Additional file 1 Additional information of sampling distributions of RD, Cohen's h and OR.

The asymptotic distribution for each of RD, Cohen's h and  $log(OR)$  can be derived by using the multivariate delta method. Suppose a random vector  $X = (X_1, \ldots, X_n)$  has a mean vector  $\mu = (\mu_1, ..., \mu_p)$  and a variance-covariance matrix  $\Sigma$ . Then, for a transformation of X is  $g(X)$ , the asymptotic distribution will be asymptotic normal  $N(\mu_{g}, \sigma_{g}^{2})$  where  $\mu_{g} = g(\mu)$  and  $\sigma_{g}^{2} = D\Sigma D^{t}$ , where *D* is the matrix of partial derivatives of  $g(X)$  with respect to X and  $D<sup>t</sup>$  denotes the transpose matrix of D. These three ES measures can be considered as a function of MAFs from case and control group. The joint distribution of estimates of MAFs at case and control group is

$$
\begin{pmatrix} \hat{p}_1 \\ \hat{p}_2 \end{pmatrix} \sim N \begin{pmatrix} p_1 \\ p_2 \end{pmatrix} \begin{bmatrix} \frac{p_1(1-p_1)}{n_1} & 0 \\ 0 & \frac{p_2(1-p_2)}{n_2} \end{bmatrix}.
$$
 Firstly, we derive the asymptotic

distribution of the estimate for RD, denoted as  $\hat{d} = \hat{p}_1 - \hat{p}_2$ . Let  $g(\hat{p}_1, \hat{p}_2) = \hat{p}_1 - \hat{p}_2$ , the expectation value of  $\hat{p}_1 - \hat{p}_2$  is  $E(g(p_1, p_2)) = p_1 - p_2$  and variance is

$$
Var(\hat{p}_1 - \hat{p}_2) = (1, -1) \times \begin{bmatrix} \frac{p_1(1-p_1)}{n_1} & 0 \\ 0 & \frac{p_2(1-p_2)}{n_2} \end{bmatrix} \times \begin{pmatrix} 1 \\ -1 \end{pmatrix} = \frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}.
$$

Hence  $\hat{d}$  is asymptotically distributed as a normal distribution  $\frac{(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}$ .  $\left(d, \frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}\right).$  $\left(d, \frac{p_1(1-p_1)}{p_2(1-p_1)}\right)$ 2  $2(1 - p_2)$ 1  $\frac{p_1(1-p_1)}{p_2(1-p_1)} + \frac{p_2(1-p_1)}{p_2(1-p_1)}$ *n*  $p_2(1-p)$ *n*  $p \left( d \frac{p_1(1-p_1)}{p_1(1-p_2)} \right)$ . The genetic association test based on RD can be defined as  $H_0: d = 0$  vs.  $H_1: d \neq 0$ , and the corresponding test statistic is

$$
\frac{\hat{d}}{\sqrt{\hat{p}(1-\hat{p}) \times (\frac{1}{n_1} + \frac{1}{n_2})}}
$$
 where  $\hat{p} = \frac{(n_1\hat{p}_1 + n_2\hat{p}_2)}{n_1 + n_2}$  is the MAF among whole ample.

Next, for Cohen's h, the estimator is  $\hat{h} = g(\hat{p}_1, \hat{p}_2) = 2 \arcsin(\sqrt{\hat{p}_1}) - 2 \arcsin(\sqrt{\hat{p}_2})$ . According to the delta method, the expectation of Cohen's h is  $E(g(p_1, p_2)) = 2 \arcsin(\sqrt{p_1}) - 2 \arcsin(\sqrt{p_2})$  and the variance is

$$
Var(g(\hat{p}_1, \hat{p}_2)) = \left(\frac{1}{\sqrt{p_1(1-p_1)}}, -\frac{1}{\sqrt{p_1(1-p_1)}}\right) \times \begin{bmatrix} \frac{p_1(1-p_1)}{n_1} & 0 \\ 0 & \frac{p_2(1-p_2)}{n_2} \end{bmatrix} \times \begin{bmatrix} \frac{1}{\sqrt{p_1(1-p_1)}} \\ -\frac{1}{\sqrt{p_1(1-p_1)}} \end{bmatrix}
$$

 $\frac{1}{-} + \frac{1}{-}$ .  $=\frac{1}{n_1} + \frac{1}{n_2}$ . The asymptotic distribution for  $\hat{h}$  is  $N\left(h, \frac{1}{n_1} + \frac{1}{n_2}\right)$ .  $\left(h, \frac{1}{n_1} + \frac{1}{n_2}\right).$  $\int$ ,  $+$  $n_1$   $n_2$  $\frac{1}{2} + \frac{1}{2}$  $n_1$  *n*  $N|h, \frac{1}{h}$  +  $\frac{1}{h}$ . The test statistic

based on the Cohen's h for  $H_0$ :*h* =0 vs.  $H_1$ :*h*  $\neq$ 0 is  $\frac{1}{1}$   $\frac{1}{2}$ 1 1  $\hat{h}$  $n_{1}$  *n h*  $+$  -. Finally, we derive the

asymptotic distribution for log(OR) as below. The estimator for log(OR) is  $\frac{p_1/(1-p_1)}{\hat{p}_2/(1-\hat{p}_2)}$  $\ln(O\hat{R}) = g(\hat{p}_1, \hat{p}_2) = \ln(\frac{\hat{p}_1/(1-\hat{p}_1)}{2\pi\hat{R}^2})$ 2/ $(1 - \mu_2)$  $p_1, \hat{p}_2$ ) =  $\ln(\frac{p_1/(1-p_1)}{\hat{p}_2/(1-\hat{p}_2)})$  $Q(\hat{R}) = g(\hat{p}_1, \hat{p}_2) = \ln(\frac{\hat{p}_1/(1-\hat{p}_2)}{2})$  $-i$  $= g(\hat{p}_1, \hat{p}_2) = \ln(\frac{\hat{p}_1/(1-\hat{p}_1)}{2})$  and the expectation is  $(g(p_1, p_2)) = \ln(\frac{P_1/(1 - P_1)}{(1 - P_2)}) = \ln(QR)$  $(1-p_2)$  $(p_1, p_2)$  =  $ln(\frac{p_1/(1-p_1)}{(1-p_2)})$ 2/ $(1 - P_2)$  $p_1, p_2$ ) $=$   $\ln(\frac{p_1/(1-p_1)}{p_2/(1-p_2)}) = \ln(OR)$  $E(g(p_1, p_2)) = \ln(\frac{p_1/(1-p_1)}{(1-p_2)}) = 1$  $-1$ . The variance is  $(g(\hat{p}_1, \hat{p}_2)) =$  $\mathbf{L}$  $\mathbf{L}$  $\mathbf{L}$  $\mathbf{L}$  $\setminus$  $\overline{\phantom{a}}$  $\vert$  $|l$  $\vert \sqrt{2}$  $-1$  $\mathbb{R}$   $\left| P_1(1 - \mu) \right|$  $\mathbf{L}$  $\mathbf{L}$  $\vert x \vert$  $\mathbf{L}$  $\vert$  $\mathbf{L}$  $\mathbb{R}^n$  $\mathbb{R}^n$ Ē  $\mid p$  $-1$  $-1$  $\times$  $-p_1$ )<sup>2</sup>  $p_2(1-p)$  $=$   $($ 1  $(1-p_1)$ 1 0  $\frac{p_2(1-p_2)}{p_2}$  $\frac{(1-p_1)}{p_2}$  0 )  $(1 - p_2)$  $\frac{1}{\sqrt{1-\frac{1}{2}}}$  $(1 - p_1)$  $(\hat{p}_1, \hat{p}_2)$  =  $\left(-\frac{1}{a}\right)$  $1^{1}$   $P_1$ 2  $(1 - p_2)$ 1  $1^{11} - P_1$  $q_1(1 - p_1)$   $p_2(1 - p_2)$  $_1$ ,  $P_2$  $p_1(1-p)$  $p_2(1-p)$ *n*  $p_1(1-p)$  $p_1(1-p_1)^p p_2(1-p_2)$  $Var(g(\hat{p}_1, \hat{p}_2))$ 

 $n_1 p_1 (1-p_1)$   $n_2 p_2 (1-p_2)$ 1 1 1  $n_1 p_1 (1-p_1)$   $n_2 p_2 (1-p_2)$  $+ -1$  $=$   $\frac{1}{\sqrt{2\pi}}$  +  $\frac{1}{\sqrt{2\pi}}$ . Therefore, the asymptotic distribution of  $\ln(Q\hat{R})$  is  $\Bigg) \cdot$  $\left(\ln(OR), \frac{1}{n_1p_1(1-p_1)} + \frac{1}{n_2p_2(1-p_2)}\right).$  $\int_{\mathbf{a}}$  $- i$  $+$  - $(-p_1)$   $n_2 p_2 (1-p_2)$ 1  $(1 - p_1)$  $ln(OR)$ ,  $\frac{1}{1}$  $n_1 p_1 (1-p_1)$   $n_2 p_2 (1-p_2)$  $N \left( \ln(OR) \right)$  +  $\frac{1}{\sqrt{2}}$  The test statistic for genetic association

L

 $\int$ 

 $(1-p_2)$ 

2<sup>(1</sup>  $P_2$ 

 $p_2(1-p)$ 

 $\binom{r}{k}$ 

 $\begin{array}{c} \end{array}$ 

2

*n*

based on log(OR) is 
$$
\frac{\ln(O\hat{R})}{\sqrt{\frac{1}{n_1 \hat{p}_1 (1 - \hat{p}_1)} + \frac{1}{n_2 \hat{p}_2 (1 - \hat{p}_2)}}}
$$
.