Fine Mapping With TWAS Results Across Multiple Tissues

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Section 1

Background and Methods

What is TWAS?

- TWAS: transcriptome-wide association study.
- To determine significant trait-expression associations. [1]
- This method increases the power of identifying functionally relevant loci by leveraging expression quantitative trait loci (eQTLs) from external references in relevant tissues. [2]

[1] Gusev et al. "Integrative approaches for large-scale transcriptome-wide association studies" 2016 Nature Genetics

[2] Bhattacharya et al. "A framework for transcriptome-wide association studies in breast cancer in diverse study populations" 2020 Genome Biology

TWAS/FUSION Software

- Functional Summary-based Imputation:

  FUSION is a suite of tools for performing a TWAS by predicting functional/molecular phenotypes into GWAS using only summary statistics (usually from GWAS). The goal is to identify associations between a GWAS phenotype and a functional phenotype that was only measured in reference data. [1]

[1] Gusev et al. "Integrative approaches for large-scale transcriptome-wide association studies" 2016 Nature Genetics

TWAS/FUSION Software

- Inputs:
  - GWAS summary statistics
  - Reference panels (i.e. precomputed functional weights (primarily gene expression) from multiple tissues)
  - Regerence LD data
- Outputs:
  - A data frame with corresponding z and p values for each SNPs.

[1] Gusev et al. "Integrative approaches for large-scale transcriptome-wide association studies" 2016 Nature Genetics

Bayesian Fine Mapping

- Why fine-map?
  - To find causal genes
  - To pinpoint variant
  - To understand genetic architecture
    - Gene enrichment
    - Cross-trait comparison, cross-tissue
- Bayesian fine-mapping outputs:
  - PIP: Posterior inclusion probability (the probability that a variant is causal)
  - 95% Credible Sets: Set of variants that contains $\geq 95\%$ probability

[3] ▸ Hilary Finucane, Broad Institute

Bayesian Fine Mapping

- Single-causal-variant PIPs:

$$\begin{aligned} PIP_j &= P(\text{j causal} \mid \text{data}) \\ &= \frac{P(\text{data} \mid \text{j causal})}{\sum_k P(\text{data} \mid \text{k causal})} \\ &= \frac{P(\text{data} \mid \text{j causal})/P(data|nocausal)}{\sum_k P(\text{data} \mid \text{k causal})/P(data|nocausal)} \\ &= \frac{\text{Bayesian Factor}_j}{\sum_k \text{Bayesian Factor}_k} \end{aligned}$$

[3] ▸ Hilary Finucane, Broad Institute

Bayesian Fine Mapping

- 95% Credible Sets (S):

$$P(\text{causal var is in S}) \geq 0.95$$

- Under Single-causal-variant assumption:

$$P(\text{causal var is in S}) = \sum_{j \in S} PIP_j$$

- To get the most compact credible set, add variant with highest PIPs untill sum to 0.95.

[3] ▸ Hilary Finucane, Broad Institute

Bayesian Fine Mapping

- Factors affecting Bayesian fine mapping power
  - LD
  - Sample Size
  - Effect size

[4] Schaid et al. Nat Rev Genet 2018

Bayesian Fine Mapping

- Multiple-causal-variant Fine-mapping (two approaches):
  - Divide the whole data into many pieces, and apply single-causal-variant fine-mapping in each piece
  - Jointly model Multiple-causal-variant

[3] Hilary Finucane, Broad Institute

Section 2

Data For Alzheimer's Disease

Overview

- Data
  - Gene Expression Matrix: Gene expression level in each tissue
    - Z-values
    - P-values
  - Correlation matrix: Correlation of expression in each tissue for each gene

Gene Expression matrix

```
dim(dat_ad_n[[1]])
```

```
## [1] 33960    49
```

```
dim(dat_ad_n[[2]])
```

```
## [1] 33960    49
```

```
dat_ad_n[[1]][1:5,1:5]
```

```
##       GENE Whole_Blood   Vagina    Uterus   Thyroid
## 1  EXOC3L2    23.14987       NA  9.249285        NA
## 2   CLASRP    12.86142       NA 30.900394 10.092551
## 3 TRAPPC6A    11.31097 1.770764        NA  6.203560
## 4    NKPD1    10.63722       NA        NA  2.276769
## 5 CEACAM19    10.52064       NA  6.806502 10.630916
```

Gene Expression matrix

```
dat_ad_n[[2]][1:5,1:5]
```

```
##       GENE Whole_Blood Vagina    Uterus  Thyroid
## 1  EXOC3L2   7.29e-119     NA  1.13e-20       NA
## 2   CLASRP    3.71e-38     NA 5.90e-210 2.98e-24
## 3 TRAPPC6A    5.79e-30 0.0383        NA 2.76e-10
## 4    NKPD1    1.00e-26     NA        NA 1.14e-02
## 5 CEACAM19    3.47e-26     NA  5.00e-12 1.07e-26
```

```
1 - pnorm(dat_ad_n[[1]][3,"Vagina"])
```

```
## [1] 0.0383
```

Correlation matrix

```
length(cov_matrix)
```

```
## [1] 33994
```

```
names(cov_matrix)[1:10]
```

```
##  [1] "MCF2L2"        "TRMT10C"       "CORO1A"        "C
##  [5] "THOP1"         "RP11-731K22.1" "DBNDD2"        "V
##  [9] "PDCD5"         "CTD-2026D20.2"
```

```
#Obtain correlation
gene = 'EXOC3L2'
cor_matrix <- cov2cor(cov_matrix[[gene]])
```

Correlation matrix

```
dim(cor_matrix)
```

```
## [1] 23 23
```

```
round(cor_matrix[15:18,15:18],3)
```

```
##           Liver   Lung Pancreas Pituitary
## Liver     1.000  0.401    0.053     0.003
## Lung      0.401  1.000    0.120    -0.143
## Pancreas  0.053  0.120    1.000    -0.137
## Pituitary 0.003 -0.143   -0.137     1.000
```

Section 3

Analysis (SuSiE)

SuSiE

```r
devtools::install_github("stephenslab/susieR")
library(susieR)
fitted_rss <- susie_rss(z-scores, R, L = 10)
```

- z-scores: A p-vector of z scores
- R: p by p correlation matrix
- L: Maximum number of components model (Credible Sets).

Implementation

- run_susie
  - Pre-process data
    - Drop NA in expression z-scores vector
    - Take out the common tissue information from expression vector and correlation matrix.
  - Fit model: susie_rss(z-scores, R, L=4)
    - Expression z-score matrix is of length p
    - Correlation matrix is p by p matrix
    - They contain same tissue information
    - L=4

Main logic

We loop through all genes. For each gene, we implement run_susie, and take out the significant tissues in Credible Sets (cs), as well as their Posterior inclusion probability (PIP) scores. We stored these information in a csv file.

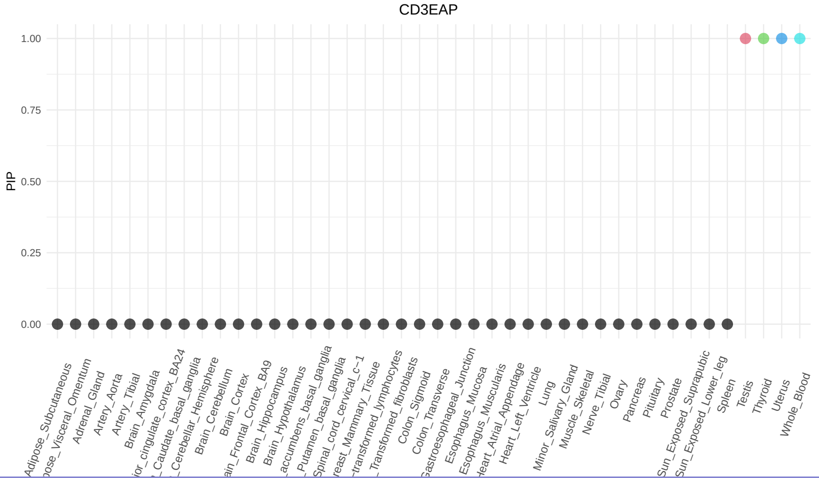
Result

```
head(all_res)
```

```
##   X variable_prob cs                tissues    GENE
## 1 1     1.0000000  1            Whole_Blood EXOC3L2
## 2 2     1.0000000  2 Adipose_Subcutaneous EXOC3L2
## 3 3     0.9999839  4                Testis EXOC3L2
## 4 4     0.9933120  3 Heart_Left_Ventricle EXOC3L2
## 5 5     1.0000000  1                Uterus  CLASRP
## 6 6     1.0000000  2               Thyroid  CLASRP
```

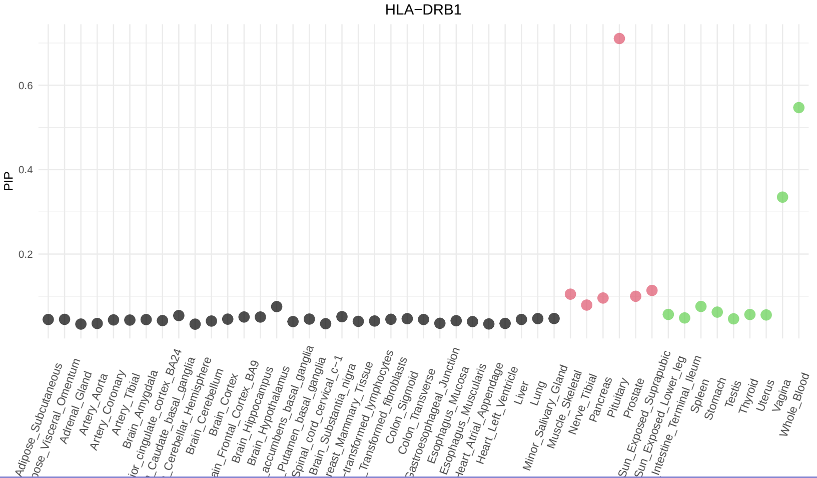
Result

```
plot_pip('CD3EAP',dat_ad,cov_matrix,all_res)
```



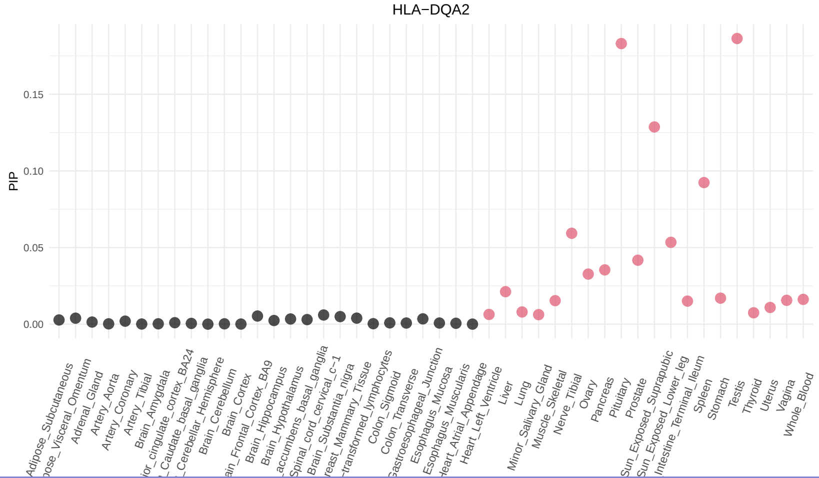
Result

```
plot_pip('HLA-DRB1',dat_ad,cov_matrix,all_res)
```



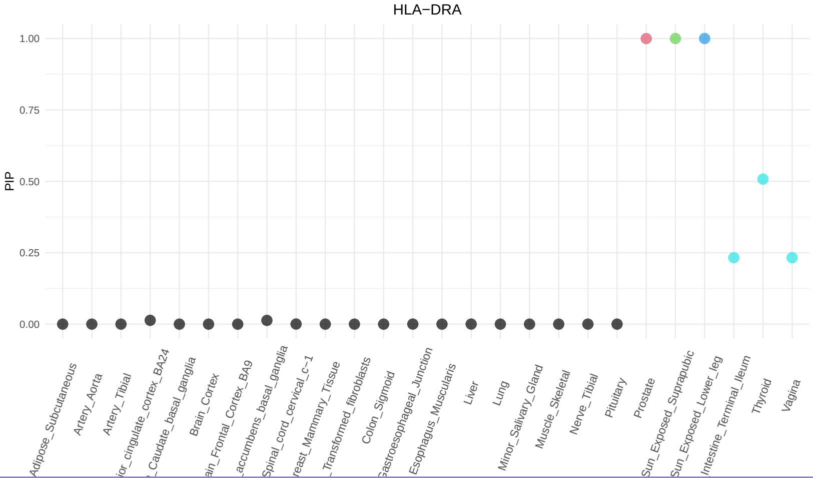
Result

```
plot_pip('HLA-DQA2',dat_ad,cov_matrix,all_res)
```



Result

```
plot_pip('HLA-DRA',dat_ad,cov_matrix,all_res)
```



Section 4

Reference

Reference

- Gusev et al. "Integrative approaches for large-scale transcriptome-wide association studies" 2016 Nature Genetics
- Wang, G., Sarkar, A., Carbonetto, P., & Stephens, M. (2020). A simple new approach to variable selection in regression, with application to genetic fine mapping. Journal of the Royal Statistical Society: Series B (Statistical Methodology). https://doi.org/10.1111/rssb.12388
- Schaid, D.J., Chen, W. & Larson, N.B. From genome-wide associations to candidate causal variants by statistical fine-mapping. Nat Rev Genet 19, 491–504 (2018). https://doi.org/10.1038/s41576-018-0016-z
- ▸ Hilary Finucane, Broad Institute