A Bayesian approach to detect QTL affecting a quantitative and binary trait

QTL-MAS workshop 2010
Aniek Bouwman, Luc Janss and Henri Heuven

WAGENINGEN UNIVERSITY
WAGENINGEN UR

Acknowledgement

- Luc Janss
  - iBay software
  - www.LucJanss.com
- Working on multi-trait version of iBay

Data QTL-MAS workshop 2010

- 3226 individuals in 5 generations (F0-F4)
- 2326 individuals have phenotypes (F0-F3)
  - Quantitative trait
  - Binary trait
- All individuals genotyped for 10,031 SNPs

Objectives

- Is there a genetic correlation between the traits?
- Determine QTL affecting either trait
- Are QTL affecting both traits?

Genetic correlation

Linear animal model in ASReml:

$$y = \mu + Zu + e$$

- h^2 quantitative trait = 0.54
- h^2 binary trait = 0.23
- r_a = 0.66

Multi-marker association

- iBay: Bayesian variable selection method
- Animal model for quantitative trait
  - $Y = \mu + \sum_k \sigma_k X_k \alpha_k + Zu + e$
- Threshold sire dam model for binary trait
  - $Y = \mu + \sum_k \sigma_k X_k \alpha_k + Z_s s + Z_d d + e$

Multi-marker association

- Scaling factors shrink allele effects in dualistic manner by applying a mixture distribution:
  - Normal distribution with probability π_0=0.95
    - Shrinks effect of most markers heavily so that they will be removed from the model
    - Explain 1% of the variation
  - Truncated normal distribution with probability π_1=(1-π_0)=0.05
    - Models the markers with important effects
    - Explain 99% of the variation

Post marker analysis

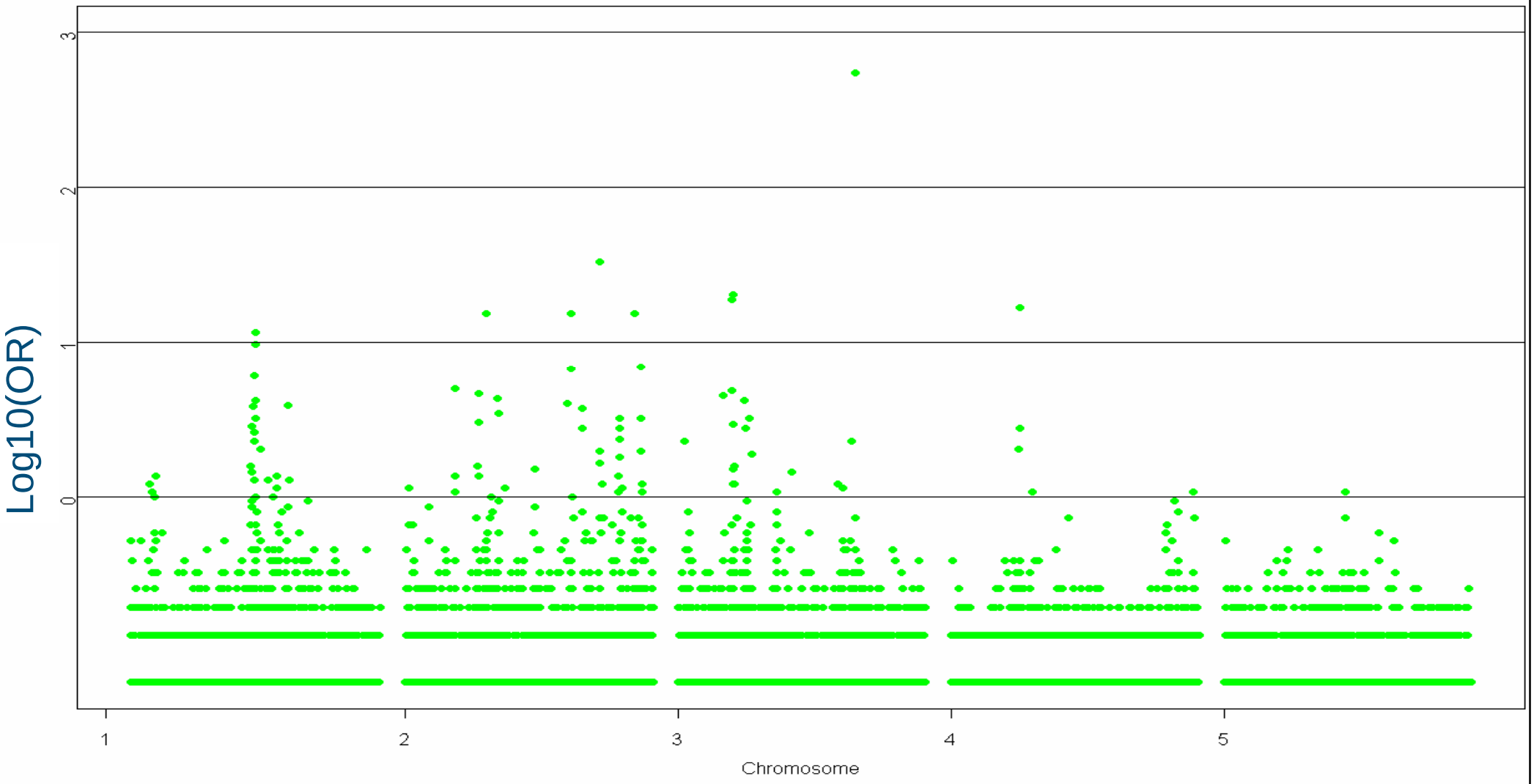
Why:

- Signal of QTL can be spread over multiple markers
  - Single markers then have moderate posterior probability and don't seem significant
- Determine if there is more than one QTL in region

How:

- Grouping markers in a window
- If more than one SNP in window has a high probability to be in the model, probability of one versus multiple QTL in window is estimated

Results quantitative trait



WAGENINGEN UNIVERSITY
WAGENINGEN UR

Significant: Log10(OR)=1

Putative: Log10(OR)=0.5

Significant SNP quantitative trait

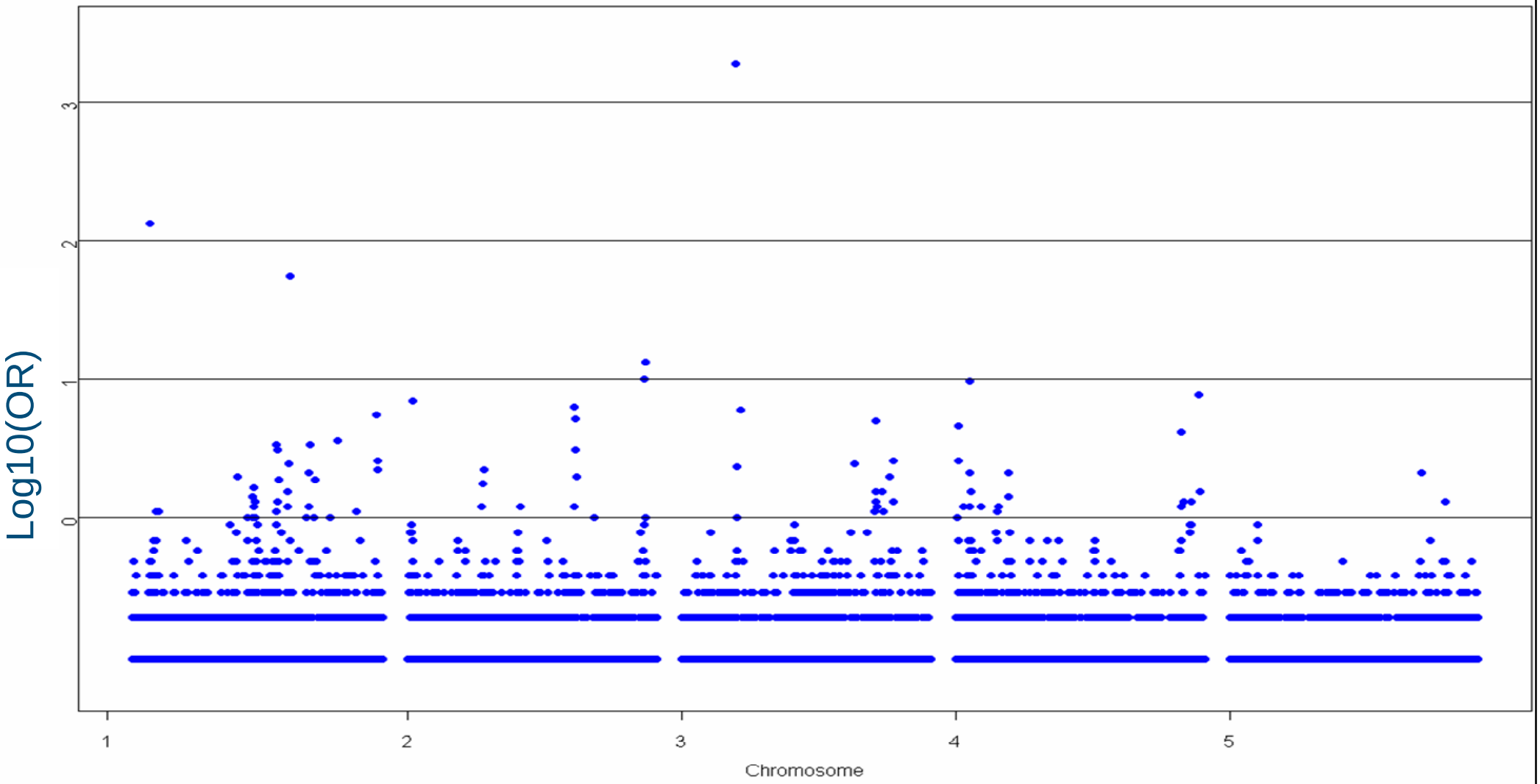
Locus	Chr	Position	OR pos/pri	var
5488	3	71,610,807	551.00	5.34
3623	2	78,604,040	32.82	4.08
4485	3	22,443,619	20.31	1.34
4480	3	22,030,629	18.75	1.17
6703	4	27,663,560	16.85	0.66
2719	2	32,741,451	15.34	1.17
3405	2	66,759,090	15.34	0.64
3905	2	92,573,498	15.34	1.25
954	1	50,009,335	11.65	3.47

And 16 putative SNP

Post marker analysis – quantitative trait

RegSize	Pr(1)	Pr(>1)	Start	End
1	1.00	0.00	5488	5488
8	0.49	0.02	3617	3624
6	0.96	0.11	4479	4484
5	0.76	0.25	4485	4489
9	0.60	0.00	6696	6704
7	0.35	0.00	2719	2725
9	0.27	0.00	3405	3413
10	0.78	0.15	3901	3910
10	0.78	0.22	951	960

Results binary trait



WAGENINGEN UNIVERSITY
WAGENINGEN UR

Significant: Log10(OR)=1

Putative: Log10(OR)=0.5

Significant SNP binary trait

Locus	Chr	Position	OR pos/pri	Prob 2ndMix	var
4480	3	22,030,629	1881.00	1.00	2.27
145	1	7,149,725	133.00	0.88	2.15
1215	1	63,017,238	55.51	0.75	2.53
3961	2	95,493,425	13.20	0.41	0.39
3948	2	94,982,901	10.01	0.34	0.40

And 13 putative SNP

Post marker analysis – binary trait

RegSize	Pr(1)	Pr(>1)	Start	End
1	1	0	4480	4480
9	0.88	0.05	137	145
10	0.86	0.075	1207	1216
8	0.525	0.085	6209	6216
10	0.48	0.02	3960	3969
3	0.42	0.04	3948	3950

Pleiotropy

SNP	Quantitative OR	Binary OR
4480	18.7	1881.0
3405	15.3	6.3
3948	6.9	10.0
1215	3.9	55.5

Bivariate model in ASReml

- B Q ~ Trait Trait.SNP !r Trait.Individual

SNP	varB	varQ	cov	r_g
none	0.046	54.5	1.05	0.66
4480+3948+1215	0.038	46.6	0.79	0.59

→ ~10%

- Both genetic variances and genetic covariance decreased,
  - SNP explain part of the covariance -> indicating pleiotropy
  - Must be more pleiotropic SNP to explain all the covariance

Consequences for selection

- Unfavourable pleiotropy causes difficulties in breeding programs
- Is there true pleiotropy by a single QTL or are there 2 linked QTL?
  - 2 linked QTL: break up genetic correlation
  - Create 2 lines and use hybrids for production

Multivariate QTL analysis

- Higher power to detect QTL, specially for traits with low heritability
- Improved precision of position

Conclusion

- Q: 9 significant and 16 putative SNP
- B: 5 significant and 13 putative SNP
- 4 SNP overlapping between traits, explain ~10% of the correlation