. When $Q^n = 0, Q^{n+1} > 0$; when $Q^n = q, Q^{n+1} < q$; thus, there is
 198 at least one fixed point in $(0, q)$. Now we assume there are at least two fixed points, say x_1 and x_2 , assume $x_1 < x_2$. By the
 199 mean value theorem, there exists one point y in (x_1, x_2) such that $h(y) = 1$, which contradicts $|h(y)| \leq r < 1$.

200

201 Assume the fixed point is q^* . We now prove that it is globally stable. Applying the mean value theorem to two points,
 202 (Q^n, Q^{n+1}) and (q^*, q^*) , we can see there exist a point z^n such that $|\frac{Q^{n+1} - q^*}{Q^n - q^*}| = |h(z^n)| \leq r < 1$. This implies that the fixed
 203 point is globally stable.

204 **Supplementary Information H: Covariances with assortative mating**

205 Here we compute the covariance among $N_p^t, N_m^t, N_p^n, N_m^n$ and X_{ch} under assortative mating. First we identify three groups
206 according to how assorting occurs:

207

208 0. Random mating;

209 1. Assortative mating and both parents are bar;

210 2. Assortative mating and both parents are non-bar.

211

212 We use an index function I to represent the parents' assorting group. $I = 0, 1, 2$ represents parents in assorting groups
213 0, 1, 2, respectively. The frequencies of A_1 and A_2 in mating group 0 are p, q . We denote the frequencies of A_1 and A_2 in
214 assorting group 1 by p_1, q_1 , and the frequencies of A_1 and A_2 in assorting group 2 by p_2, q_2 , where

$$\begin{aligned} p_1 &= \frac{uc_1 + vc_2}{uc_1 + 2vc_2 + wc_3}, \\ p_2 &= \frac{u(1 - c_1) + v(1 - c_2)}{u(1 - c_1) + 2v(1 - c_2) + w(1 - c_3)}. \end{aligned} \quad [H1]$$

215 Before calculating the covariances, we introduce some useful notation and identities. Write

$$\begin{aligned} \alpha &= [p(c_2 - c_3) - q(c_2 - c_1)]v + pq(c_3 - c_1); \\ \beta &= (c_3 + c_1 - 2c_2)(q_1 + q_2) + 2(c_2 - c_1); \\ \bar{x} &= E(X_{ch}) = uc_1 + 2vc_2 + wc_3. \end{aligned} \quad [H2]$$

Then

$$\begin{aligned} q_1 - q &= p - p_1 \\ &= p - \frac{uc_1 + vc_2}{uc_1 + 2vc_2 + wc_3} \\ &= p - \frac{pc_1 + v(c_2 - c_1)}{pc_1 + qc_3 + v(2c_2 - c_1 - c_3)} = \frac{[p(c_2 - c_3) - q(c_2 - c_1)]v + pq(c_3 - c_1)}{\bar{x}} \\ &= \frac{\alpha}{\bar{x}}. \end{aligned} \quad [H3]$$

Similarly, we have $q_2 - q = p - p_2 = \frac{-\alpha}{1 - \bar{x}}$, which also means

$$q_1 = q + \frac{\alpha}{\bar{x}}; \quad q_2 = q - \frac{\alpha}{1 - \bar{x}}; \quad p_1 = p - \frac{\alpha}{\bar{x}}; \quad p_2 = p + \frac{\alpha}{1 - \bar{x}}.$$

216 We can replace p_1, p_2, q_1, q_2 in the equilibrium condition

$$217 \quad v = (1 - r)pq + r\bar{x}p_1q_1 + r(1 - \bar{x})p_2q_2 \quad [H4]$$

and obtain

$$\begin{aligned} v - pq &= r\bar{x} \left[\frac{(p - q)\alpha}{\bar{x}} - \frac{\alpha^2}{\bar{x}^2} \right] + r(1 - \bar{x}) \left[\frac{(q - p)\alpha}{1 - \bar{x}} - \frac{\alpha^2}{(1 - \bar{x})^2} \right] \\ &= \frac{-r\alpha^2}{\bar{x}(1 - \bar{x})}. \end{aligned} \quad [H5]$$

Now we calculate the covariances.

$$\begin{aligned} Cov(X_{ch}, N_m^t) &= E(X_{ch}N_m^t) - E(X_{ch})E(N_m^t) \\ &= vc_2 + wc_3 - (uc_1 + 2vc_2 + wc_3)q \\ &= [2p(c_2 - c_3) - 2q(c_2 - c_1)]v + pq(c_3 - c_1) \\ &= \alpha. \end{aligned} \quad [H6]$$

218 Next we calculate $Cov(N_A^a, N_B^b)$, where N_A^a and N_B^b are two different elements from $\{N_p^t, N_m^t, N_p^n, N_m^n\}$. From eq. [F2] we
219 know this is equal to $pq - v$, which also equals $\frac{r\alpha^2}{\bar{x}(1 - \bar{x})}$, as in equation [H5].
220

221 We now calculate $Cov(X_{ch}, N_m^n)$. Within the same assorting group, X_{ch} and N_m^n are conditionally independent; that
222 is, $E[Cov(X_{ch}, N_m^n | I)] = 0$; $Cov(X_{ch}, N_m^n) = Cov(E(X_{ch} | I), E(N_m^n | I))$.
223

Since

$$\begin{aligned}
E[E[X_{ch}|I]] &= E(X_{ch}) = uc_1 + 2vc_2 + wc_3; \\
E(X_{ch}|I = 0) &= p^2c_1 + 2pqc_2 + q^2c_3; \\
E(X_{ch}|I = 1) &= p_1^2c_1 + 2p_1q_1c_2 + q_1^2c_3; \\
E(X_{ch}|I = 2) &= p_2^2c_1 + 2p_2q_2c_2 + q_2^2c_3
\end{aligned} \tag{H7}$$

we have

$$\begin{aligned}
Cov(X_{ch}, N_m^n) &= rx[E(X_{ch}|I = 1) - E(X_{ch})](q_1 - q) + r(1 - x)[E(X_{ch}|I = 2) - E(X_{ch})](q_2 - q) \\
&= r\alpha[E(X_{ch}|I = 1) - E(X_{ch}|I = 2)]
\end{aligned} \tag{H8}$$

Using the expression $q_1 = q + \frac{\alpha}{\bar{x}}$; $q_2 = q - \frac{\alpha}{1-\bar{x}}$ and the definitions in [H2], we have

$$\begin{aligned}
E(X_{ch}|I = 1) - E(X_{ch}|I = 2) &= (p_1^2c_1 + 2p_1q_1c_2 + q_1^2c_3) - (p_2^2c_1 + 2p_2q_2c_2 + q_2^2c_3) \\
&= [(c_3 + c_1 - 2c_2)q_1^2 + 2(c_2 - c_1)q_1 + c_1] - [(c_3 + c_1 - 2c_2)q_2^2 + 2(c_2 - c_1)q_2 + c_1] \\
&= (q_1 - q_2)[(c_3 + c_1 - 2c_2)(q_1 + q_2) + 2(c_2 - c_1)] \\
&= \frac{\alpha\beta}{\bar{x}(1-\bar{x})}.
\end{aligned} \tag{H9}$$

224 Thus, $Cov(X_{ch}, N_m^n) = \frac{r\alpha^2\beta}{\bar{x}(1-\bar{x})} = \beta(pq - v) = \beta Cov(N_A^a, N_B^b)$.

225 Supplementary Information J: Causal analysis

226 The last section (A unified causal framework) of the main paper makes heavy use of previous studies in causal analysis. Here
 227 we provide a short introduction to the key notions related to this analysis as well as proofs to some of our results.

228 In this framework, causal relationships can be represented by graphs, where vertices (or nodes) correspond to random
 229 variables (later we use vertices/nodes/variables interchangeably), and edges will represent relationships between the random
 230 variables. A directed edge represents a causal relationship if all the edges are directed, in which case, the relationship can also
 231 be represented by a pair of vertices. A directed acyclic graph (DAG), which is a common setting in causal analysis, is a graph
 232 in which there are no cycles. Sometimes, as in our model, there are also bidirected edges, which represent the existence of
 233 hidden confounders between the variables. A path is a sequence of edges such that each edge starts with the vertex ending
 234 the preceding edge. A directed path is a path where each edge is an arrow that points from the first to the second vertex of
 235 the pair. We call Y a parent of X if there exist a directed edge from Y to X , or conversely, X is a child of Y . We call Z an
 236 ancestor of X if there is a directed path from Z to X , and conversely, X is a descendant of Z .

237 Consider a DAG with nodes X_1, X_2, \dots, X_n and denote the set of parents of X_i by Pa_i or $Pa(X_i)$, and the set of ancestors
 238 of X_i by An_i or $An(X_i)$. Then the causal information of this DAG is encoded in the decomposition $P(X_1, X_2, \dots, X_n) =$
 239 $\prod_i P(X_i | Pa_i)$. ($P(X_1, X_2, \dots, X_n)$ is said to be compatible with a DAG if such a decomposition holds.) This decomposition
 240 guarantees that the model is Markovian, i.e., Pa_i screens off all the effect of X_i 's ancestors, which means $P(X_i | Pa_i) =$
 241 $P(X_i | Pa_i, An_i - Pa_i)$. Formally, a Markovian model M is defined as $(V, G, P(X_i | Pa_i))$, where V is the set of variables, G is a
 242 DAG, and $P(X_i | Pa_i)$ are the conditional probabilities that make up the joint distribution of X_1, X_2, \dots, X_n .

243 Another way to look at a DAG is a functional model perspective, which assumes that $X_i = f_i(Pa_i, U_i)$, where f_i is a
 244 function and U_i is a set of hidden variables which screen off all the randomness between X_i and Pa_i . In the setting of a
 245 DAG, U_i 's are jointly independent so that the model is Markovian. Because U_i 's are jointly independent, $P(X_1, X_2, \dots, X_n) =$
 246 $\sum_{U_i} \prod_i P(X_i | Pa_i, U_i) = \prod_i P(X_i | Pa_i)$. Thus these two ways of looking at the same causal diagram are obviously equivalent
 247 in the setting of a DAG, i.e., for each set of $P(X_i | Pa_i)$, there is a set of f_i 's and U_i 's that generate the same joint distribution,
 248 and vice versa.

249 A functional model can be further extended to a causal diagram with both unidirected and bidirected edges, where it is no
 250 longer assumed that U_i 's are jointly independent. Such models are called 'semi-Markovian', since X_i is still determined by
 251 Pa_i and U_i , and the joint distribution is determined once the joint distribution of U_i 's is known. Similarly to a Markovian
 252 model represented by a DAG, a semi-Markovian functional model has its probabilistic equivalent given by $P(X_1, X_2, \dots, X_n) =$
 253 $\prod_i P(X_i | Pa_i, U_i)$, where U_i 's are not necessarily all independent. The proof of such equivalency can be found in Druzdze and
 254 Simon (1993) (S2). Formally, the probabilistic model can be represented as $(V, U, G_{VU}, P(X_i | Pa_i, U_i))$, where V is the set
 255 of observable variables, $U = \cup_i U_i$ is the set of hidden variables, and G_{VU} is the graph with nodes in both V and U . The
 256 corresponding graph G for observed variables can then be obtained by adding bidirected edges between two nodes if the two
 257 variables are confounded by variables in U ; i.e. there exists a path $X_i \leftarrow \dots \leftarrow U_k \rightarrow \dots \rightarrow X_j$, where all nodes except X_i and
 258 X_j in the path are in U . The corresponding functional model can be represented as (V, U, G_{VU}, f_i) . Because of the equivalency
 259 mentioned above, we choose one of the two perspectives (probabilistic or functional) for convenience in this section. A model
 260 can either be referred to as $(V, U, G, P(X_i | Pa_i, U_i))$ or as (V, U, G_{VU}, f_i) , depending on the context.

261 We now introduce some of the graphical tools for describing and analyzing the relationships between the variables we studied
 262 in the main paper. First, we introduce the idea of d -separation in a semi-Markov model in the presence of bidirected edges,
 263 and then introduce the notions of a front-door path and a back-door path.

264 A path p is said to be d -separated (or blocked) by a set of vertices ($S7$) if and only if either

- 265 • p contains one of the following three patterns of edges:
 266 $I \rightarrow M \rightarrow J, I \leftrightarrow M \rightarrow J, I \leftarrow M \rightarrow J$, such that M is in Z .
- 267 • p contains one of the following three patterns of edges:
 268 $I \rightarrow M \leftarrow J, I \leftrightarrow M \leftarrow J, I \leftrightarrow M \leftrightarrow J$ such that M is not in Z and no descendant of M is in Z .

269 Note here that Z can be the empty set, in which case p is said to be blocked (by the empty set) if and only if there exists
 270 one of the following three edge patterns: $I \rightarrow M \leftarrow J, I \leftrightarrow M \leftarrow J, I \leftrightarrow M \leftrightarrow J$. p is said to be active if it is not blocked.

271 A front-door path from X to Y is a path starting with an edge pointing away from X , i.e. a path starting with $X \rightarrow \dots$.
 272 An active front-door path has the form $X \rightarrow \dots \rightarrow \dots \rightarrow Y$, and is also called a causal path.

273 A back-door -path from X to Y is a path starting with an edge pointing to X , i.e. a path starting with $X \leftarrow \dots$. An active back-
 274 door path is a backdoor path such that there is no collider structure. i.e. $\rightarrow M \leftarrow$, which means no $I \rightarrow M \leftarrow J, I \leftrightarrow M \leftarrow J$
 275 or $I \leftrightarrow M \leftrightarrow J$. Such paths are also called non-causal paths.

276 For a path from X to Y to be active, there exists a probability dependence between X and Y , i.e. $P(Y) \neq P(Y|X)$.
 277 However, such dependence can be either causal, through a front-door path, or non-causal, through back-door paths. Thus, to
 278 identify causal effects, we need to cancel non-causal effects. It is then natural to ask whether causal effects can be identified
 279 using observed data and, if they can be identified, how can this be done. To answer these questions, we introduced a
 280 systematic approach developed by Pearl (S3), namely, the *do* operator, and the identification of an interventional distribution
 281 for semi-Markovian models (S5, S6).

282 Recall the functional causal model M with n variables, X_1, X_2, \dots, X_n , and $X_i = f_i(Pa_i, U_i)$. $P(X_j = x_j | do(X_i = x_i))$ in
 283 the graph G , where $P_M(X_j = x_j | do(X_i = x_i))$, is defined as $P(X_j = x_j)$ in model M' , which we denote by $P_{M'}(X_j = x_j)$.

284 Here G' is a new model where X_i is fixed at x_i ; i.e., we change $X_i = f_i(Pa_i, U_i)$ to $X_i = x_i$. This can be understood as
 285 removing all the edges pointing toward X_i and make it fixed. For other sets of variables Y and Z , we can similarly define
 286 $P(Y|do(Z))$. The problem is then to identify this expression using observed data, which naturally leads to the definition of
 287 identifiability (see Tian and Pearl (S5)):

288 The causal effect of a set of variables T on a disjoint set of variables S is said to be identifiable from a graph G (of the
 289 observed variables) if the quantity $P(S|do(T))$ can be uniquely calculated from the positive joint distribution of the observed
 290 variables, i.e. $P_{M_1}(S|do(T)) = P_{M_2}(S|do(T))$ for any two models with graph G of observed variables and their joint distribution.

291 Full graphical criteria have been obtained for the identifiability of causal effects in semi-Markovian models, as well as the
 292 procedure for identifying such causal effects (S5, S6). Using the methods in these papers (as well as the additional definition of
 293 $P(X_{pa}|T_{pa}, NT_{pa}, G_{pa})$, equation [20] in the main paper), all the expressions used in the main paper, such as those in equation
 294 [22] and [23] are identifiable and can be calculated according to the procedure. (Of course, in empirical cases, there will be
 295 more restrictions on the potential distributions, which means that the counterexamples used to illustrate the non-identifiability
 296 of some graphs may be problematic. However, these restrictions will not influence the expression of a causal effect when it is
 297 identifiable.)

298 In the process of determining identifiability of a causal effect, or calculating a causal effect if it is identifiable, a very useful
 299 technique is the *do*-calculus (S2). Here we show a naive version of it, which can be expressed by the following three rules.

- 300 • $P(Y|do(X), Z, W) = P(Y|do(X), Z)$ if Z blocks all the paths from W to Y .
- 301 • $P(Y|do(X), Z) = P(Y|X, Z)$ if Z blocks all back-door paths from X to Y . (We also say Z satisfies the back-door criteria.)
- 302 • $P(Y|do(X), Z) = P(Y|Z)$ if Z blocks all causal paths from X to Y .

303 These rules will be used later in this section to prove the results at the end the main paper. First, however, we introduce by
 304 introducing path-specific effects, natural direct effects and natural indirect effects.

305 Having introduced the *do* operator, we now use it to calculate the total causal effect of a variable X on another variable
 306 Y , represented as $P(Y = y|X = x') - P(Y = y|X = x)$. (We can average over Y if we want to calculate the expected causal
 307 effect.) However, such a causal effect is the joint effect of all the causal paths from X to Y . A natural question then is whether
 308 we can identify the causal effect in each path, i.e., the path-specific effects.

309 An intuitive understanding of path-specific effect is that it is the effect of only changing X from x to x' for the path under
 310 study while keeping other paths unchanged. Applying this to mediation analysis, the 'natural direct effect', an extension of
 311 'direct effect' in path analysis, can be defined as the path specific effect of the 'direct path'. The 'natural indirect effect', an
 312 extension of 'indirect effect', can be defined as the path specific effect of the path mediated by the mediator. (The sign and
 313 direction of change varies for 'natural direct effect' and 'natural indirect effect', but both can be viewed as path specific effects.)
 314 Using this intuition, we can see how equations [24] and [25] work. These can be viewed as the path specific effect of path 1'
 315 from $T_{pa} = x$ to $T_{pa} = y$ and the opposite path specific effect of path 4' from $T_{pa} = y$ to $T_{pa} = x$. Such a decomposition is also
 316 called the 'mediation formula' (S4). (For a formal definition of path specific effects using counterfactuals and the corresponding
 317 identification criteria, see Avin et al. (S8))

318 Now refer to the casual diagram in the main paper (repeated here as Figure S1, which corresponds to Figure 1 in the main
 319 paper). We turn to proving the results at the end of the main paper, namely, to show that when equations [29–33] hold, the
 320 quantities in [26], [27], [28] are the same.

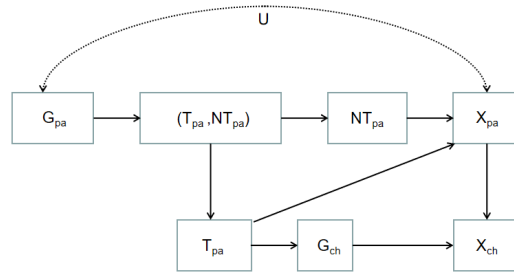


Fig. S1. A unified causal diagram for genetic nurturing, population subdivision and assortative mating

321 The results can be proven using *do* calculus and the fact that T_{pa} and NT_{pa} are independent. To show how this works, we
 322 explain the derivation of the expression for $P(X_{ch}|do(NT_{pa} = x))$ and some key subsequent steps. The rest of the proof should
 323 be easy to understand.

324 Notice that for equations [26], [27] and [28], we can always decompose the change from $x = (x_m, x_p)$ to $y = (y_m, y_p)$ into
 325 two steps: the first step changes mother's genotype with father's genotype fixed, i.e., changes from (x_m, x_p) to (y_m, x_p) ; and
 326 the second changes father's genotype with mother's genotype fixed, i.e., changes from (y_m, x_p) to (y_m, y_p) . Since the two steps

327 are similar, we only need to prove that the statement is true for the first step. The second step then follows naturally, and so
 328 does the general statement.

Thus, without loss of generality, we assume $x = (x_m, z)$ and $y = (y_m, z)$, and prove the statement in this case.

$$\begin{aligned}
 & P(X_{ch}|do(NT_{pa} = x)) \\
 &= \sum_{T_{pa}} P(X_{ch}|T_{pa}, do(NT_{pa} = x))P(T_{pa}|do(NT_{pa} = x)) \quad (\text{Law of total probability}) \\
 &= \sum_{T_{pa}} P(X_{ch}|T_{pa}, do(NT_{pa} = x))P(T_{pa}) \quad (\text{Rule 3 of } do\text{-calculus}) \\
 &= \sum_{\substack{T_{pa} \\ X_{pa}}} P(X_{ch}|T_{pa}, X_{pa}, do(NT_{pa} = x))P(X_{pa}|T_p, do(NT_{pa} = x))P(T_{pa}) \\
 & \quad \quad \quad (\text{Law of total probability}) \\
 &= \sum_{\substack{T_{pa} \\ X_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(X_{pa}|T_{pa}, do(NT_{pa} = x))P(T_{pa}) \\
 & \quad \quad \quad (\text{Rule 3 of } do\text{-calculus}) \tag{J1} \\
 &= \sum_{\substack{T_{pa} \\ X_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(X_{pa}|T_{pa}, do(NT_{pa} = x), G_{pa})P(T_{pa})P(G_{pa}|T_{pa}, do(NT_{pa} = x)) \\
 & \quad \quad \quad (\text{Law of total probability}) \\
 &= \sum_{\substack{T_{pa} \\ X_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(X_{pa}|T_{pa}, NT_{pa} = x, G_{pa})P(T_{pa})P(G_{pa}|T_{pa}, do(T_{pa} = x)) \\
 & \quad \quad \quad (\text{Rule 2 of } do\text{-calculus}) \\
 &= \sum_{\substack{T_{pa} \\ X_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(X_{pa}|T_{pa}, NT_{pa} = x, G_{pa})P(T_{pa})P(G_{pa}|T_{pa}) \\
 & \quad \quad \quad (\text{Rule 3 of } do\text{-calculus})
 \end{aligned}$$

Recall that

$$\begin{aligned}
 & P(X_m|T_m, NT_m = y_m, G_m) - P(X_m|T_m, NT_m = x_m, G_m) = F_1(X_m, y_m, x_m); \\
 & P(X_m|T_m = y_m, NT_m, G_m) - P(X_m|T_m = x_m, NT_m, G_m) = F_1(X_m, y_m, x_m); \\
 & P(X_p|T_p, NT_p = y_p, G_p) - P(X_p|T_p, NT_p = x_p, G_p) = F_{1'}(X_p, y_p, x_p); \\
 & P(X_p|T_p = y_p, NT_p, G_p) - P(X_p|T_p = x_p, NT_p, G_p) = F_{1'}(X_p, y_p, x_p); \\
 & P(X_{ch}|T_{pa} = y, X_{pa}) - P(X_{ch}|T_{pa} = x, X_{pa}) = F_2(X_{ch}, y, x).
 \end{aligned} \tag{J2}$$

Then

$$\begin{aligned}
 & P(X_{ch}|do(NT_{pa} = y)) - P(X_{ch}|do(NT_{pa} = x)) \\
 &= \sum_{\substack{T_{pa} \\ X_{pa} \\ G_{pa}}} \left\{ P(X_{ch}|T_{pa}, X_{pa}) \left[P(X_{pa}|T_{pa}, NT_{pa} = y, G_{pa}) - P(X_{pa}|T_{pa}, NT_{pa} = x, G_{pa}) \right] \right. \\
 & \quad \quad \quad \left. \times P(T_{pa})P(G_{pa}|T_{pa}) \right\} \tag{J3} \\
 &= \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{T_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(T_{pa}, G_{pa})P(X_p|T_p, NT_p = z, G_p)
 \end{aligned}$$

For the transmitted alleles, we have

$$\begin{aligned}
& P(X_{ch}|do(T_{pa} = x)) \\
&= \sum_{NT_{pa}} P(X_{ch}|NT_{pa}, do(T_{pa} = x))P(NT_{pa}|do(T_{pa} = x)) \\
&= \sum_{NT_{pa}} P(X_{ch}|NT_{pa}, do(T_{pa} = x))P(NT_{pa}) \\
&= \sum_{\substack{NT_{pa} \\ X_{pa}}} P(X_{ch}|NT_{pa}, X_{pa}, do(T_{pa} = x))P(X_{pa}|NT_{pa}, do(T_{pa} = x))P(NT_{pa}) \\
&= \sum_{\substack{NT_{pa} \\ X_{pa}}} P(X_{ch}|T_{pa} = x, X_{pa})P(X_{pa}|NT_{pa}, do(T_{pa} = x))P(NT_{pa}) \tag{J4} \\
&= \sum_{\substack{NT_{pa} \\ X_{pa} \\ G_{pa}}} \left\{ P(X_{ch}|T_{pa} = x, X_{pa})P(X_{pa}|NT_{pa}, do(T_{pa} = x), G_{pa})P(NT_{pa}) \right. \\
&\quad \left. \times P(G_{pa}|NT_{pa}, do(T_{pa} = x)) \right\} \\
&= \sum_{\substack{NT_{pa} \\ X_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa} = x, X_{pa})P(X_{pa}|NT_{pa}, T_{pa} = x, G_{pa})P(NT_{pa}, G_{pa}).
\end{aligned}$$

Thus,

$$\begin{aligned}
& P(X_{ch}|do(T_{pa} = y)) - P(X_{ch}|do(T_{pa} = x)) \\
&= \sum_{\substack{NT_{pa} \\ X_{pa} \\ G_{pa}}} \left\{ P(X_{ch}|T_{pa} = y, X_{pa}) [P(X_{pa}|NT_{pa}, T_{pa} = y, G_{pa}) - P(X_{pa}|NT_{pa}, T_{pa} = x, G_{pa})] \right. \\
&\quad \left. \times P(NT_{pa}, G_{pa}) \right\} \\
&+ \sum_{\substack{NT_{pa} \\ X_{pa} \\ G_{pa}}} \left\{ [P(X_{ch}|T_{pa} = y, X_{pa}) - P(X_{ch}|T_{pa} = x, X_{pa})] \right. \\
&\quad \left. \times P(X_{pa}|NT_{pa}, T_{pa} = x, G_{pa})P(NT_{pa}, G_{pa}) \right\} \\
&= \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{NT_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa} = y, X_{pa})P(NT_{pa}, G_{pa})P(X_p|T_p = z, NT_p, G_p) \tag{J5} \\
&\quad + F_2(X_{ch}, y_m, x_m) \sum_{\substack{NT_{pa} \\ X_{pa} \\ G_{pa}}} P(X_{pa}|NT_{pa}, T_{pa} = x, G_{pa})P(NT_{pa}, G_{pa}) \\
&= \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{NT_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa} = y, X_{pa})P(NT_{pa}, G_{pa})P(X_p|T_p = z, NT_p, G_p) + F_2(X_{ch}, y, x)
\end{aligned}$$

Since $P(X_{ch}|T_{pa} = y, X_{pa}) = F_2(X_{ch}, y, \alpha) + P(X_{ch}|T_{pa} = \alpha, X_{pa})$ for any $\alpha = (\alpha_1, \alpha_2)$, and using the fact that

$\sum_{X_m} F_1(X_m, y_m, x_m) = 1 - 1 = 0$ we have

$$\begin{aligned}
& \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{NT_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa} = y, X_{pa})P(NT_{pa}, G_{pa})P(X_p|T_p = z, NT_p, G_p) \\
&= \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{\alpha \\ G_{pa}}} P(X_{ch}|T_{pa} = y, X_{pa})P(NT_{pa} = \alpha, G_{pa})P(X_p|T_p = z, NT_p = \alpha_2, G_p) \\
&= \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{\alpha \\ G_{pa}}} P(X_{ch}|T_{pa} = y, X_{pa})P(T_{pa} = \alpha, G_{pa})P(X_p|NT_p = z, T_p = \alpha_2, G_p) \\
&= \sum_{\substack{X_p \\ \alpha \\ G_{pa}}} F_2(X_{ch}, y, \alpha)P(T_{pa} = \alpha, G_{pa})P(X_p|NT_p = z, T_p = \alpha_2, G_p) \sum_{X_m} F_1(X_m, y_m, x_m) \\
&\quad + \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{\alpha \\ G_{pa}}} P(X_{ch}|T_{pa} = \alpha, X_{pa})P(T_{pa} = \alpha, G_{pa})P(X_p|NT_p = z, T_p = \alpha_2, G_p) \\
&= \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{\alpha \\ G_{pa}}} P(X_{ch}|T_{pa} = \alpha, X_{pa})P(T_{pa} = \alpha, G_{pa})P(X_p|NT_p = z, T_p = \alpha_2, G_p) \\
&= \sum_{X_{pa}} F_1(X_m, y_m, x_m) \sum_{\substack{T_{pa} \\ G_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(T_{pa}, G_{pa})P(X_p|T_p, NT_p = z, G_p)
\end{aligned} \tag{J6}$$

This means that expression [26] is

$$\begin{aligned}
& [P(X_{ch}|do(T_{pa} = y)) - P(X_{ch}|do(T_{pa} = x))] \\
& \quad - [P(X_{ch}|do(NT_{pa} = y)) - P(X_{ch}|do(NT_{pa} = x))] \\
& = F_2(X_{ch}, y, x).
\end{aligned} \tag{J7}$$

Similarly, expression [28] can be represented as

$$\begin{aligned}
& F_2(X_{ch}, y, x) \sum_{\substack{NT_{pa} \\ X_{pa} \\ G_{pa}}} P(X_{pa}|NT_{pa}, T_{pa} = x, G_{pa})P(NT_{pa}, G_{pa}) \\
& = F_2(X_{ch}, y, x).
\end{aligned} \tag{J8}$$

329 Thus, we only need to prove that the difference in [27] is $F_2(X_{ch}, y, x)$.

Similarly to the previous analysis, we can write

$$\begin{aligned}
& P(X_{ch}|NT_{pa} = x) \\
& = \sum_{T_{pa}} P(X_{ch}|T_{pa}, NT_{pa} = x)P(T_{pa}|NT_{pa} = x) \\
& = \sum_{\substack{T_{pa} \\ X_{pa}}} P(X_{ch}|T_{pa}, X_{pa}, NT_{pa} = x)P(X_{pa}|T_{pa}, NT_{pa} = x)P(T_{pa}) \\
& \quad \text{(Law of total probability, independence of } T_{pa} \text{ and } NT_{pa}) \\
& = \sum_{\substack{T_{pa} \\ X_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(X_{pa}|T_{pa}, NT_{pa} = x)P(T_{pa}) \quad \text{(Rule 1 of } do\text{-calculus).}
\end{aligned} \tag{J9}$$

Thus

$$\begin{aligned}
& P(X_{ch}|NT_{pa} = y) - P(X_{ch}|NT_{pa} = x) \\
& = \sum_{\substack{T_{pa} \\ X_{pa}}} P(X_{ch}|T_{pa}, X_{pa})P(T_{pa})[P(X_{pa}|T_{pa}, NT_{pa} = y) - P(X_{pa}|T_{pa}, NT_{pa} = x)].
\end{aligned} \tag{J10}$$

330 This expression will be in general different from that of $P(X_{ch}|do(NT_{pa} = y)) - P(X_{ch}|do(NT_{pa} = x))$ in equation [J3],
331 which means Kong et al.'s estimate of indirect effect is biased. Actually, this bias can be shown even in the simplest example
332 represented by equations [9a], [9b] and [9c], where the indirect effect estimated by Kong et al. would be $\beta_2 = \frac{ed}{1-e}$, while the
333 true indirect effect is ed . (This again proves that Kong et al.'s method only works when genetic nurturing is weak, and we can
334 assume $1 - e \approx 1$ and $\beta_2 \approx ed$.)

For transmitted alleles, we have

$$\begin{aligned}
& P(X_{ch}|T_{pa} = x) \\
&= \sum_{NT_{pa}} P(X_{ch}|NT_{pa}, T_{pa} = x)P(NT_{pa}|T_{pa} = x) \\
&= \sum_{NT_{pa}} P(X_{ch}|NT_{pa}, T_{pa} = x)P(NT_{pa}) \quad (\text{Independence of } NT_{pa} \text{ and } T_{pa}) \\
&= \sum_{\substack{NT_{pa} \\ X_{pa}}} P(X_{ch}|NT_{pa}, X_{pa}, T_{pa} = x)P(X_{pa}|NT_{pa}, T_{pa} = x)P(NT_{pa}) \\
&= \sum_{\substack{NT_{pa} \\ X_{pa}}} P(X_{ch}|X_{pa}, T_{pa} = x)P(X_{pa}|NT_{pa}, T_{pa} = x)P(NT_{pa}) \quad (\text{Rule 1 of } do\text{-calculus})
\end{aligned} \tag{J11}$$

Thus

$$\begin{aligned}
& P(X_{ch}|T_{pa} = y) - P(X_{ch}|T_{pa} = x) \\
&= F_2(X_{ch}, y, x) \sum_{\substack{NT_{pa} \\ X_{pa}}} P(X_{pa}|NT_{pa}, T_{pa} = y)P(NT_{pa}) \\
&+ \sum_{X_{pa}} P(X_{ch}|T_{pa} = x, X_{pa}) \sum_{NT_{pa}} P(NT_{pa})[P(X_{pa}|NT_{pa}, T_{pa} = y) - P(X_{pa}|NT_{pa}, T_{pa} = x)] \\
&= F_2(X_{ch}, y, x) + \sum_{X_{pa}} P(X_{ch}|T_{pa} = x, X_{pa}) \sum_{T_{pa}} P(T_{pa})[P(X_{pa}|T_{pa}, NT_{pa} = y) - P(X_{pa}|T_{pa}, NT_{pa} = x)] \\
&= F_2(X_{ch}, y, x) + \sum_{X_{pa}} P(X_{ch}|T_{pa} = x, X_{pa}) \sum_{\alpha} P(T_{pa} = \alpha)[P(X_{pa}|T_{pa} = \alpha, NT_{pa} = y) - P(X_{pa}|T_{pa} = \alpha, NT_{pa} = x)] \\
&= F_2(X_{ch}, y, x) + \sum_{\substack{\alpha \\ X_{pa}}} P(X_{ch}|T_{pa} = \alpha, X_{pa})P(T_{pa} = \alpha)[P(X_{pa}|T_{pa} = \alpha, NT_{pa} = y) - P(X_{pa}|T_{pa} = \alpha, NT_{pa} = x)] \\
&\quad + \sum_{\substack{\alpha \\ X_{pa}}} F_2(X_{ch}, x, \alpha)P(T_{pa} = \alpha)[P(X_{pa}|T_{pa} = \alpha, NT_{pa} = y) - P(X_{pa}|T_{pa} = \alpha, NT_{pa} = x)] \\
&= F_2(X_{ch}, y, x) + P(X_{ch}|NT_{pa} = y) - P(X_{ch}|NT_{pa} = x) \\
&\quad + \sum_{\alpha} F_2(X_{ch}, x, \alpha)P(T_{pa} = \alpha) \sum_{X_{pa}} [P(X_{pa}|T_{pa} = \alpha, NT_{pa} = y) - P(X_{pa}|T_{pa} = \alpha, NT_{pa} = x)] \\
&= F_2(X_{ch}, y, x) + P(X_{ch}|NT_{pa} = y) - P(X_{ch}|NT_{pa} = x).
\end{aligned} \tag{J12}$$

335 and $F_2(X_{ch}, y, x)$ is the difference in [27], which completes the proof.

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