# Simultaneous Selection of Multiple Important Single Nucleotide Polymorphisms in Familial Genome Wide Association Studies Data

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## Twin Studies: What and Why

**Behavior = Gene + Environment**

- **Objective**: detect genes that influence behavioral disorders, e.g. alcohol dependence, drug abuse, anorexia;
- Twin Studies gather data from families with twin children instead of independent individuals;
- Shared environment in families reduce sample size required to detect genetic signals;
- Genetic effect determine by associating behavioral trait with Single Nucleotide Polymorphisms (SNP).

- **Challenges:**
  - ➢ Huge number of SNPs: ~500k
  - ➢ Non-independent data structure makes it hard to model all SNPs simultaneously.

$$\begin{array}{c} \text{Father} \\ \text{Mother} \\ \text{Twin 1} \\ \text{Twin 2} \end{array} \begin{pmatrix} 1 & 0 & 0.5 & 0.5 \\ 0 & 1 & 0.5 & 0.5 \\ 0.5 & 0.5 & 1 & 0.5 \\ 0.5 & 0.5 & 0.5 & 1 \end{pmatrix} = \mathbf{K}, \text{ the kinship matrix}$$

- **State-of-the-art:**
  - ➢ Ignore dependent data – loses information, needs large samples
  - ➢ Model single-SNPs and choose from ordered $p$-values – ignores dependence among SNPs

## Move over $p$-values!

Say we want to detect which of 100 SNPs in a gene are significant.

***p*-values:**

1. Start with model with no SNPs (null model);
2. Add an SNP, get $p$-value with respect to null model;
3. Repeat for all SNPs. Select SNPs with low $p$-values.

**Bad:**

- **Ignores dependence of SNPs;**
- **Cannot detect weak signals: often the case in SNP studies**

**Our solution: *e*-values.**

1. Start from model with *all* SNPs: **takes care of correlation of SNPs;**
2. Fix a SNP effect to 0 in the model, get $e$-value with respect to full model by comparing two *model distributions*: **this helps detect weak SNP effects.**

## Statistical model

$$\boldsymbol{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{\gamma} + \boldsymbol{\epsilon} \text{ (Linear Mixed Model)}$$

- $\boldsymbol{Y}$ = quantitative trait values for members in a family, $\mathbf{X}$ = matrix of SNP values inside a gene, $\mathbf{Z}$ = random effect design matrix, $\boldsymbol{\gamma} \sim N(\mathbf{0}, \sigma_a^2\mathbf{K})$ is the vector of random effects, and $\boldsymbol{\epsilon} \sim N(\mathbf{0}, \sigma_e^2\mathbf{I})$ the random error term. Dependency inside a family is captured through $\boldsymbol{\gamma}$.
- To detect non-zero entries in $\boldsymbol{\beta}$, first get its maximum likelihood estimate, say $\widehat{\boldsymbol{\beta}}$. Use generalized bootstrap [1] with a large standard deviation to approximate its distribution, say $[\widehat{\boldsymbol{\beta}}]$.
- Replace $j^{\text{th}}$ coordinate of $\widehat{\boldsymbol{\beta}}$ and the bootstrap samples with 0. Name them $\widehat{\boldsymbol{\beta}}_{0,j}$ and $[\widehat{\boldsymbol{\beta}}_{0,j}]$, respectively.
- Then $e$-value of SNP = tail probability for $q^{\text{th}}$ percentile of $[E(\widehat{\boldsymbol{\beta}}_{0,j})]$ with respect to $[E(\widehat{\boldsymbol{\beta}})]$, where $E(.)$ is an *evaluation function* that takes higher value for a point closer to the center of $[\widehat{\boldsymbol{\beta}}]$, and smaller value for points away from it.
- Select SNPs with $e$-value < 0.5, for $q = 0.9$.

## Results

**Competing methods**

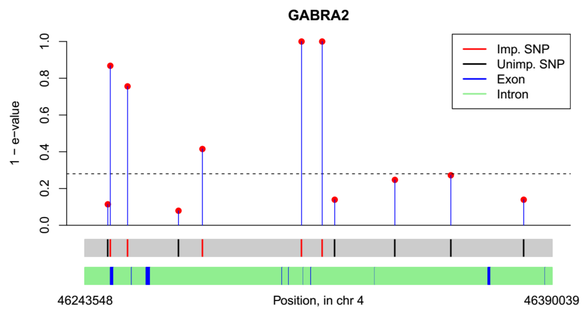
**RFGLS**: Combines single-SNP $p$-values---from a mixed effect model---using the Benjamini-Hochberg procedure [3].

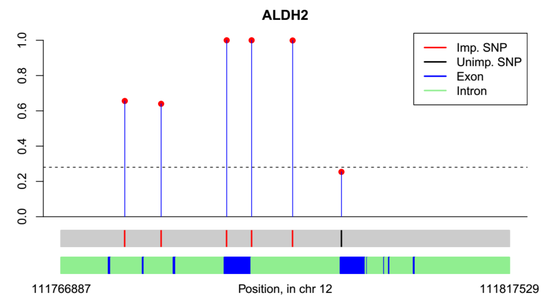
**mBIC2**: model selection using a version of BIC---ignores familial structure [2].

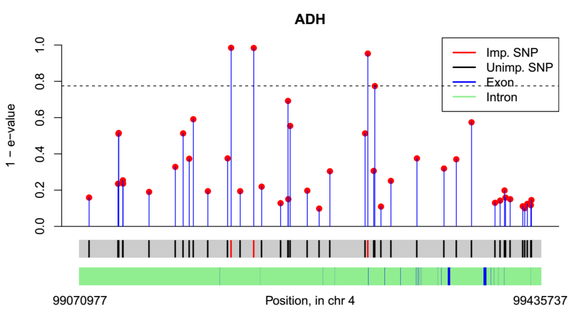
**Genome-wide Twin Studies application**

Data from the Minnesota Center for Twin and Family Research (MCTFR) Genome-Wide Association Study sample: 7188 individuals, 527,893 SNP markers [4]. Response variable is **amount of alcohol consumption**, consider 9 widely studied genes known to be associated with alcohol consumption.

| Gene | Total no. of SNPs | No. of SNPs detected by | | |
|---|---|---|---|---|
| | | $e$-value | RFGLS+BH | mBIC2 |
| GABRA2 | 11 | 5 | 0 | 0 |
| ADH | 44 | 3 | 1 | 0 |
| OPRM1 | 47 | 25 | 1 | 0 |
| CYP2E1 | 9 | 5 | 0 | 0 |
| ALDH2 | 6 | 5 | 0 | 1 |
| COMT | 15 | 14 | 0 | 0 |
| SLC6A3 | 18 | 4 | 0 | 0 |
| SLC6A4 | 5 | 0 | 0 | 0 |
| DRD2 | 17 | 0 | 0 | 1 |




**(1) GABRA2**

5 of 11 SNPs have non-zero effect: 4 very close to exons. The SNPs rs1808851, rs279856 are at perfect linkage disequilibrium with rs279858, a known associated SNP.

**(2) ALDH2**

5 of 6 tested SNPs have effect: rs7398343, rs7297186, rs3803167, rs10219736, rs3742004. Importantly all of them overlap with/ very close to coding regions.

**(3) ADH1 to ADH7 genes**

6 of 21 tested SNPs have $e$-values above threshold. Previously detected rs1229984 is in between two of them. First two are possibly novel: in the uncharacterized gene LOC100507053.

**References:**

[1] Chatterjee, S. and Bose, A. *Ann. Statist.* **2005**, *33*, 414–436.
[2] Frommelet, F. et al, *Comput. Stat. Data Anal.*, **2012**, *56*, 1038–1051.
[3] Li, X. and others, *Hum. Hered.* **2011**, *71*, 67–82.
[4] McGue et al, *Behav. Genet.* **2013**, 43, doi:10.1007/s10519-013-9606-x.
Main paper available at: https://arxiv.org/abs/1802.01141