

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

¹Gusev et al. “Integrative approaches for large-scale transcriptome-wide association studies” 2016 Nature Genetics

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

TWAS/FUSION Softwar

- 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

¹Gusev et al. “Integrative approaches for large-scale transcriptome-wide association studies” 2016 Nature Genetics

TWAS/FUSION Softwar

- 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.

¹Gusev 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

Bayesian Fine Mapping

- Single-causal-variant PIPs:

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

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 until sum to 0.95.

Bayesian Fine Mapping

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

⁴Schaid 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

Section 2

Data For Alzheimer's Disease

Section 3

Analysis (SuSiE)

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