

The multivariate Marginal Epistasis Test

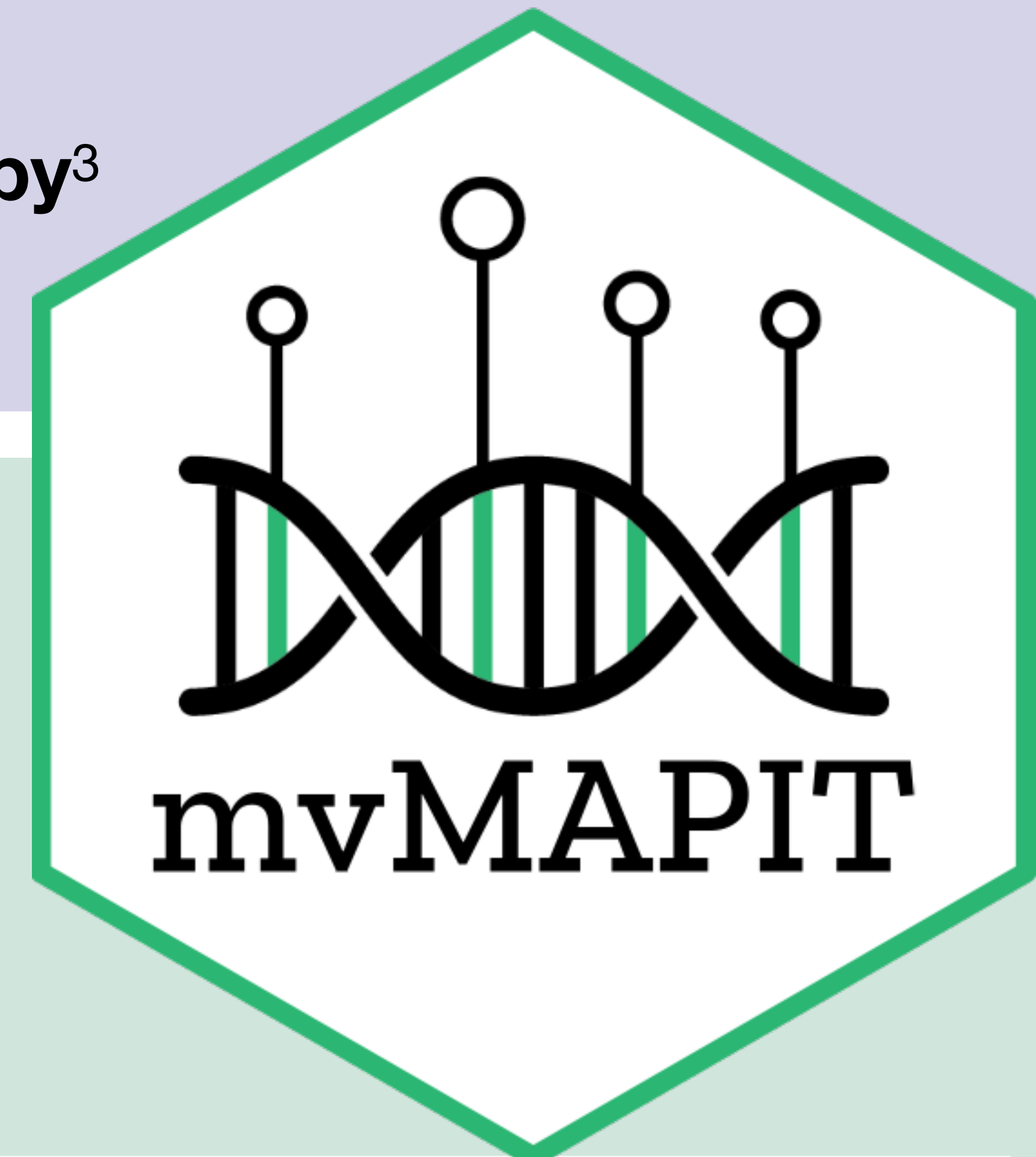
Leveraging genetic correlation between traits improves the detection of epistasis in genome-wide association studies

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Rationale

- **Epistasis** could explain **missing heritability**^{1,2}
- **Genetic correlations** between traits maintained by **pleiotropy**³
- **Multivariate modelling** improves GWAS⁴

1 Manolio et al. (2009)
2 Zuk et al. (2012)
3 Chebib and Guillaume (2021)
4 Zhou and Stephens (2014)



Methods

Model
$$\mathbf{Y} = \underbrace{\sum_{l \neq j} \beta_l \mathbf{x}_l^T}_{\text{Linear Effect Size } \beta_l} + \underbrace{\sum_{l \neq j} \alpha_l (\mathbf{x}_j \circ \mathbf{x}_l)^T}_{\text{Interaction Effect Size } \alpha_l} + \mathbf{E}$$

Normal Assumptions

- $\mathbf{M}_j \sim \text{MN}(0, \mathbf{V}_\beta, \mathbf{K})$ Additive Variance Component
- $\mathbf{Z}_j \sim \text{MN}(0, \mathbf{V}_\alpha, \sigma^2 \mathbf{G})$ Pairwise Epistatic Variance Component
- $\mathbf{E} \sim \text{MN}(0, \mathbf{V}_E, \mathbf{I})$ Error Term

Parameter Estimation

$$\hat{\sigma}_{j,(cd)}^2 = \mathbf{y}_c^T \mathbf{H}_j \mathbf{y}_d$$

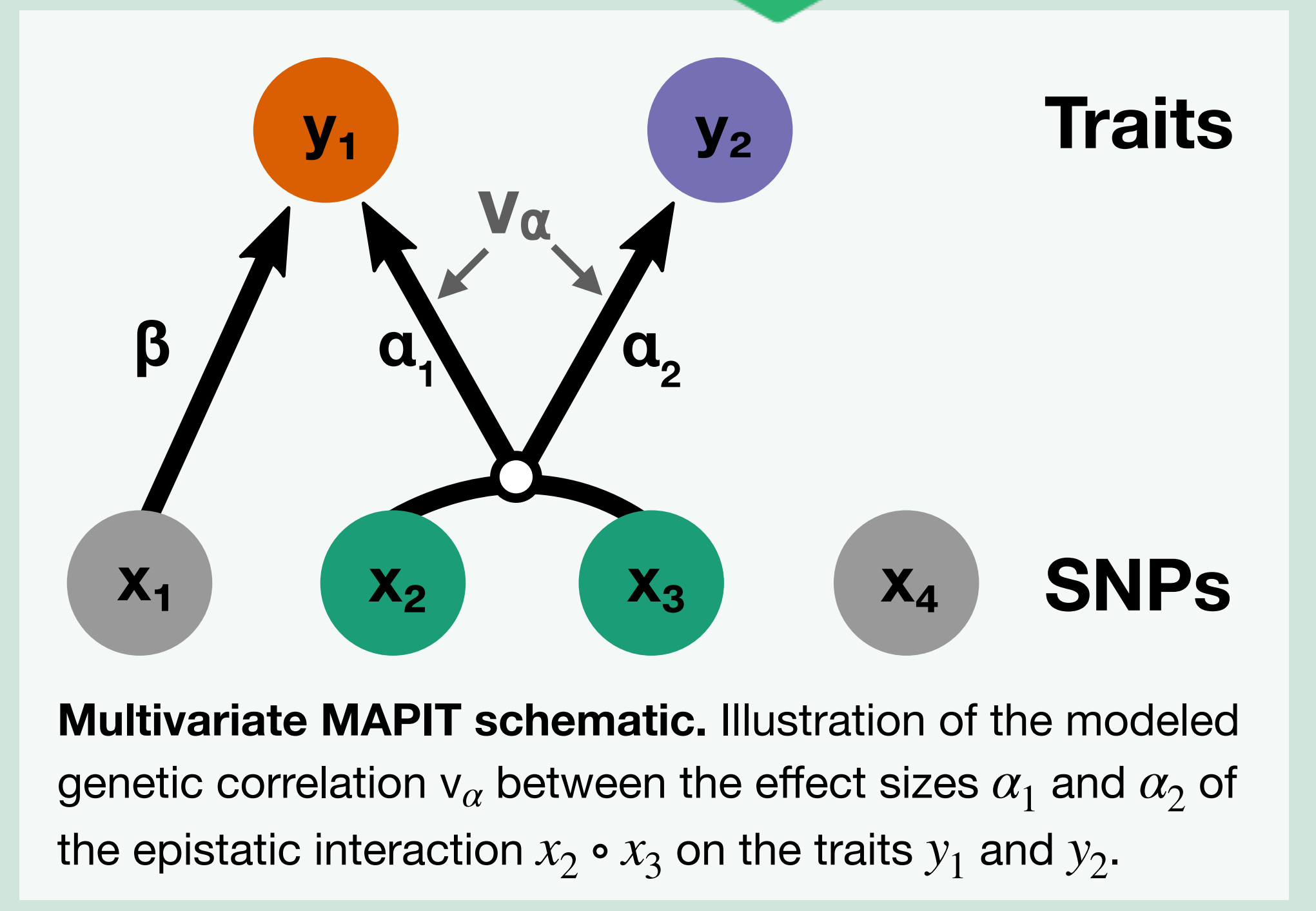
$$\text{Var}[\hat{\sigma}_{j,(cd)}^2] = \mathbf{y}_c^T \mathbf{H}_j^T \mathbf{V}_{j,(cd)} \mathbf{H}_j \mathbf{y}_d + \mathbf{y}_c^T \mathbf{H}_j^T \mathbf{V}_{j,(dd)} \mathbf{H}_j \mathbf{y}_c$$

Use **MQS** to find **point estimates** of parameters and compute **z-scores**.

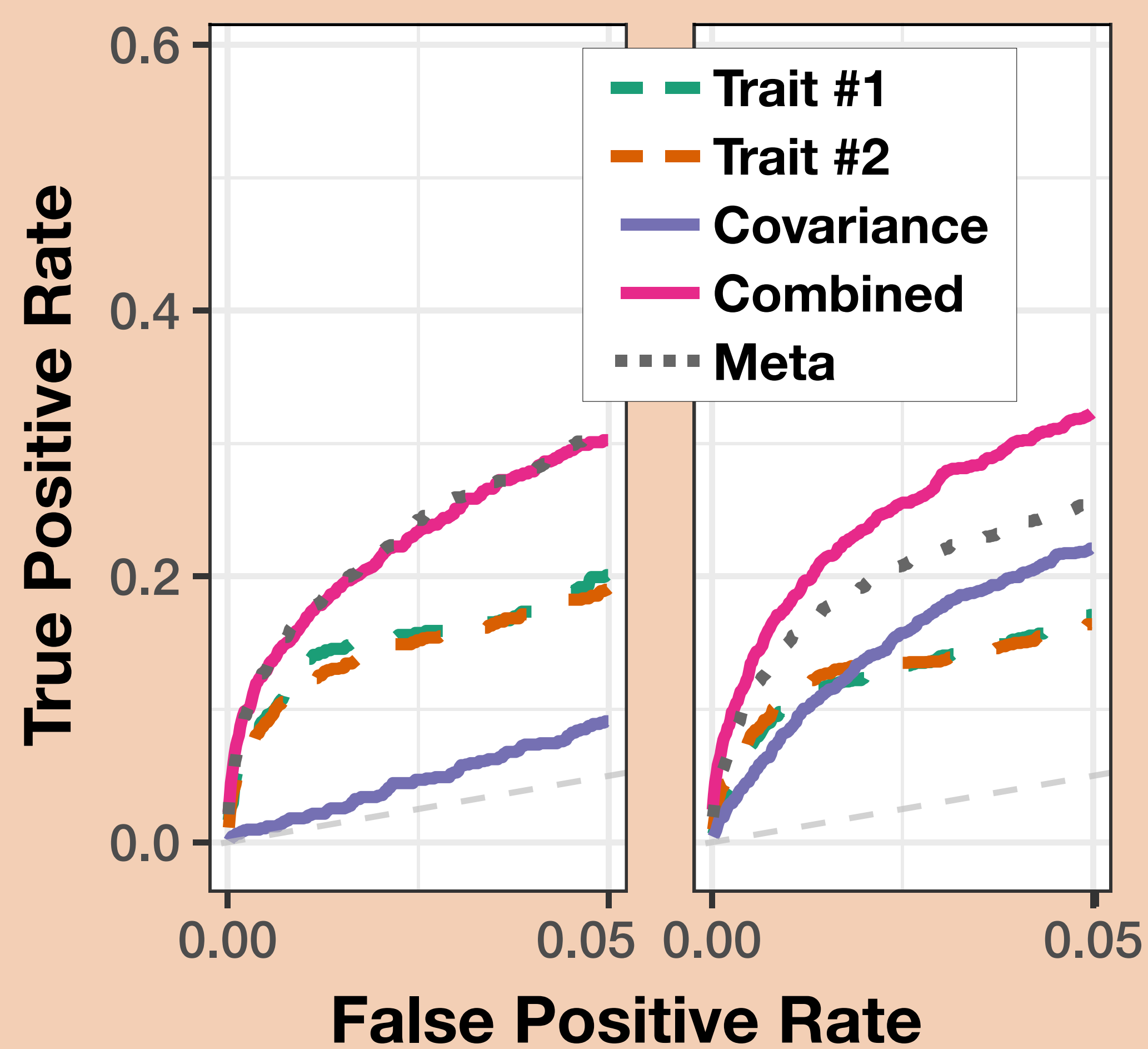
Hypothesis Testing

$$H_0 : \mathbf{Z}_j = 0 \Leftrightarrow H_0 : \sigma^2 = 0$$

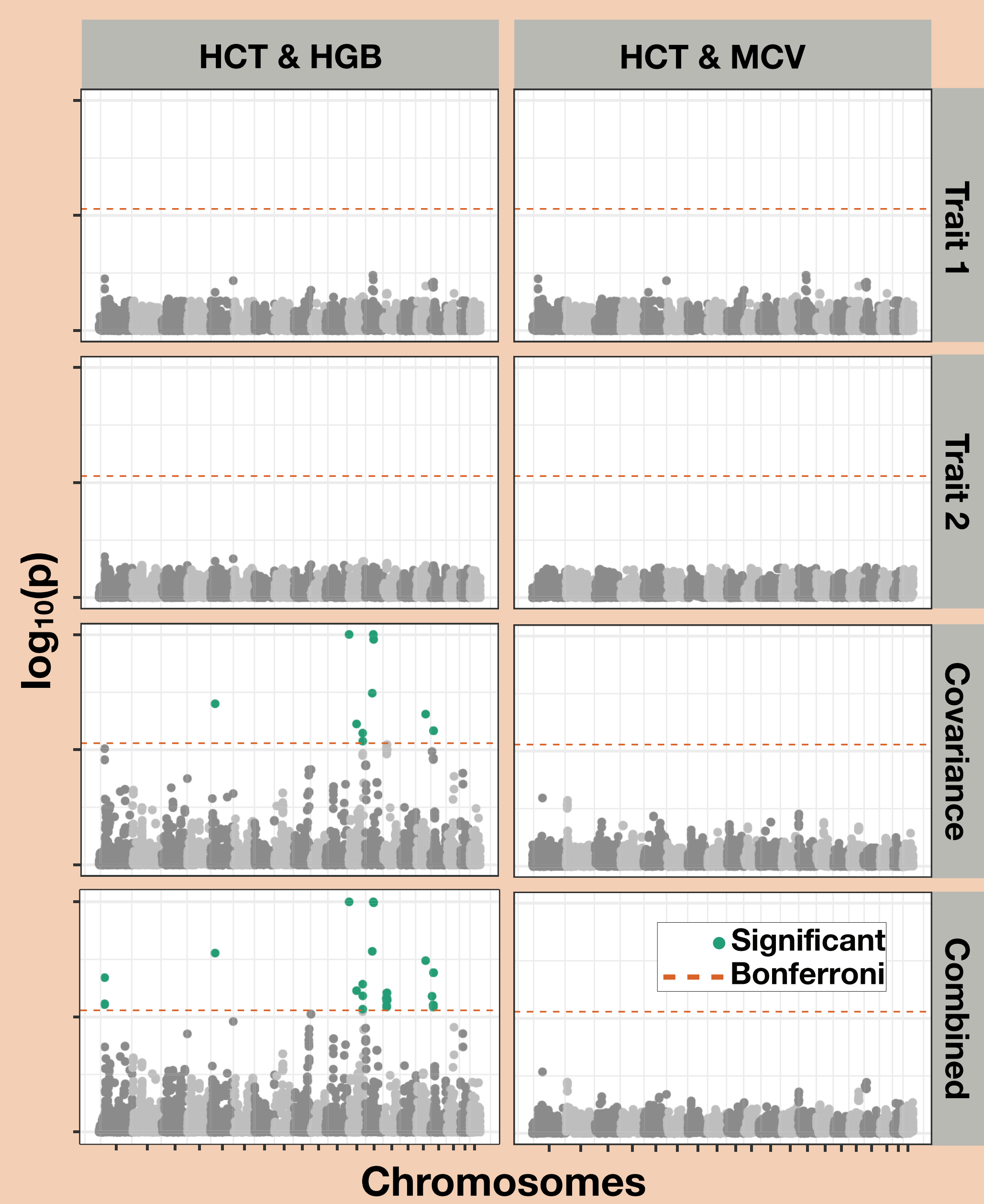
Under H_0 **nonlinear contributions** to the trait are **zero**.
Compute z-scores for all **variance and covariance components**.
Combine P-values with Fisher's method.



Results



- Simulations**
- **Sensitivity** of covariance statistic **increases with correlation** between effect sizes
 - **Combined statistic** outperforms univariate and simple meta analysis



Hematology in Mice

- **Covariance statistic** reveals strong signal of **pairwise epistasis**
- Genetic correlations **independent** of trait correlations

