Concordance analysis: from QTL to candidate causative mutations

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Objective

To narrow down from a QTL region containing a large number of polymorphisms to a limited number of candidate causative mutations

Trait – rear leg set side view (RLSV)

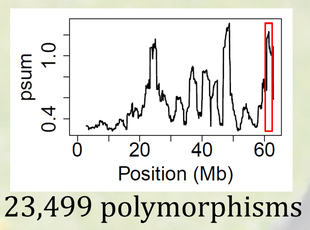
Illustration adapted from primholstein.com

Correlated with culling rate (de Jong, 1997)

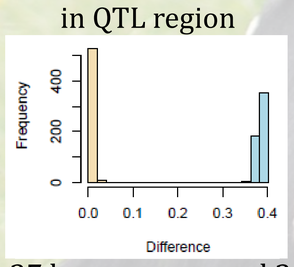
Data

- QTL mapping & status prediction: 50K SNP data
  - 3,154 Holstein bulls
  - Deregressed proofs for RLSV
- Concordance analysis: 71 sequences from 1000 bull genome project

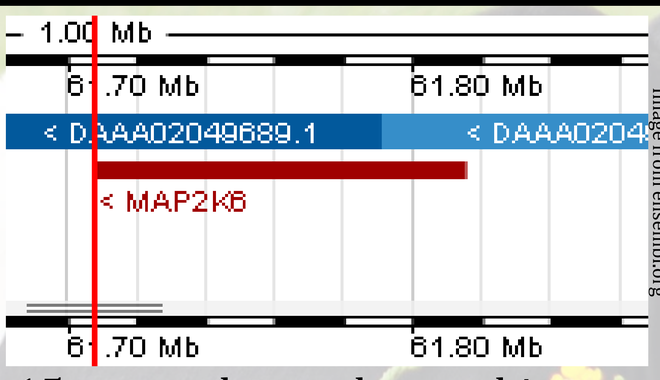
Example – chr 19:60.2-62.5 Mb



23,499 polymorphisms in QTL region



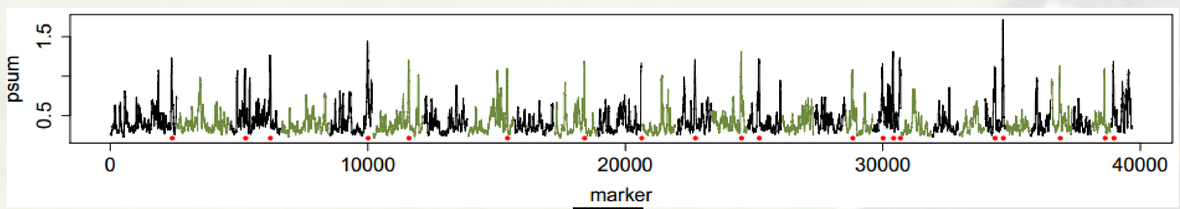
37 homozygous and 34 heterozygous individuals



15 concordant polymorphisms
Intronic/downstream of ***MAP2K6***
Involved in **chondrocyte development** in mice (Zhang *et al.*, 2006)

1) QTL mapping

- Bayes C using GS3 (Legarra *et al.*, 2009), π fixed at 0.01
- Selection of regions based on the sum of posterior marker inclusion probabilities
- 20 intervals of 40 markers (~ 2.5 Mb) selected

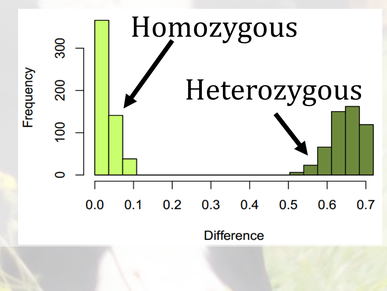


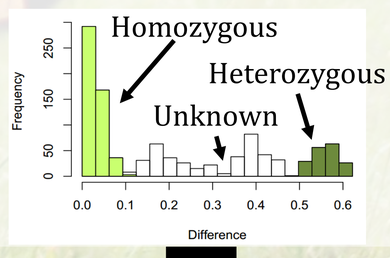
2) Status prediction

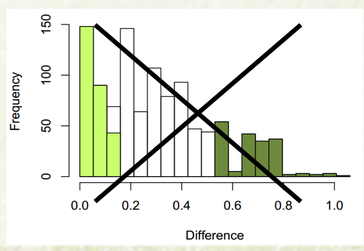
- Marker effects estimated during QTL mapping used to derive QTL status
- Subinterval of 10 markers to reduce noise

Effect haplotype 1	0 +	0 -	0.1 +	0.1 +	0 +	0 +	0 -	0.2 +	0 +	0.1	= **-0.1**
Haplotype 1	1	1	2	2	1	1	1	2	1	2	
Haplotype 2	2	1	2	2	2	2	1	2	1	1	
Effect haplotype 2	0.4 +	0 -	0.1 +	0.1 +	0.2 +	0.3 +	0 -	0.2 +	0 +	0	= **0.7**

Example: difference = 0.8 → clustering → heterozygous







3) Concordance analysis

Sequences → keep polymorphisms in QTL region if:

- Polymorphisms concordant with QTL status for at least 90% of the individuals
- Genotype quality ≥ 20 in at least 5 homozygous and 5 heterozygous individuals

QTL	Polymorphism
homozygous	1/1
~~homozygous~~	~~1/2~~
homozygous	2/2
~~heterozygous~~	~~1/1~~
heterozygous	1/2
~~heterozygous~~	~~2/2~~

Conclusions & Perspectives

Good results for some QTL, but not for QTL influenced by multiple mutations
→ Next steps: imputation, association study using multiple breeds

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