Selecting Important Single Nucleotide Polymorphisms in Twin Studies: the *e*-value approach

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An Interdisciplinary Doctoral Fellowship collaboration

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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.

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

- **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

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

- $\boldsymbol{Y}$ = 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^{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^{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.

Results

Simulation

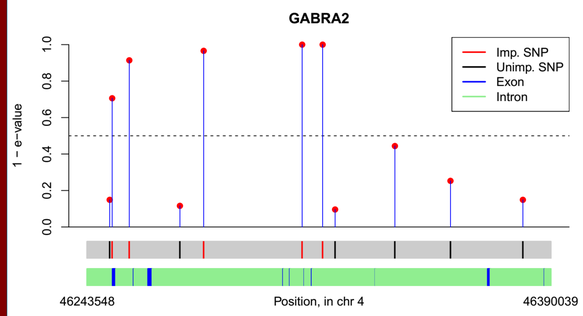
- 50 total SNPs: 4 of them have positive effect, each explaining h/6% pf total variance;
- 100 Families with twins, having kinship matrix **K**.
- **Methods compared:** (a) Linear regression model selection using Bayesian Information Criterion (BIC), (b) Get *p*-values and correct for multiple testing (PVAL).

TP = True Positive proportion, Size = model size:
both averaged from 100 replications

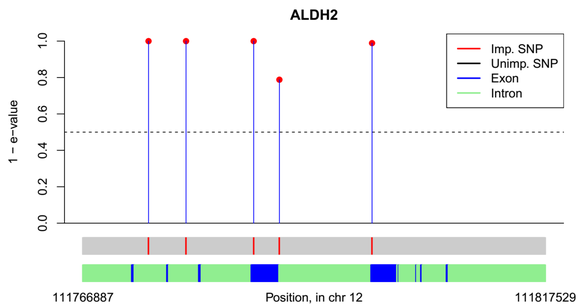
Method	*h* = 5		*h* = 1		*h* = 0	
	TP	**Size**	**TP**	**Size**	**TP**	**Size**
BIC	0.20	3.72	0.08	2.61	0.03	1.94
PVAL	0.03	0.30	0.03	0.30	0.003	0.18
***e*-value (*q* = 0.6)**	0.28	3.88	0.12	2.78	0.03	1.94

Genome-wide Twin Studies application

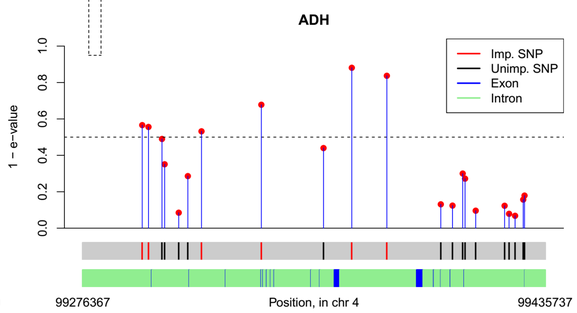
Data from the Minnesota Center for Twin and Family Research (MCTFR) Genome-Wide Association Study sample: 7188 individuals, 527,893 SNP markers [2]. Response variable is **amount of alcohol consumption**.
We consider 9 widely studied genes known to be associated with alcohol consumption and select important SNPs from them using *e*-values (q = 0.9).



(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
All 5 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] McGue et al. *Behav. Genet.* **2013**, 43, doi:10.1007/s10519-013-9606-x.

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