Supplementary Notes

Mathematical formulations

Our model to be solved is:

$$Y = u_i + u_g + \varepsilon \tag{1}$$

Where $u_i \sim N\left(0, \sigma_i^2 K_i\right)$, $u_g \sim N\left(0, \sigma_g^2 K_g\right)$, and $\varepsilon \sim N(0, \sigma_e^2 I)$.

Step 1: estimating the genetic variance component σ_g^2

First, we controlled the population structure through solving σ_g^2 to remove the correlation between individuals. We use Y_c, a centered Y, to regress on the random term u_g and errors ε as follows:

$$Y_c = u_g + \varepsilon \tag{2}$$

where $Y_c = Y - \bar{Y}$, $\bar{Y}$ is the average of Y, $u_g \sim N\left(0, \sigma_g^2 K_g\right)$, and $\varepsilon \sim N(0, \sigma_e^2 I)$. The eigen-decomposition of K_g is $K_g = U_x S_x U_x^{-1}$, where $S_x = \begin{bmatrix} \lambda_{x1} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \lambda_{xn} \end{bmatrix}$ is a matrix of eigenvalues. A new parameter $\delta = \frac{\sigma_{\mathrm{e}}^2}{\sigma_g^2}$ is defined so that $Y_c \sim MVN\left(0, \sigma_g^2\left(K_g + \delta I\right)\right)$. The estimated variance components for σ_g^2, σ_e^2 are therefore written in the following equations.

$$\hat{\sigma}_g^2 = \frac{1}{n} \sum_{i=1}^{n} \frac{V_{xi}^2}{(\hat{\delta} + \lambda_{xi})} \tag{3}$$

$$\hat{\sigma}_e^2 = \frac{\hat{\delta}}{n} \sum_{i=1}^{n} \frac{V_{xi}^2}{(\hat{\delta} + \lambda_{xi})} \tag{4}$$

Where $V_x = {U_x}^T Y_c$, λ_{xi} is the eigen value, $\hat{\delta}$ can be estimated by solving the non-linear equation below through Newton-Raphson method.

$$\sum_{i=1}^{n} \left[\frac{n V_{xi}^2}{\left(\sum_{i=1}^{n} \frac{V_{xi}^2}{(\delta + \lambda_{xi})} \right) (\delta + \lambda_{xi})^2} - \frac{1}{(\delta + \lambda_{xi})} \right] = 0 \tag{5}$$

In Newton-Raphson method, we let $g(\delta_n) = \sum_{i=1}^{n} \left[\frac{nV_{ij}^2}{\left(\sum_{i=1}^{n} \frac{v_{xi}^2}{(\delta_n+\lambda_{xi})}\right)(\delta_n+\lambda_{xi})^2} - \frac{1}{(\delta_n+\lambda_{xi})} \right]$,

then by repeating the process: $\delta_{n+1} = \delta_n - \frac{g(\delta_n)}{g'(\delta_n)}$, until $|\delta_{n+1} - \delta_n| \leq 10^{-6}$, we can approximately solve the equation, yielding an estimate of δ (the variance ratio). Then we can calculate the estimates of $\hat{\sigma}_g^2$ and $\hat{\sigma}_e^2$. Then the decorrelation matrix $\widehat{D}_x$ can be formed:

$$\widehat{D}_x = \left(\hat{\sigma}_g^2 S_x + \hat{\sigma}_e^2 I\right)^{-\frac{1}{2}} U_x^T \tag{6}$$

Proof of the soundness of the decorrelation procedure

In equation (2) $Y_c = u_g + \varepsilon$

$$\begin{aligned} Var(Y_c) &= \sigma_g^2 K_g + \sigma_e^2 I \\ &= \sigma_g^2 U_x S_x U_x^T + \sigma_e^2 U_x U_x^T \\ &= U_x\left(\sigma_g^2 S_x + \sigma_e^2 I\right) U_x^T \end{aligned}$$

The following derivation justifies that $D_x = \left(\sigma_g^2 S_x + \sigma_e^2 I\right)^{-\frac{1}{2}} U_x^T$ will lead to the desired property that $Var(D_x Y) = I$.

$$\begin{aligned} Var(D_x Y) &= D_x Var(Y) D_x^T \\ &= D_x U\left(\sigma_g^2 S_x + \sigma_e^2 I\right) U_x^T D_x^T \\ &= \left(\sigma_g^2 S_x + \sigma_e^2 I\right)^{-\frac{1}{2}} U_x^T U_x \left(\sigma_g^2 S_x + \sigma_e^2 I\right) U_x^T \left(\left(\sigma_g^2 S_x + \sigma_e^2 I\right)^{-\frac{1}{2}} U_x^T\right)^T \\ &= \left(\sigma_g^2 S_x + \sigma_e^2 I\right)^{-\frac{1}{2}} U_x^T U_x \left(\sigma_g^2 S_x + \sigma_e^2 I\right) U_x^T U_x \left(\sigma_g^2 S_x + \sigma_e^2 I\right)^{-\frac{1}{2}} \\ &= \left(\sigma_g^2 S_x + \sigma_e^2 I\right)^{-\frac{1}{2}} I \left(\sigma_g^2 S_x + \sigma_e^2 I\right) I \left(\sigma_g^2 S_x + \sigma_e^2 I\right)^{-\frac{1}{2}} \\ &= \left(\sigma_g^2 S_x + \sigma_e^2 I\right)^0 \\ &= I \end{aligned}$$

Hence multiplying the decorrelation matric D_x to Y can control the population stratification by removing the correlation between individuals.

Step 2: solving the local variance component σ_l^2

After getting the decorrelation matrix $\widehat{D}_x$ from step 1, we applied this matrix to Y_c, and get ${Y_c}^* = \widehat{D}_x Y_c$. So, equation (1) can be reformat to equation (7) as below, where

$u_i \sim N\left(0, \sigma_i^2 K_i\right)$. The next step was to solve σ_i^2 using low-rank trick proposed by FaST-LMM.

$$Y_c^{\ *} = u_i + \varepsilon \tag{7}$$

For details, please refer to the original paper of FaST-LMM (Lippert et al. 2011).

Details of running ILMM, LOCAL, EMMAX, SKAT

ILMM, LOCAL, and EMMAX (Kang et al. 2010) methods are all implemented in Jawamix5 (Long et al. 2013; Xiong et al. 2019). More details can be found in the user manual in the GitHub (https://github.com/theLongLab/Jawamix5) for reference.

1. Convert genotype file from .csv format to .hdf5 format
    a. Command line: java ‑ Xmx4g –jar /path/to/jawamix5.jar import -ig genotype.csv -o genotype.hdf5
    b. Parameters:
        i. -ig: input genotype file in plain text (.CSV format)
        ii. -o: output in HDF5 in format
    c. Input file: genotype.csv
    d. Output file: genotype.hdf5
2. Generate the genetic relationship matrices (GRM) based on input genotype file
    a. Command line: java –Xmx4g –jar /path/to/jawamix5.jar kinship -ig genotype.hdf5 -o genotype.kin
    b. Parameters:
        i. -ig: input genotype file in HDF5 format
        ii. -o: the output file prefix
    c. Input file: genotype.hdf5
    d. Output files:
        i. genotype.kin.rescaled.IBS
3. Run ILMM method
    a. Command line: java –Xmx4g –jar /path/to/jawamix5.jar compound -ig genotype.hdf5 -ip phenotype.tsv -o ./ILMM_res/ -ik_g genotype.kin.rescaled.IBS -ic hic_info.txt
    b. Parameters:
        i. -ig: input genotype file in HDF5 format
        ii. -ip: phenotype file
        iii. -o: output folder
        iv. -ik_g: the global genetic relationship matrices file

v. -ic: input regions

c. Input files:

i. genotype.hdf5

ii. phenotype.tsv

iii. genotype.kin.rescaled.IBS

iv. hic_info.txt (three columns separated by tab, an example listed below)

```
#header: Index   Region1(chr; start; end)    Region2
#content: C0      1;840000;850000       1;890000;900000
```

d. Output file:

i. ./ILMM_res/xxx.csv

4. Run LOCAL method

a. Command line: java–Xmx4g –jar /path/to/jawamix5.jar local -ig genotype.hdf5 -ip phenotype.tsv -o ./LOCAL_res/ -ik_g genotype.kin.rescaled.IBS -w 5000

b. Parameters:

i. -ig: input genotype file in HDF5 format

ii. -ip: phenotype file

iii. -o: output folder

iv. -w: tiling window size

v. -ik_g: the global genetic relationship matrices file

c. Input file:

i. genotype.hdf5

ii. phenotype.tsv

iii. genotype.kin.rescaled.IBS

d. Output file:

i. ./LOCAL_res/xxx.csv

5. Run EMMAX method

a. Command line: java–Xmx4g –jar /path/to/jawamix5.jar emmax -ig genotype.hdf5 -ip phenotype.tsv -o ./EMMAX_res/ -ik genotype.kin.rescaled.IBS -p 0.05

b. Parameters:

i. -ig: input genotype file in HDF5 format

ii. -ip: phenotype file

iii. -o: output folder

iv. -ik: genetic relationship matrices file generated by function “kinship” or other user defined method

        v. -p: Bonferroni correction, variants whose p-values above 0.05/number of tests will not be written to the file.

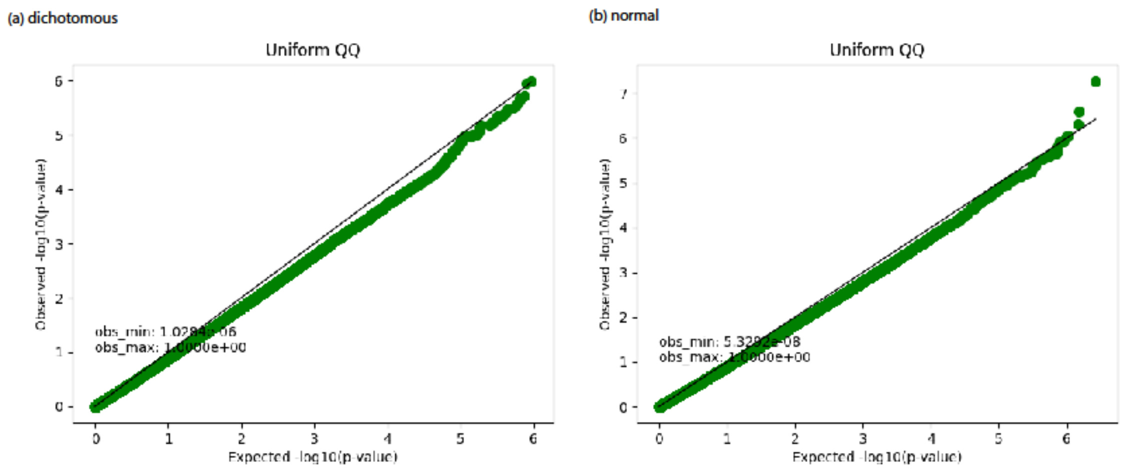
   c. Input file:
        i. genotype.hdf5
        ii. phenotype.tsv
        iii. genotype.kin.rescaled.IBS
   d. Output file:
        i. ./EMMAX_res/xxx.top

SKAT (Wu et al. 2010; Wu et al. 2011) was download as an R package (https://cran.r-project.org/web/packages/SKAT/index.html) and the p-values for regions were obtained by first computing the parameters and residuals for SKAT using following command line a).

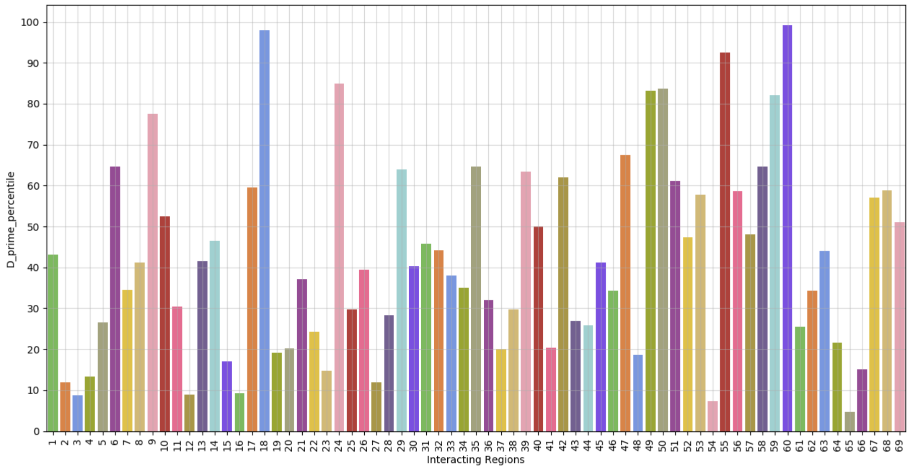
a) >> obj<-SKAT_Null_Model(y ~ 1, out_type="D"), where y denotes phenotype matrix, out_type=”D” means the phenotype is dichotomous.

To perform the association studies between the SNPs set and the phenotype, we used the command line b)

b) >> res_p_value <- SKAT(x, obj)$p.value. Here, obj is generated by either a) or b) and x refers to genotype matrix for all SNPs in the SNPs set. “res_p_value” is the p-value for a tested SNP set associated with phenotype y. Please refer to the manual of SKAT for more details.



Supplementary Figure S1. Uniform QQ plot for simulated phenotype under null hypothesis. (a): Dichotomous phenotype (0 or 1); (b): Phenotype from normal distribution (mean zero and standard deviation 1).



Supplementary Figure S2. D’ values for 69 interacting regions associated with both ASD and gene expressions in the brain tissues.

References

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