

**Supplementary information**

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**Distinction between the effects of parental and fetal genomes on fetal growth**

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## Supplementary Information

### Distinction between the effects of parental and fetal genomes on fetal growth

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Supplementary Note

## Meta-analysis

To meta-analyze  $n$  variants using a fixed-effects model we performed the following analysis. Assume the effect of variant  $i$  is estimated as  $\beta_i$  and the standard error of the estimate is  $\sigma_i^2$ . In the meta-analysis we treat the effect estimate of the variant as an observation from a normal distribution with some true mean  $\mu_i$  and variance  $\sigma_i^2$ :  $\beta_i \sim \mathcal{N}(\mu_i, \sigma_i^2)$ . Then the log-likelihood of the meta-data is:

$$l(\mu_1, \mu_2, \dots, \mu_n) = -\frac{1}{2} \sum_{i=1}^n \frac{1}{\sigma_i^2} (\beta_i - \mu_i)^2.$$

Assuming the effects are all truly the same,  $\mu = \mu_1 = \mu_2 = \dots = \mu_n$ , then the maximum likelihood estimate of  $\mu$  is

$$\hat{\mu} = \frac{\sum_{i=1}^n \frac{1}{\sigma_i^2} \beta_i}{\sum_{i=1}^n \frac{1}{\sigma_i^2}}.$$

The likelihood ratio statistic for testing if  $\mu \neq 0$  against  $\mu = 0$  has a  $\chi^2$ -distribution with one degree of freedom:

$$2(l(\hat{\mu}, \hat{\mu}, \dots, \hat{\mu}) - l(0, 0, \dots, 0)) \sim \chi_1^2.$$

To test for heterogeneity we test the alternative hypothesis of all the  $\mu$ s being different against them all being the same. Under this alternative hypothesis the maximum likelihood estimate of  $\mu_i$  is  $\beta_i$  and the following likelihood ratio statistic has a  $\chi^2$ -distribution with  $n - 1$  degrees of freedom:

$$2(l(\beta_1, \beta_2, \dots, \beta_n) - l(\hat{\mu}, \hat{\mu}, \dots, \hat{\mu})) = 0 - 2 \left( -\frac{1}{2} \sum_{i=1}^n \frac{1}{\sigma_i^2} (\beta_i - \hat{\mu})^2 \right) = \sum_{i=1}^n \frac{1}{\sigma_i^2} (\beta_i - \hat{\mu})^2 \sim \chi_{n-1}^2.$$

## Maximum likelihood estimation of paternal, maternal and non-transmitted maternal effects

In order to estimate paternal, maternal and non-transmitted maternal effects we use a maximum likelihood framework and estimated parameters with the EM algorithm. Let:

$g_{Pi}$  = allele transmitted to proband  $i$  from father

$g_{Mi}$  = allele transmitted to proband  $i$  from mother

$g_{Ni}$  = the allele of the mother not transmitted to proband  $i$

$$g_i^T = (1, g_{Pi}, g_{Mi}, g_{Ni})$$

$y_i$  = birth weight of proband

$\beta$  = column vector of  $p$  parameters

$$h_{Pi} = p(g_{Pi} = 1)$$

$$h_{Mi} = p(g_{Mi} = 1)$$

$$h_{Ni} = p(g_{Ni} = 1)$$

$Q$  is a  $p \times 4$  matrix specifying the genetic model

$$y_i \sim \mathcal{N}(\beta^T Q g_i, \sigma^2)$$

The log-likelihood is then

$$\begin{aligned}
 l(\beta, \sigma^2) &= \sum_{i=1}^n -\frac{1}{2} \log(\sigma^2) - \frac{1}{2\sigma^2} (y_i - \beta^T Q g_i)^2 \\
 \tilde{l}(\beta, \sigma^2) &= E(l(\beta, \sigma^2)) = -\frac{1}{2} \left[ n \log(\sigma^2) + \frac{1}{\sigma^2} \sum_{i=1}^n E(y_i - \beta^T Q g_i)^2 \right] = \\
 &= -\frac{1}{2} \left[ n \log(\sigma^2) + \frac{1}{\sigma^2} \sum_{i=1}^n (y_i^2 - 2\beta^T Q E(g_i) y_i + \beta^T Q E(g_i g_i^T) Q^T \beta) \right] = \\
 &= -\frac{1}{2} \left[ n \log(\sigma^2) + \frac{1}{\sigma^2} (S_{YY} - 2\beta^T \gamma + \beta^T G \beta) \right]
 \end{aligned}$$

where

$$\begin{aligned}
 S_{YY} &= \sum_{i=1}^n y_i^2 \\
 \gamma &= Q \sum_{i=1}^n E(g_i) y_i \\
 G &= Q \left( \sum_{i=1}^n E(g_i g_i^T) \right) Q^T
 \end{aligned}$$

We have that

$$\begin{aligned}
 E g_i &= (1, E g_{Pi}, E g_{Mi}, E g_{Ni}) \\
 E(g_i g_i^T) &= \begin{bmatrix} 1 & E g_{Pi} & E g_{Mi} & E g_{Ni} \\ E g_{Pi} & E g_{Pi}^2 & E g_{Pi} g_{Mi} & E g_{Pi} g_{Ni} \\ E g_{Mi} & E g_{Pi} g_{Mi} & E g_{Mi}^2 & E g_{Mi} g_{Ni} \\ E g_{Ni} & E g_{Pi} g_{Ni} & E g_{Mi} g_{Ni} & E g_{Ni}^2 \end{bmatrix} = \begin{bmatrix} 1 & E g_{Pi} & E g_{Mi} & E g_{Ni} \\ E g_{Pi} & E g_{Pi} & E g_{Pi} g_{Mi} & E g_{Pi} g_{Ni} \\ E g_{Mi} & E g_{Pi} g_{Mi} & E g_{Mi} & E g_{Mi} g_{Ni} \\ E g_{Ni} & E g_{Pi} g_{Ni} & E g_{Mi} g_{Ni} & E g_{Ni} \end{bmatrix}
 \end{aligned}$$

For the EM algorithm the expectations are calculated given the maximum likelihood estimates from the previous iteration.

The  $\beta$  that maximizes  $\tilde{l}$  is

$$\tilde{\beta} = G^{-1} \gamma$$

Evaluating  $\tilde{l}$  at  $\tilde{\beta}$  gives

$$\begin{aligned}
 \tilde{l}(\tilde{\beta}, \sigma^2) &= -\frac{1}{2} \left[ n \log(\sigma^2) + \frac{1}{\sigma^2} (S_{YY} - 2\gamma^T G^{-1} \gamma + \gamma^T G^{-1} G G^{-1} \gamma) \right] \\
 &= -\frac{1}{2} \left[ n \log(\sigma^2) + \frac{1}{\sigma^2} (S_{YY} - \gamma^T G^{-1} \gamma) \right]
 \end{aligned}$$

and therefore

$$\tilde{\sigma}^2 = \frac{1}{n} (S_{YY} - \gamma^T G^{-1} \gamma) = \frac{1}{n} (S_{YY} - \gamma^T \tilde{\beta})$$

maximizes  $\tilde{l}(\tilde{\beta}, \sigma^2)$ .

**Example:** Maternal and child (proband) effect.

$$y_i \sim \mathcal{N}(\alpha + \beta_M(g_{Mi} + g_{Ni}) + \beta_C(g_{Mi} + g_{Pi}), \sigma^2)$$

$$Q = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix}$$

$$\beta = (\alpha, \beta_M, \beta_C)^T$$

**Example:** Maternal effect.

$$y_i \sim \mathcal{N}(\alpha + \beta_M(g_{Mi} + g_{Ni}), \sigma^2)$$

$$Q = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 \end{bmatrix}$$

$$\beta = (\alpha, \beta_M)^T$$