Power and precision of mapping genes in simulated F2 crosses using whole genome sequence data.

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F2 data in the past

- Many porcine F2 crosses were established for gene mapping experiments

Divergent lineages as founder breeds for F2 designs

- Distantly related (ASIA x EU, e.g. Rückert & Bennewitz 2010)
- Closely related (EU x EU, e.g. Boysen et al. 2010)

Available datasets

- Exact phenotypes for a lot of traits
- Mostly genotyped with microsatellite markers (low mapping resolution)

- Linkage mapping: no historical meioses can be considered

→ many QTL could be found, however, the confidence intervals were large
Can we use F2 data in the era of GENOMICS to precisely map genes?
Applying new next generation sequencing (NGS) techniques on F2 data might lead to powerful datasets for GWAS at reasonable costs.
Current simulation study: What’s it about?

Investigation of power and precision in GWAS using simulated sequence data in

- F2 designs with closely related founder breeds (i.e. EU x EU),
- F2 designs with distantly related founder breeds (i.e. ASIA x EU),
- and the pooled data of both designs.

We compare:

- F2 designs derived from closely and distantly related founder breeds
- Impact of pooling F2 data
- Purebred population vs. F2 crosses
- Small vs. large number of founder animals in F2 designs
Phylogeny of the founder breeds (drift model)

- Protocol is based on what is known about the phylogeny of pigs (Frantz et al. 2013).
- No selection → stepwise reduction of Ne to realize realistic population sizes
- Generation interval: 2.5 years
- Genomes:
  - 2 chromosomes à 1 M
  - 2 mutations/individual/generation
**F2 crossing scheme**

- **EU1**
  - #2 (#10) ♂

- **EU2**
  - #10 (#50) ♀

  - **F1**
    - #10 ♂, #50 ♀

  - **EU1 x EU2**
    - 500 F2 individuals

- **AS**
  - #2 (#10) ♂

- **EU2**
  - #10 (#50) ♀

  - **F1**
    - #10 ♂, #50 ♀

  - **AS x EU2**
    - 500 F2 individuals

- **EU2**
  - #75 ♂, #75 ♀

  - mating within

  - **EU2**
    - 500 purebred individuals
F2 crossing scheme

EU1  EU2  AS  EU2  EU2
#2 (#10)♂  #10 (#50)♀  #2 (#10)♂  #10 (#50)♀  #75♂, #75♀

F1  F1  
#10♂, #50♀  #10♂, #50♀

Pooling data: Joint analysis

EU1xEU2  ASxEU2  EU2
500 F2 individuals  500 F2 individuals  500 purebred individuals
Individuals to be evaluated

EU1
#2 (#10) ♂  
#10 (#50) ♀  

EU2
#10 (#50) ♂  

F1
#10 ♂, #50 ♀  

EU1xEU2
500 F2 individuals

EU2
#75 ♂, #75 ♀  
mating within
EU2

AS
#2 (#10) ♂  
#10 (#50) ♀  

EU2
#10 (#50) ♂  

F1
#10 ♂, #50 ♀  

ASxEU2
500 F2 individuals

EU2
500 purebred individuals
Design of the traits

- Causative SNPs (QTN) were simulated in the pool of all individuals to be evaluated
  - Random but known positions

- Variance components are set so that \( h^2 \approx 0.5 \) is valid for the populations
Single marker regression using **Genome-wide Complex Trait Analysis** (Yang et al. 2014)

Mixed linear model:

\[ y_i = \mu \times b_j \times SNP_{ij} + g_i + e_i \]

- \(y_i\) phenotype of individual \(i\)
- \(\mu\) overall mean
- \(b_j\) regression coefficient of marker \(j\)
- \(SNP_{ij}\) gene content of SNP \(j\) of individual \(i\)
- \(g_i\) random polygenetic effect with \(g \sim N(0, G\sigma_g^2)\) and \(G\) being the GRM
- \(e_i\) residual of individual \(i\)

- QTL mapping on chromosome 1 (2)
- Chromosome 2 (1) to model population structure (GRM)
  - SNPs to be tested are excluded from the GRM (MLMe)
- p-values were adjusted using Bonferroni correction, \(\alpha = 0.01\) (genome wide)
Results: Averaged values across all 50 replicates (10 simulations á 5 traits)

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Power increase in F2 data compared to purebred populations: Highest power in pooled data

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Precision: F2 designs with closely related founders almost reach the precision of purebred populations

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Pooling data increases the precision in F2 designs derived from distantly related founder breeds

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Where is the benefit to use (pooled) F2 sequence data in GWAS?

**EUxEU**
- Precise mapping results $\rightarrow$ short LD blocks

**ASIAxEU**
- High mapping power $\rightarrow$ increased gene frequencies
- Low precision $\rightarrow$ long LD blocks

**Pooling data**
- Increase in power $\rightarrow$ enlarged sample size
- Increase in precision compared to single analysis of ASIAxEU $\rightarrow$ reduced LD block length

This is in agreement with Toosi et al. (2009) and Bennewitz and Wellmann (2014).
Can we use F2 data in the era of GENOMICS to precisely map genes?
Applying NGS techniques on F2 data leads to suitable datasets for GWAS at reasonable costs.

F2 data at a maximum marker density provides a powerful and (cost) efficient possibility to (fine) map genes when the founder breeds are closely related or can be pooled.
Thank you!

This study was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG).