Some aspects of Genome Wide Association Studies (GWAS)

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1. Intro to GWAS

2. Genetic Relationships
   - A simple approach: Genomic Control (GC)
   - Structured Association (SA)
   - Regression Control
   - Principal Component (PC) Adjustment
   - Estimating kinship
   - Mixed Regression Models

W. Astle, D.J. Balding (2009) Population Structure and Cryptic Relatedness in Genetic Association Studies
Statistical Science **24(4)**, 451–471

Outline

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Question: Which SNPs have an influence on the phenotypic trait?

Possible problems

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- ascertainment bias (e.g. cases are sampled from some clinic, controls somewhere else)
- more markers than repetitions (“$n \ll p$ problem”)

Some free GWAS software packages

- PLINK
  `http://pngu.mgh.harvard.edu/~purcell/plink/`
- R packages
  - GWASTools
    `http://bioconductor.org/packages/release/bioc/html/GWASTools.html`
    Bioconductor package, install in R with

    ```
    source("http://bioconductor.org/biocLite.R")
    biocLite("GWASTools")
    ```
  - GenABEL etc.
    `http://genabel.org/packages`
    CRAN package, install in R with

    ```
    install.packages("GenABEL")
    ```

Outline

Different scenarios

Whether we have to compensate for relatedness in the data depends on the where the indivuduals come from.

- Crossing scheme (e.g. in plant breeding): Individuals are F1 (or Fn) generation of two homozygous individuals
- Pedigree is known (up to possible errors)
- Individuals are somehow related but pedigree is unknown
- Individuals are sampled from large population, but there may be some population structure

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The test statistic is T^2/V, where T measures for a locus the difference in allele frequencies between cases and controls, and V approximates the variance of T for the case of neutrality an unrelated samples. Under the latter conditions, T^2/V is approximately χ_1^2-distributed.

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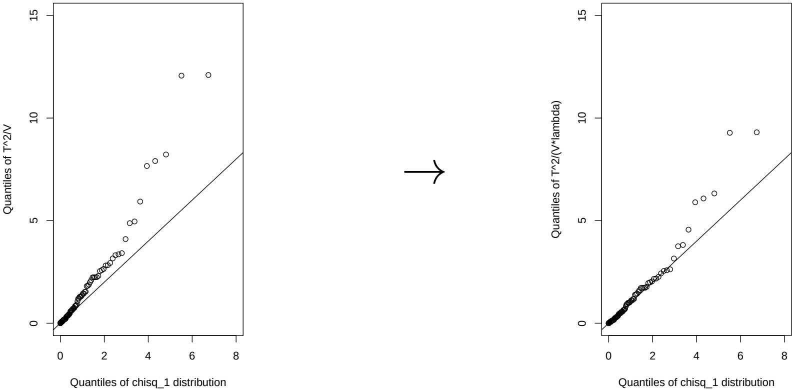
Fitting λ is based on the assumption that only few SNPs are in strong causal association with the test statistic.

Instead of T^2/V use $T^2/(\lambda \cdot V)$, where λ is chosen to make the distribution fit χ^2_1 (up to outliers).



The outliers are candidate loci to be associated with the trait.

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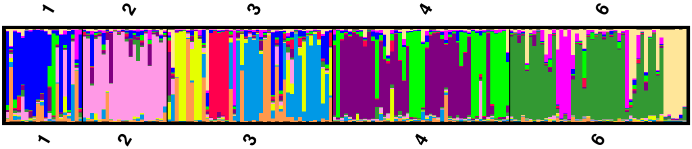

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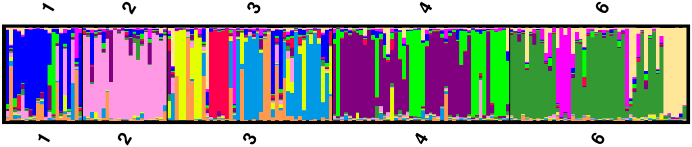

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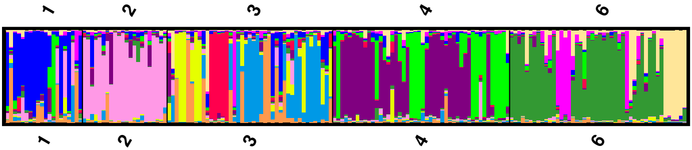

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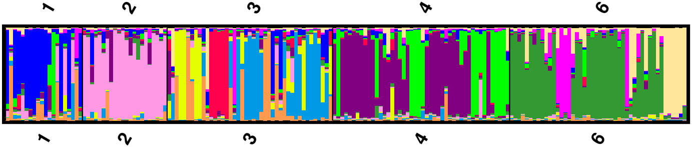

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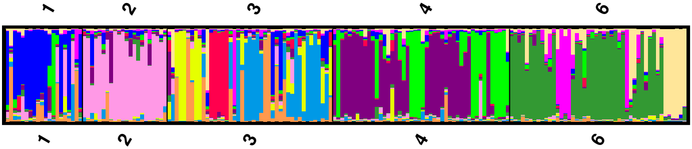

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- SA does not explicitely account for pedigree-level relationships

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- allow flexibility of regression methods

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Principal Component Adjustment

- similar to regression control, but uses PCA (instead of backward selection and regularization) to avoid overfitting
- well-founded for island models
- not clear how well it works for more complex cryptic relatedness

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Kinship coefficients based on marker data

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If *p* is the frequency of allele *A* and x_i and x_j count the A alleles (0,1, or 2) of *i* and *j*, then

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$$\mathrm{Cov}(x_i, x_j) = 4p(1-p)K_{ij}.$$

Thus, K_{ij} can be estimated from genome-wide covariances of allele counts:

$$\widehat{K}_{ij} = \frac{1}{L}\sum_{\ell=1}^{L}\frac{(x_{i\ell}-2p_\ell)\cdot(x_{j\ell}-2p_\ell)}{4p_\ell(1-p_\ell)}$$

where L is the number of loci and p_ℓ is the frequency of allele A at locus ℓ. (At each locus we choose one allele and call it A).

To refine the estimates of p_ℓ and K we can iteratively apply the formulas

$$\widehat{p}_\ell = \frac{\sum_{ij} \left(\widehat{K}^{-1}\right)_{ij} x_{j\ell}}{\sum_{ij} \left(\widehat{K}^{-1}\right)_{ij}}$$

and

$$\widehat{K}_{ij} = \frac{1}{L} \sum_{\ell=1}^{L} \frac{(x_{i\ell} - 2\widehat{p}_\ell) \cdot (x_{j\ell} - 2\widehat{p}_\ell)}{4\widehat{p}_\ell(1 - \widehat{p}_\ell)}.$$

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For human populations $\sim$ 100.000 SNPs are usually required to obtain reasonable estimates of K.

So far we have not accounted for LD btw. markers. This can be done with hidden-Markov models (HMMs).

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- y_i is the trait of interest for individual i
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- δ_i is the polygenetic contribution of all other loci ("small, additive, genetic effects distributed across the genome").

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$$y_i - (\alpha + x_i\beta + \delta_i) \sim \mathcal{N}\left(\vec{0}, \sigma^2(1 - h^2)I\right)$$

Software

EMMA allows fast likelihood-ratio tests with linear mixed models

H.M. Kang *et al.* (2008) Efficient control of population structure in model organism association mapping.
Genetics **178**, 1709–1723

GenABEL contains the command GRAMMAR, which uses an even faster approximative method and may thus have reduced power.

Y.S. Aulchenko,D.-J. de Koning, C. Haley (2007)
Genomewide Rapid Association Using Mixed Model and Regression: A Fast and Simple Method For Genomewide Pedigree-Based Quantitative Trait Loci Association Analysis
Genetics **177**, 577–585

"[. . .] *the common apporoach of 'correcting for population structure' may be misguided*".

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Accounting for population structure and kinship does not avoid false positives due to **pleiotropy**, **multiple causal factors** or **epistasis**.
Suggest to rather correct for confounding effects in general.
Among methods based on the idea that effects of K should be corrected, those are more robust that don't infer K from island model but estimate confounding effects K directly from data, e.g.

J. Yu *et al.* (2006) A unified mixed-model method for association mapping that accounts for multiple levels of relatedness.
Nat. Genet. **38**, 203–208