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Linkage analysis of the XVIth QTLMAS simulated dataset using QTLMap

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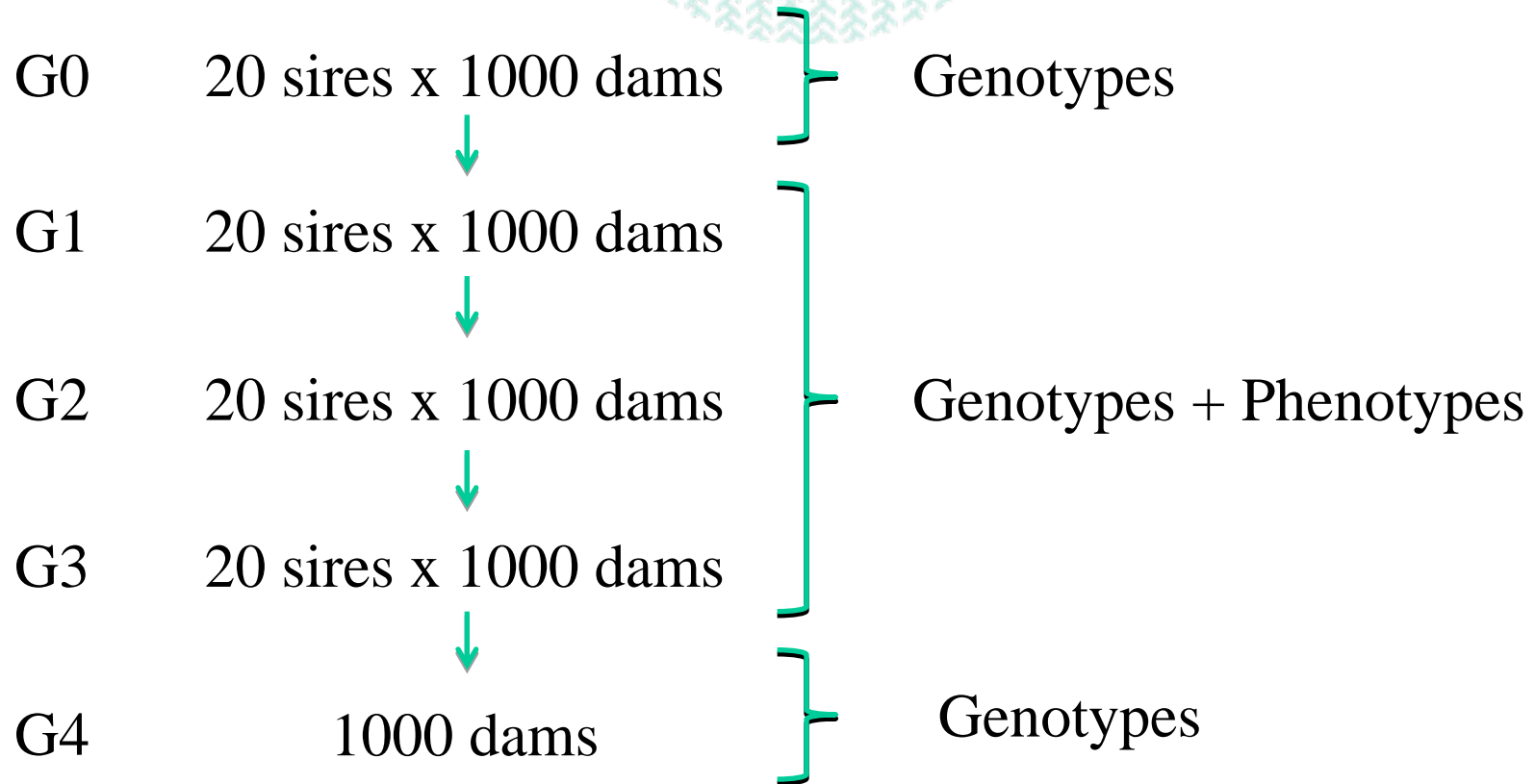


Aim

More and more association analyses, often without any use of linkage

- ➔ Does LA analyses still add some information ?
- ➔ Is LA better than association in false positive discovery ?
- ➔ It could be an interesting comparison point for the organizers

Dataset



5 chromosomes / 10000 SNP (1/0.05Mb) / 3 traits

QTLMap

A software for trait dissection in mixture of full and half-sib families using genomic markers

Single QTL	X	LA
Multi QTL		LD LDLA

Multi Trait	X	LA
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QTLMap

A software for trait dissection in mixture of full and half-sib families using genomic markers

Single QTL	X	LA
Multi QTL		LD LDLA
Multi Trait	X	LA

Linkage Analysis

- Full Mixture model, a likelihood approach

Parental phase probability

$$\text{Likelihood} = \prod_i \sum_{hs_i} p(hs_i / M) \prod_j \sum_{hd_j} p(hd_j / hs_i, M)$$

$$\prod_k \sum_{t_{ijk}} p(t_{ijk} / hd_j, hs_i, M) \cdot f(y_{ijk} / t_{ijk}, \sigma^2)$$

Transmission probability
at position x

Penetrance function

Linkage Analysis

- linearized model, the regression approach

$$\Pi_i \Pi_j \Pi_k f(y_{ijk} / \sum_{t_{ijk}} p(t_{ijk} / hd_j, hs_j, M) \cdot t_{ijk}, \sigma^2)$$

- The only most probable sire and dam phases are considered

- The penetrance is a normal with as a mean the weighted QTL effect

➔ $y \approx \mathcal{N}(\mu, V=I\sigma^2)$

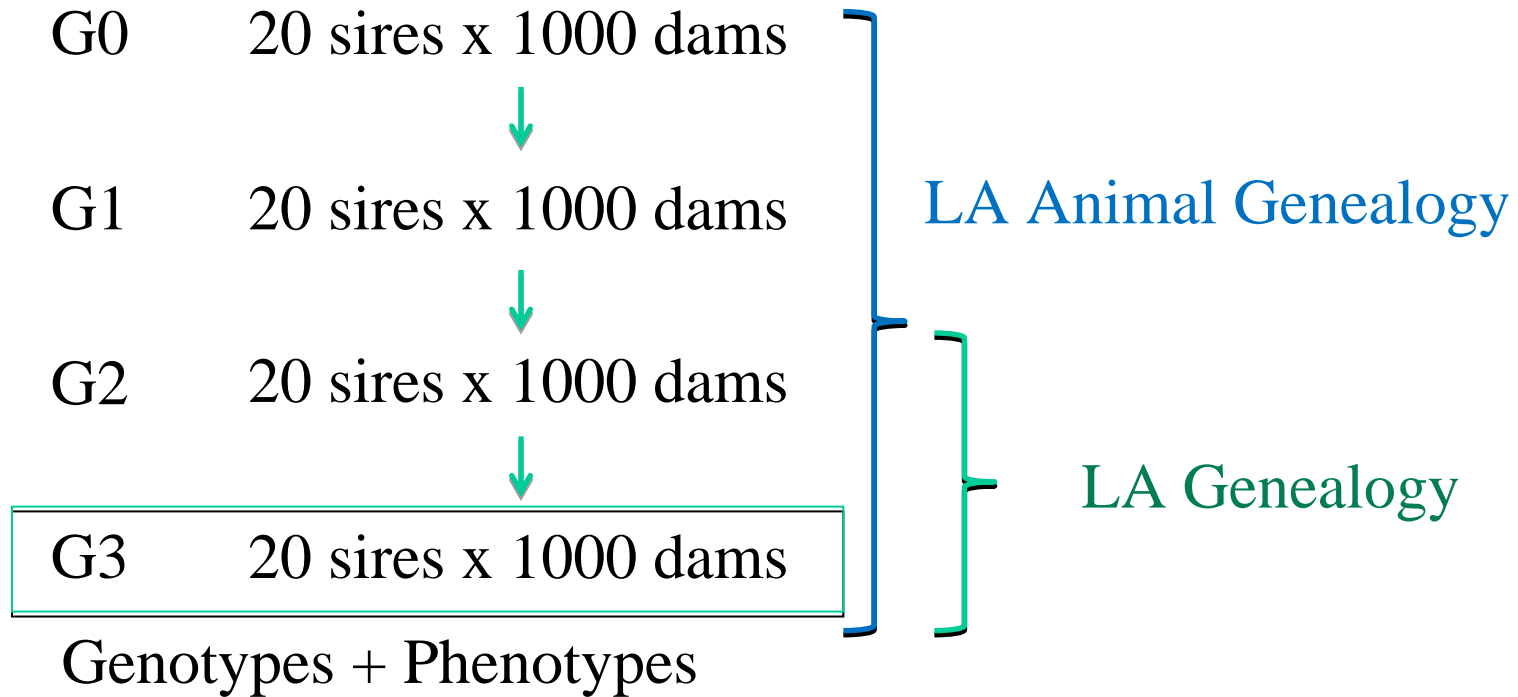
Linkage Analysis

- mixed model (including an animal effect)

➔ $y \approx \mathcal{N}(\mu, V=A\sigma_a^2 + I\sigma_e^2)$

- The user gives the pedigree and heritability
- QTLMap computes the relationship matrix A
- The effects are estimated by a BLUP

LA vs. LA Animal



LA vs. LA Animal

- No difference in QTL detection was observed in this dataset
 - It would be interesting to test this method in a small family structured design
- ➡ Focus on LA analysis
- Use of all the design (G0-G1-G2-G3)
- ➡ 60 independant families (3000 phenotypes)

Single QTL

Detection of 9 QTL using 3000 animals:

- Two were not observed using only the G3 animals
- Surprisingly QTL affecting trait 2 on chromosome 5 is less significant
- A few QTL have a location shift

➔ There are more than one QTL location on Chr 1 and 5
Chr1: 19 (trait 2), 52 (trait 1) and 80cM (trait 3)
Chr5: 71 (trait 2) and 79cM (trait 1)

Single QTL

Detection of 9 QTL using 3000 animals:

- Two were not observed using only the G3 animals
- Surprisingly QTL affecting trait 2 on chromosome 5 is less significant
- A few QTL have a location shift

➔ There are more than one QTL location on Chr 1 and 5

➔ Some of the QTL affecting different traits share the same location (pleiotropy ?)

Chr4: 23 and 26cM for traits 1 and 2, respectively

Multi-QTL

0 vs 2 QTL

-No significant QTL

1 vs 2 QTL

- Chr1 / Trait 3: 60 and 84cM
- Chr5 / Trait 2: 25 and 68cM

➔ Chr1 seems to carry 3 QTL, around 20, 60 and 84 cM
Chr5 seems to carry a QTL at 25cM in addition of the QTL detected around 70 and 80cM

Multi-Trait

Chromosome 1:

Single- and Multi-QTL analyses:

Chr1 seems to carry 3 QTL, around 20, 60 and 84 cM

Multi-trait analyses:

Single-QTL (three traits):	1 QTL at 60cM
Single-QTL (traits 1 / 2):	1 QTL at 19cM
Single-QTL (traits 1 / 3):	1 QTL at 78cM
3QTL (traits 1 / 2 / 3) :	QTL at 19, 70 and 80cM

- QTL at 60cM is probably a false positive
There are 2 pleiotropic QTL at 19 and 78cM

Multi-Trait

Chromosome 4:

Multi-trait using traits 1 and 2: 1 QTL at 23.5cM

➔ The QTL at 23.5cM is pleiotropic

The off topic slide

With the Linkage Disequilibrium (LD) analysis, we do not find the QTL on Chromosome 2 while the QTL on Chr 3 is shifted

	Chr2	Chr3
LA	0.79 ***	0.36***
LD	0.80 NS	0.49***

➔ Using the LA seems to be interesting for Chr2. Hard to conclude for Chr3

Conclusion

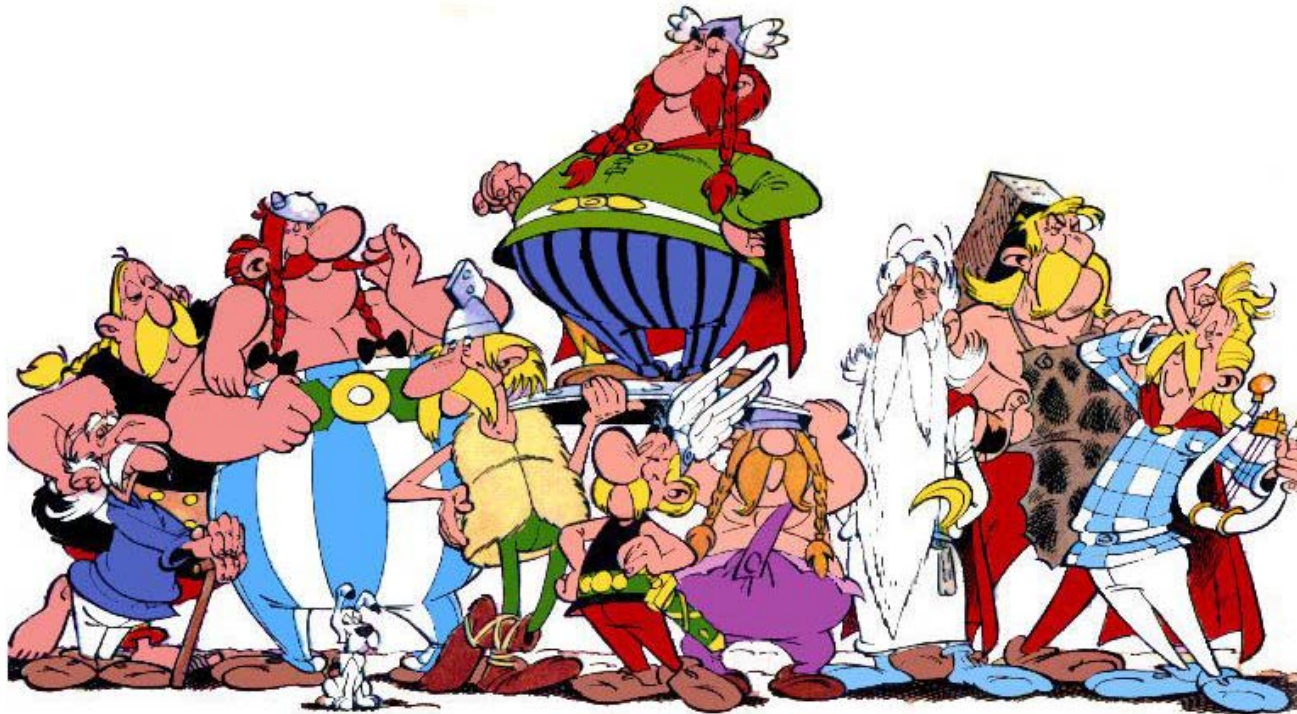
Chromosome	Trait	Location (M)	Effect (2a)	Effect (trait std)	
1	1	0.19	137.32	0.87	Multi-QTL + Multi-trait
1	2	0.19	5.93	0.87	
1	1	0.78	125.35	0.79	
1	3	0.78	0.02	0.96	
2	3	0.79	0.02	0.7	Single-QTL
3	3	0.365	0.02	0.875	
4	1	0.235	92.03	0.58	Multi-Trait
4	2	0.235	5.74	0.67	
5	1	0.785	116.42	0.79	Single-QTL
5	2	0.25	6.71	0.775	Multi-QTL
5	2	0.68	7.38	0.852	

- 8 QTL were detected, three of them being pleiotropic
- Using different models allows the identification of additional QTL but also to precise locations or avoid false positive
- LA sometimes is more interesting than LD



We will see tomorrow how wrong we are !

Thank you for your attention



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