Mapping quantitative trait loci in mice

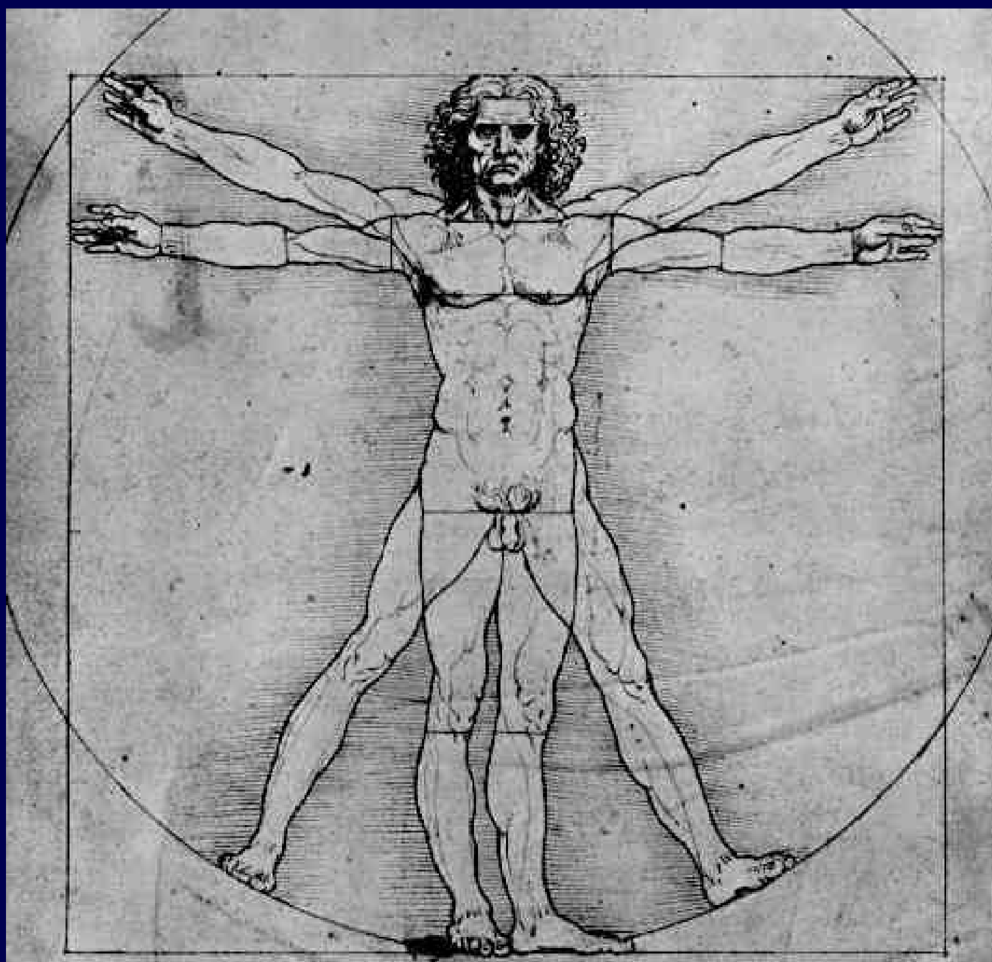
Karl W Broman

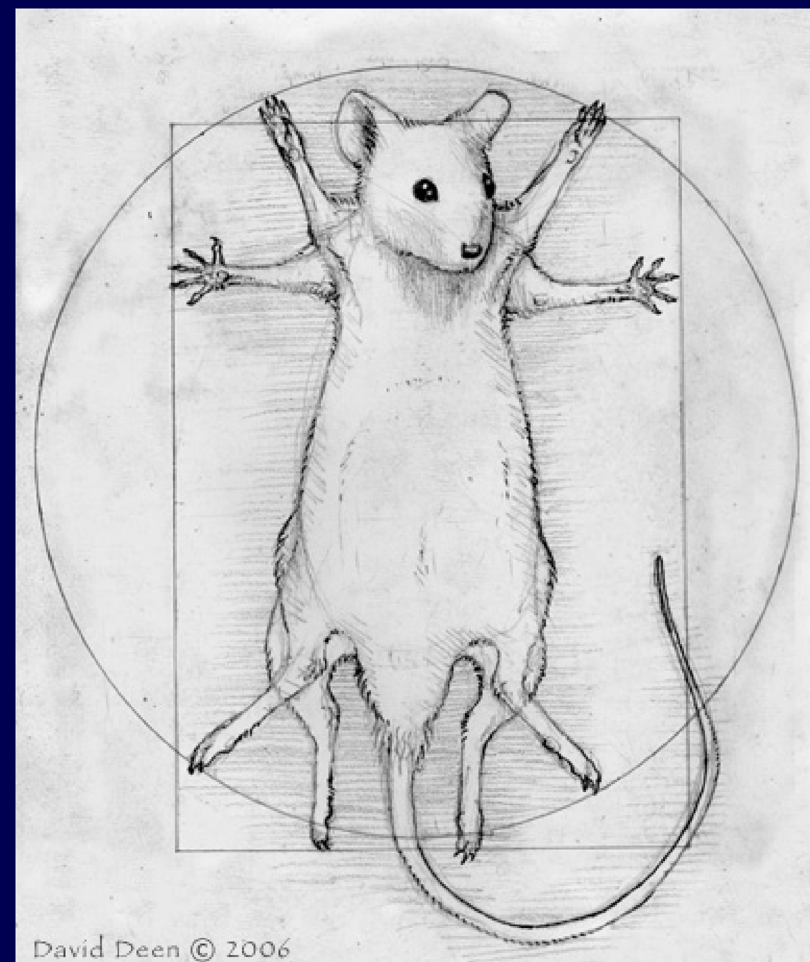
Biostatistics & Medical Informatics

University of Wisconsin – Madison

www.biostat.wisc.edu/~kbroman

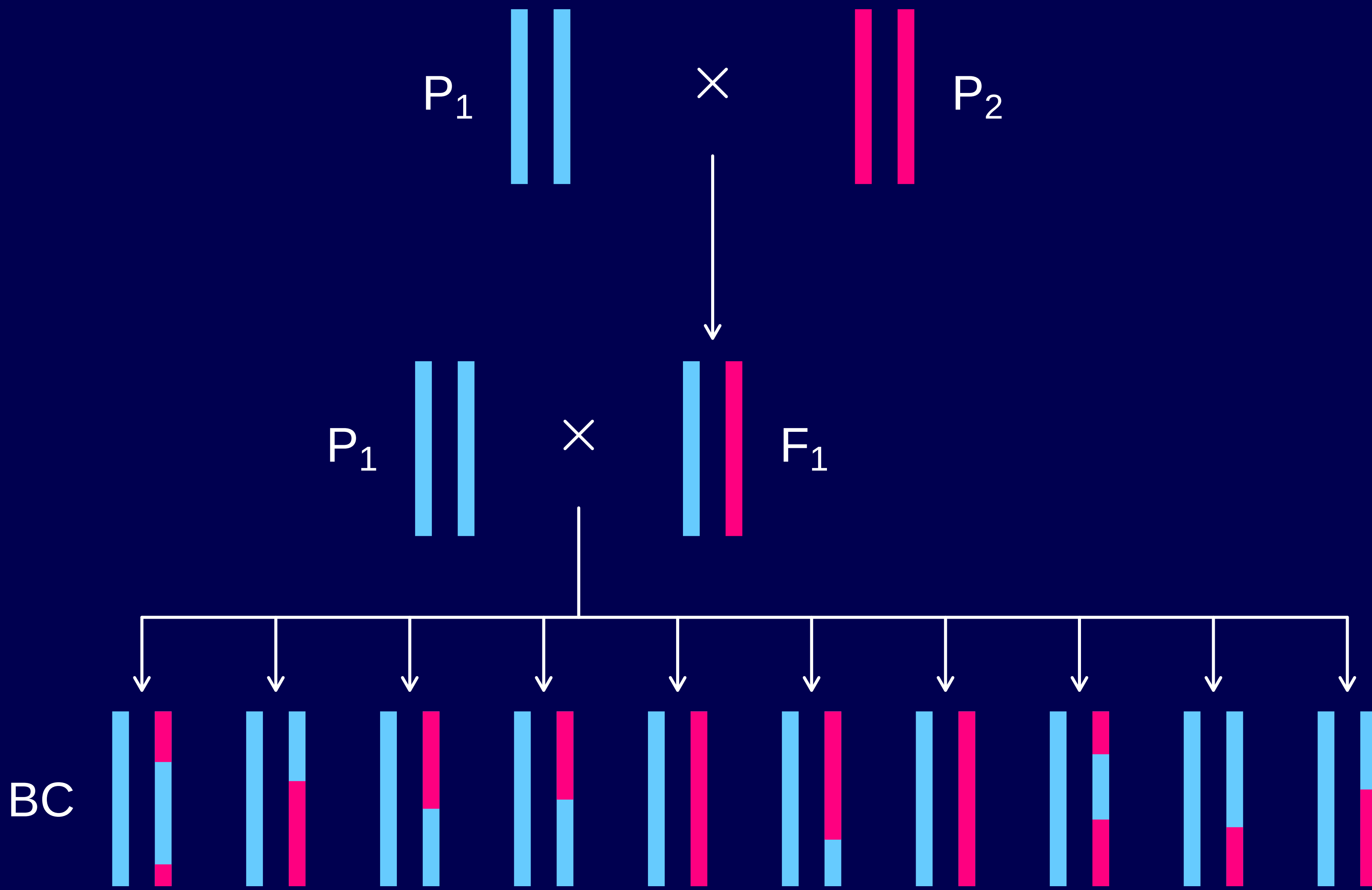
Human vs mouse



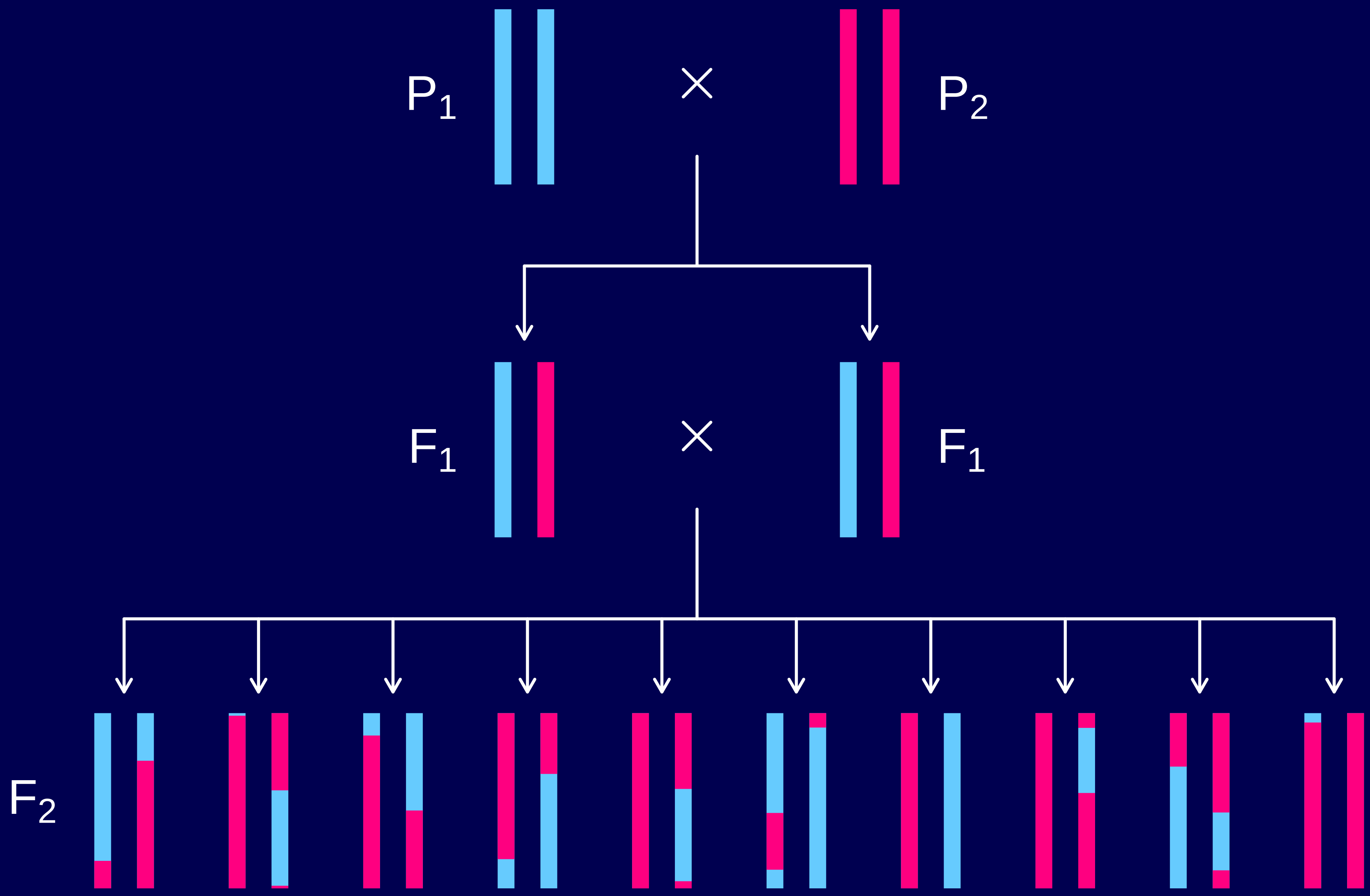


www.daviddeen.com

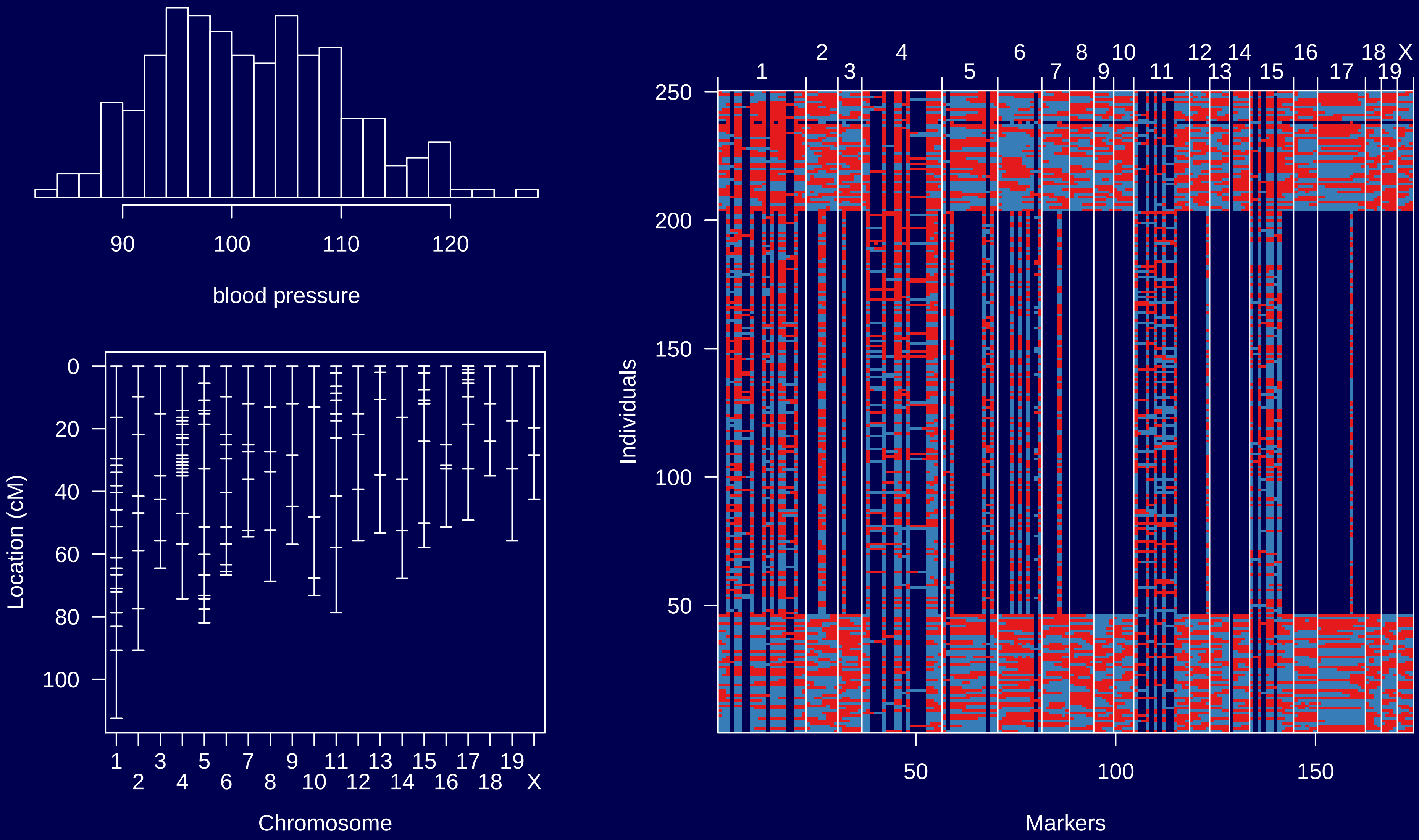
Backcross



Intercross

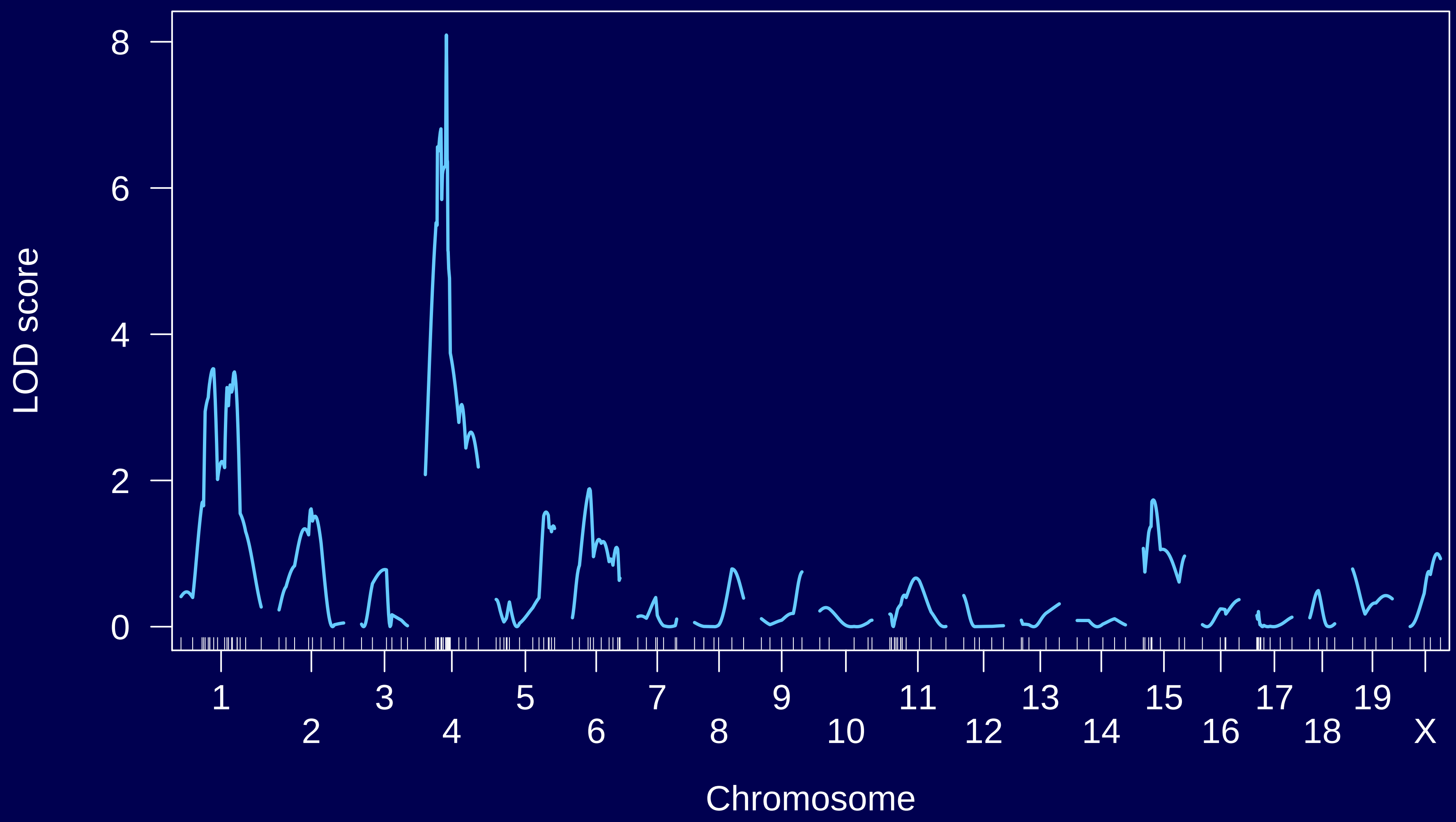


Data



Sugiyama et al. Genomics 71:70-77, 2001

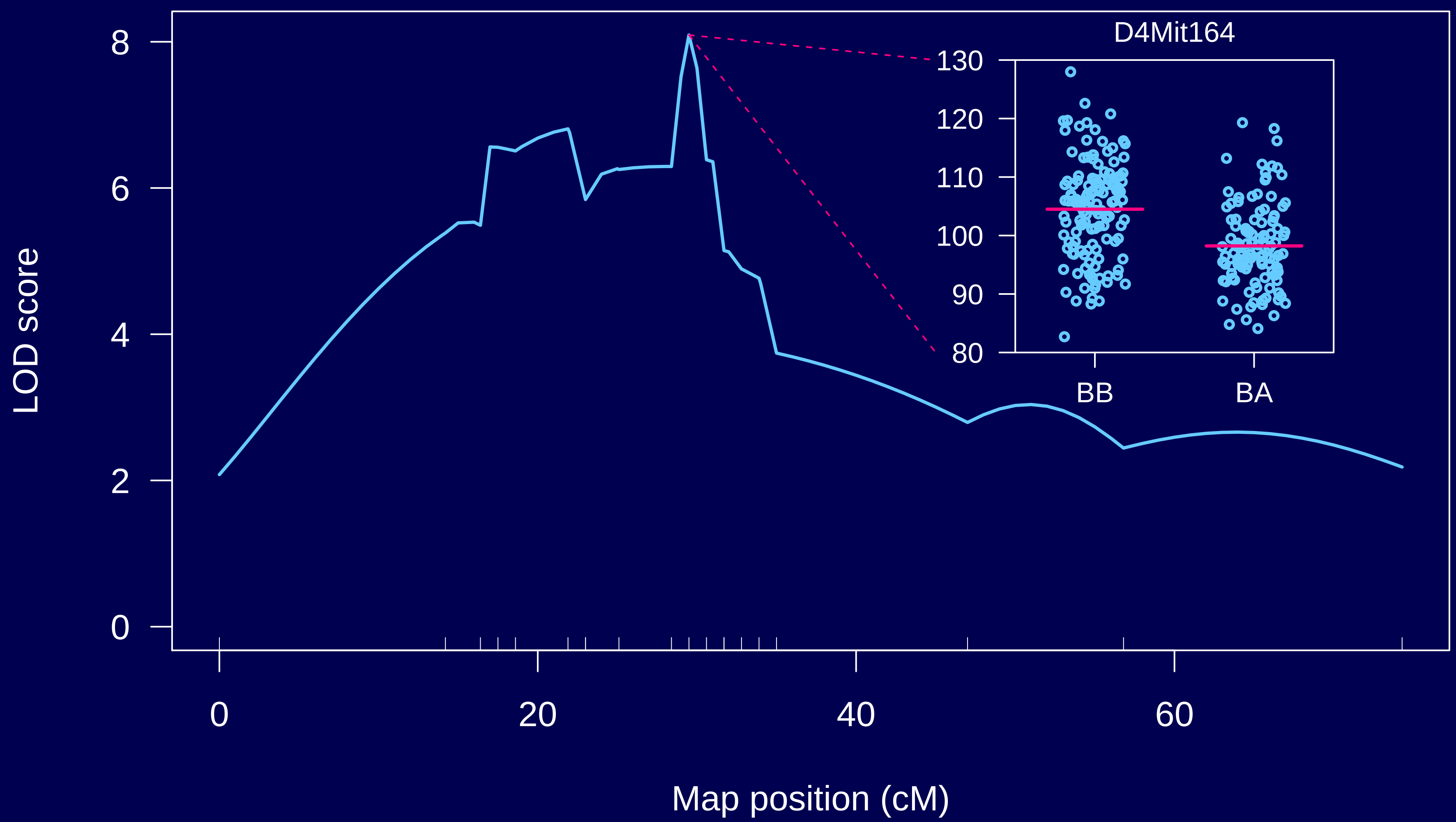
LOD curves



LOD score
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 X
Chromosome

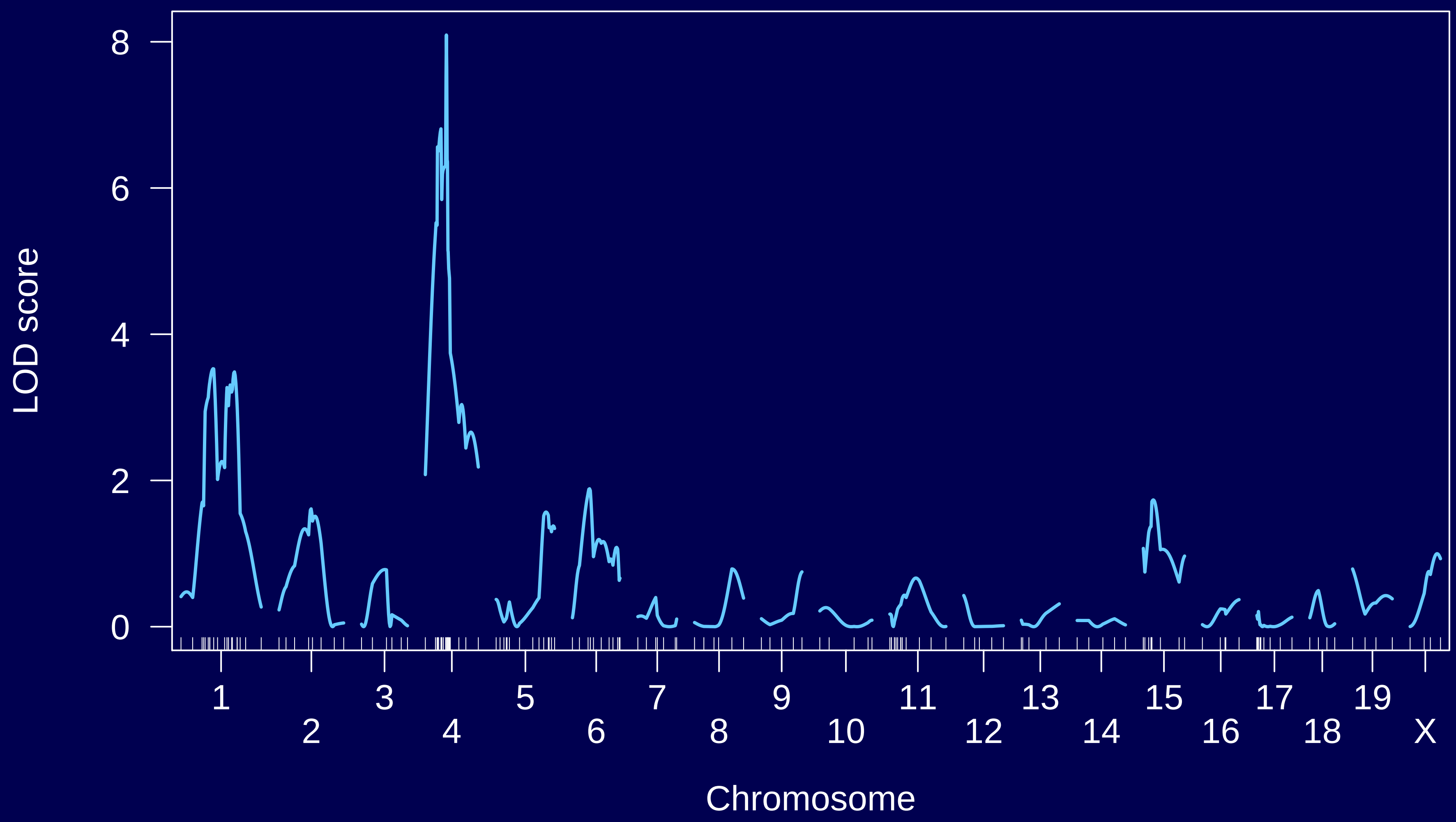
LOD curves

LOD curves



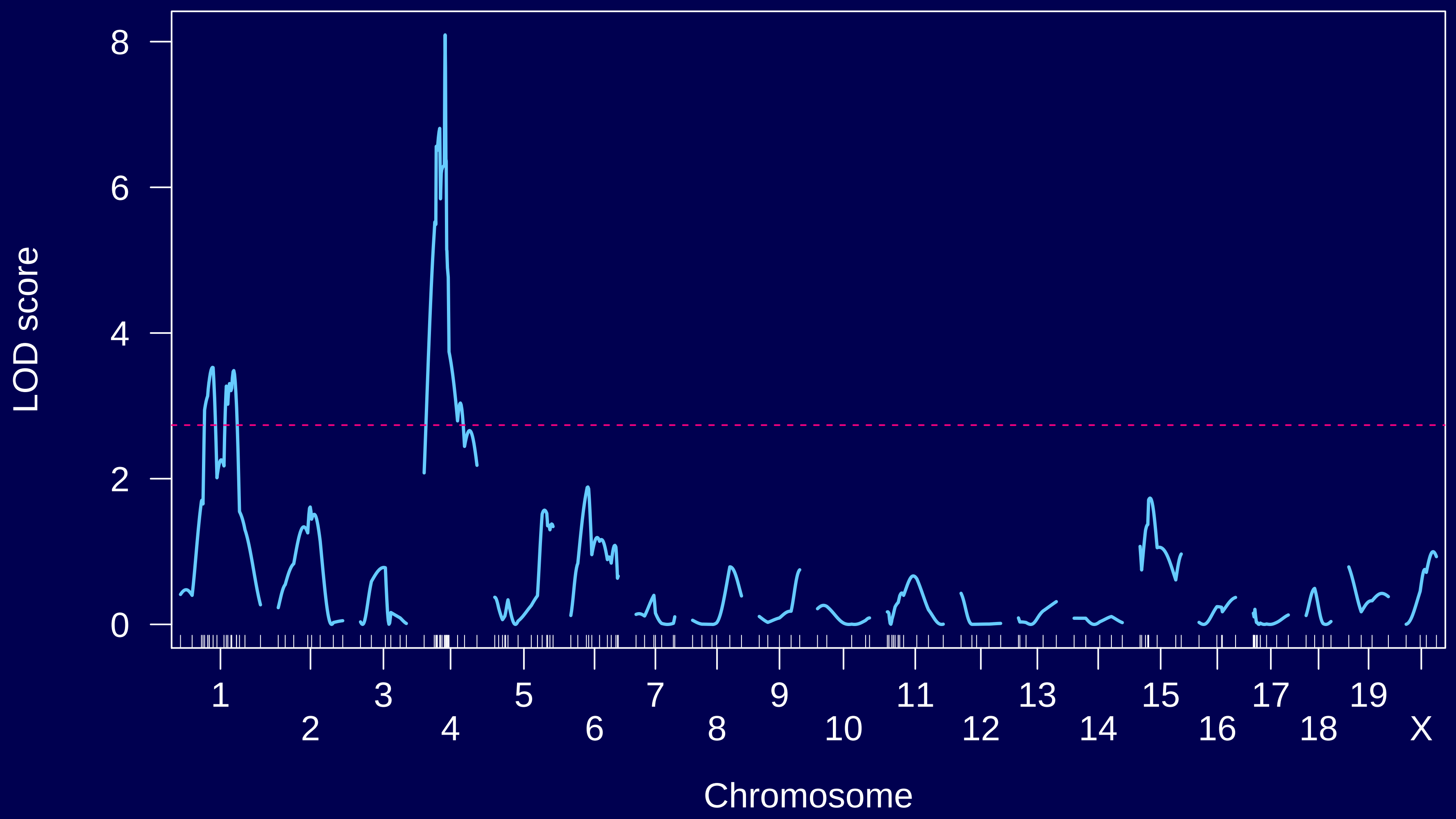
LOD score
Map position (cM)
0
2
4
6
8
0
20
40
60
D4Mit164
130
120
110
100
90
80
BB
BA

LOD curves



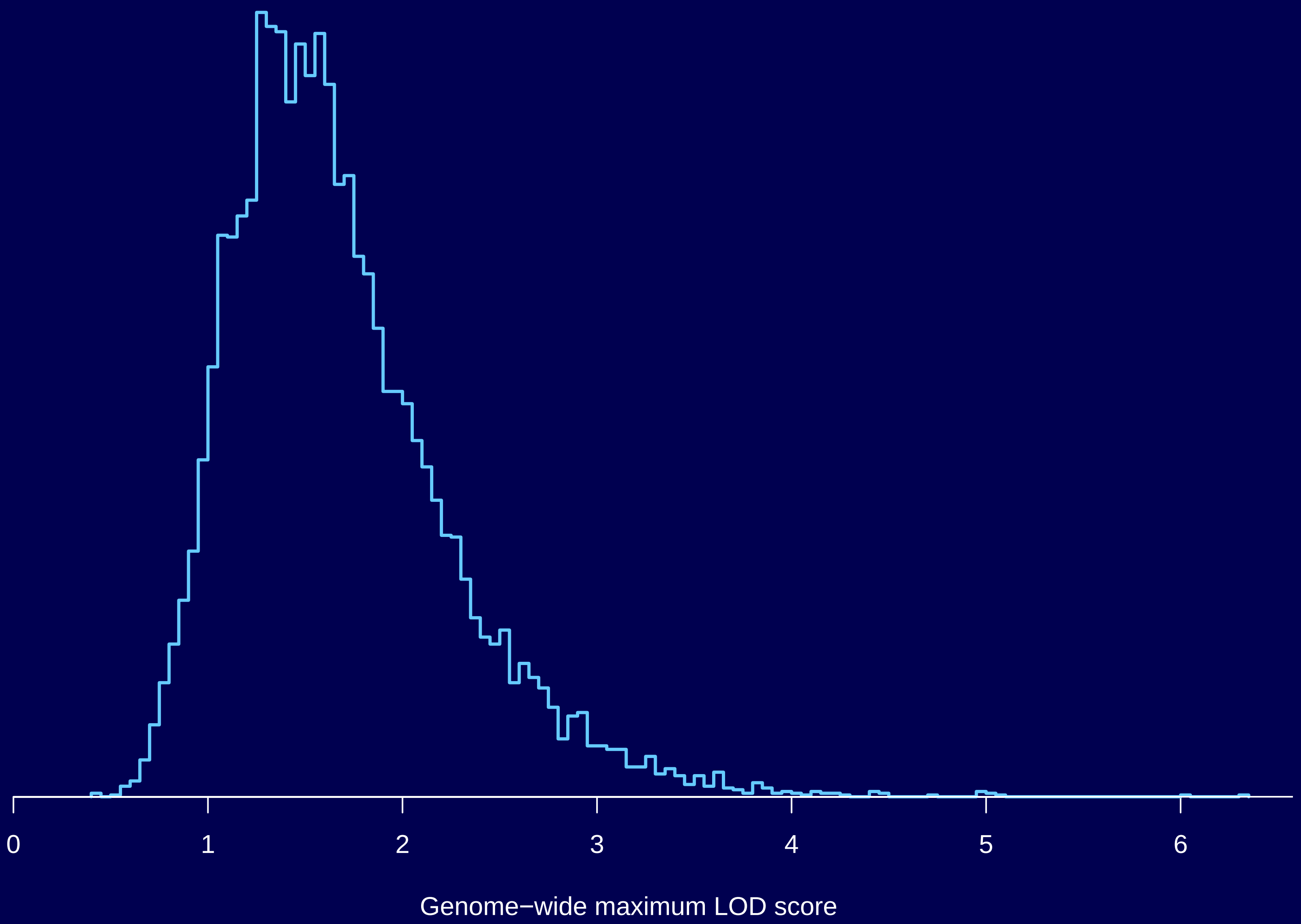
LOD score
0
2
4
6
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

LOD curves

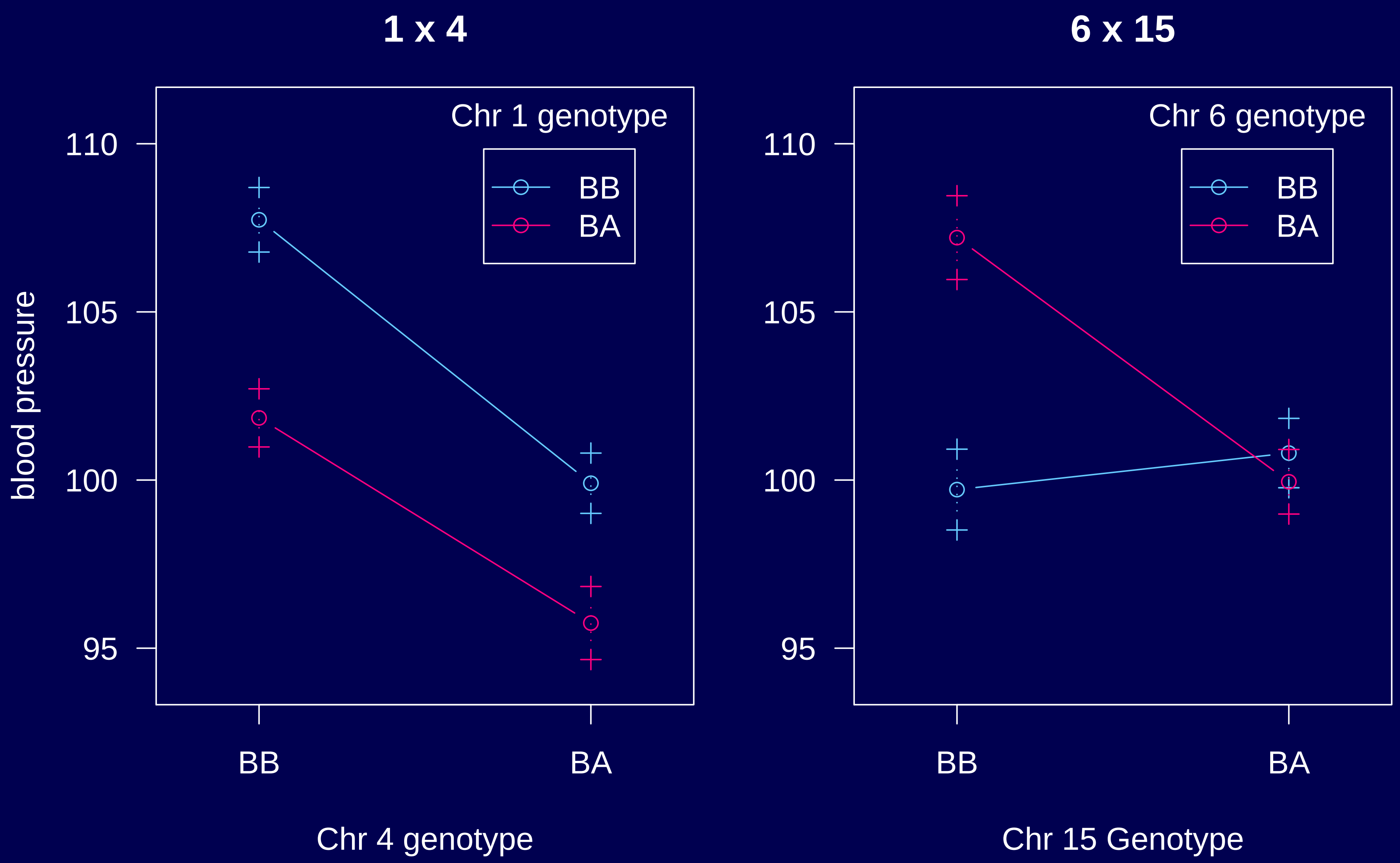


LOD score
8
6
4
2
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

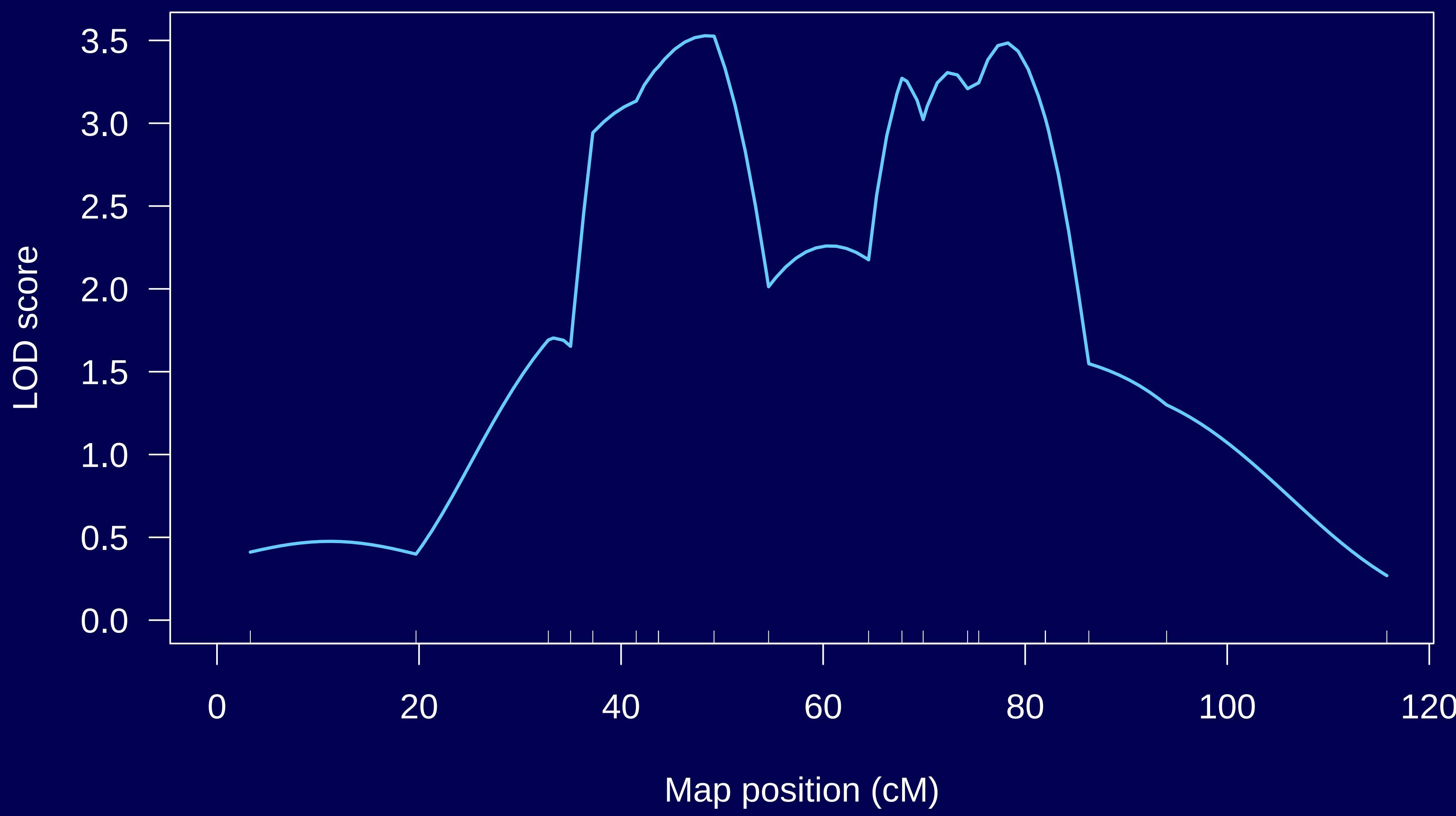
Permutation results



Epistasis

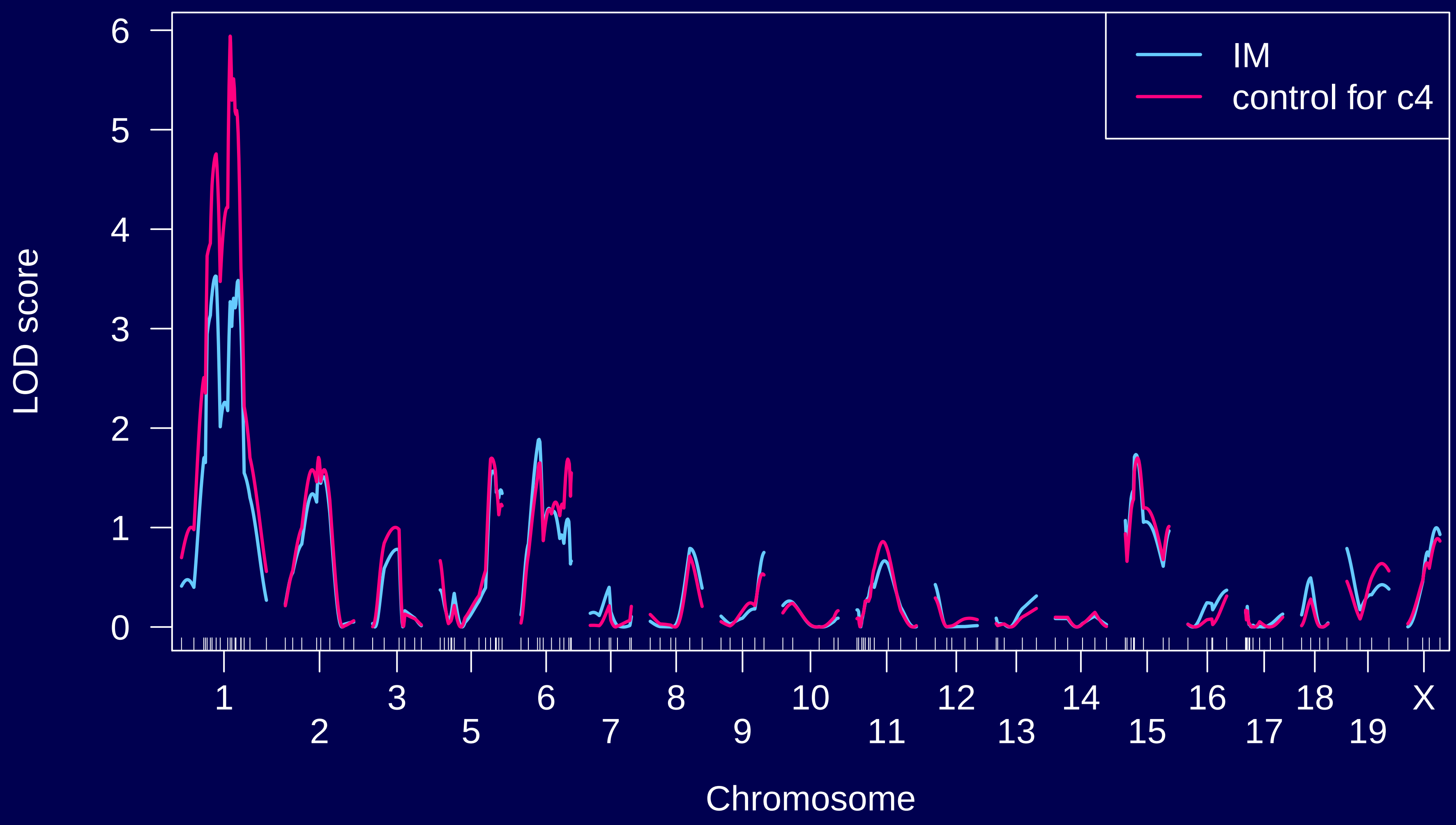

1 x 4
6 x 15
Chr 1 genotype
Chr 6 genotype
BB
BA
blood pressure
110
105
100
95
Chr 4 genotype
Chr 15 Genotype

Linked QTL?



LOD score
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
100
120
Map position (cM)

Control for chr 4



Model selection

- Choose class of models
- Fit a model
- Search model space
- Compare models

Target

- Selection of a model includes two types of errors:
  - Miss important terms (QTLs or interactions)
  - Include extraneous terms

- Identify as many correct terms as possible, while controlling the rate of inclusion of extraneous terms.

- More concerned about extraneous loci than about extraneous interactions.

What is special here?

- Goal: identify the major players
- A continuum of ordinal-valued covariates (the genetic loci)
- Association among the covariates
  - Loci on different chromosomes are independent
  - Along chromosome, a very simple (and known) correlation structure

Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

$$y = \mu + \sum \beta_j q_j + \epsilon \qquad \text{which } \beta_j \neq 0?$$

$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - T\,|\gamma|$$

Additive QTL

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$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - T\,|\gamma|$$

0 vs 1 QTL: $\text{pLOD}(\emptyset) = 0$

$\text{pLOD}(\{\lambda\}) = \text{LOD}(\lambda) - T$

Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

$$y = \mu + \sum \beta_j q_j + \epsilon \qquad \text{which } \beta_j \neq 0?$$

$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - T\,|\gamma|$$

For the mouse genome:

T = 2.69 (BC) or 3.52 (F_2)

Experience

- Controls rate of inclusion of extraneous terms
- Forward selection over-selects
- Forward selection followed by backward elimination works as well as MCMC
- Need to define performance criteria
- Need large-scale simulations

Broman & Speed, JRSS B 64:641-656, 2002

Epistasis

$$y = \mu + \sum \beta_j q_j + \sum \gamma_{jk} q_j q_k + \epsilon$$

$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - T_m |\gamma|_m - T_i |\gamma|_i$$

T_m = as chosen previously

T_i = ?

Idea 1

Imagine there are two additive QTL and consider a 2d, 2-QTL scan.

T_i = 95th percentile of the distribution of

$$\max \mathrm{LOD}_f(s,t) - \max \mathrm{LOD}_a(s,t)$$

Idea 1

Imagine there are two additive QTL and consider a 2d, 2-QTL scan.

T_i = 95th percentile of the distribution of

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For the mouse genome:

T_m = 2.69 (BC) or 3.52 (F_2)

T_i^H = 2.62 (BC) or 4.28 (F_2)

Idea 2

Imagine there is one QTL and consider a 2d, 2-QTL scan.

$T_m + T_i$ = 95th percentile of the distribution of

$$\max \text{LOD}_f(s,t) - \max \text{LOD}_1(s)$$

Idea 2

Imagine there is one QTL and consider a 2d, 2-QTL scan.

$T_m + T_i$ = 95th percentile of the distribution of

$$\max \text{LOD}_f(s,t) - \max \text{LOD}_1(s)$$

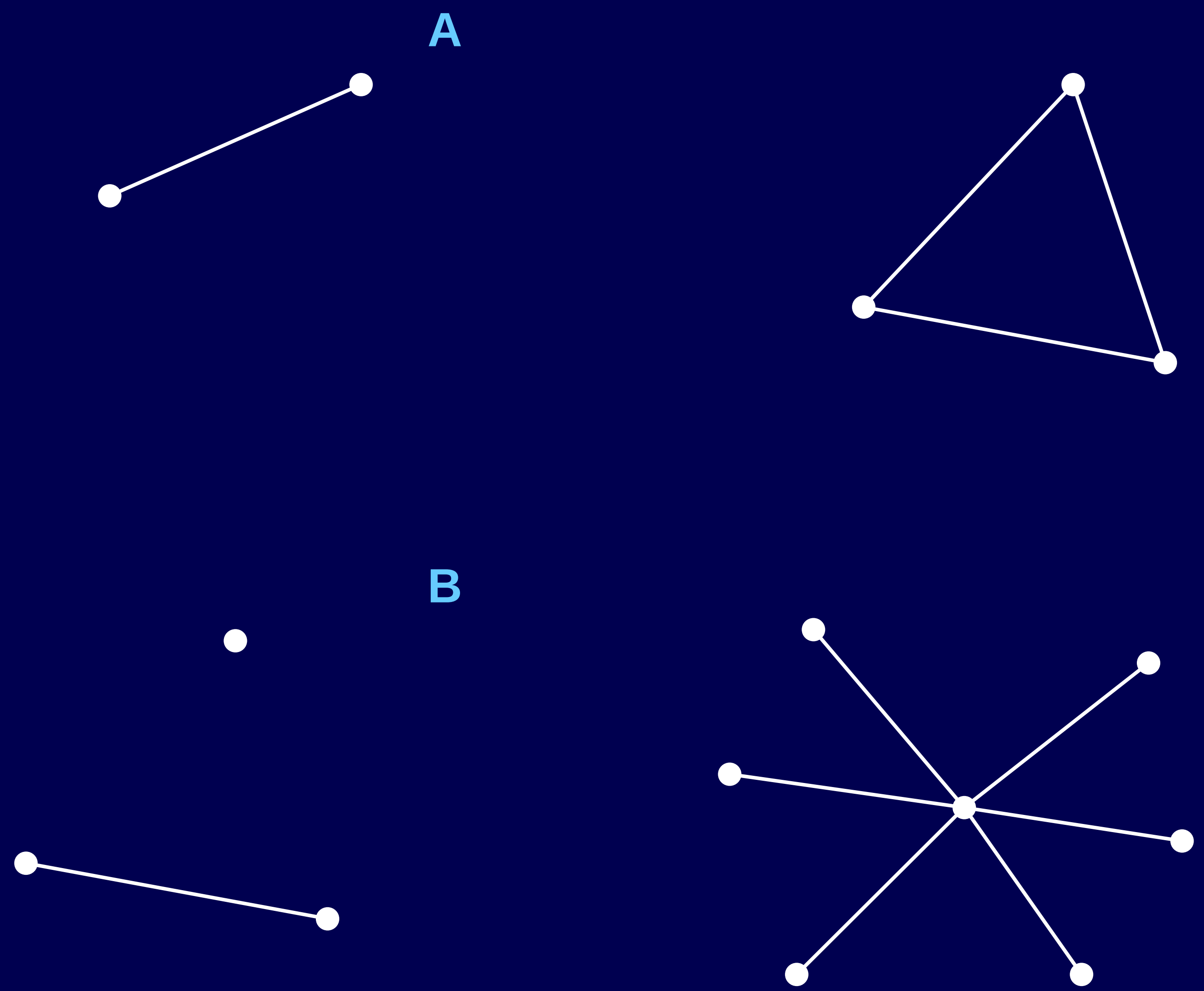
For the mouse genome:

T_m = 2.69 (BC) or 3.52 (F_2)

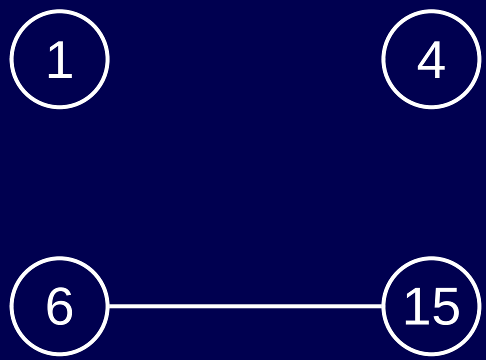
T_i^H = 2.62 (BC) or 4.28 (F_2)

T_i^L = 1.19 (BC) or 2.69 (F_2)

Models as graphs

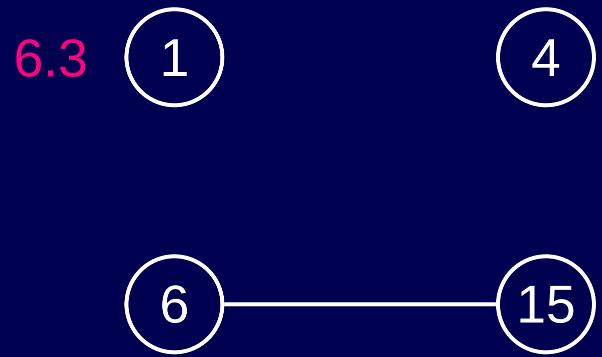


Results



LOD = 23.1

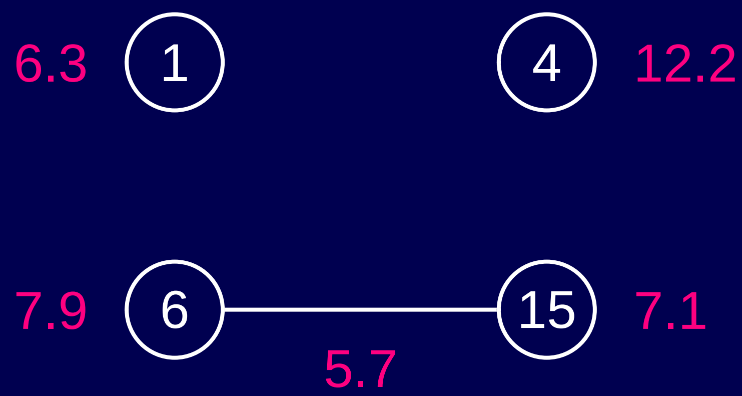
Results



LOD = 23.1

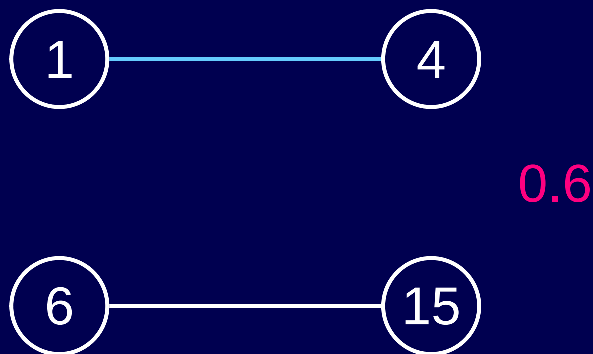
$T_m = 2.69$ $T_i^H = 2.62$ $T_i^L = 1.19$ $T_m + T_i^H = 5.31$ $T_m + T_i^L = 3.88$ $2T_m = 5.38$

Results



$T_m = 2.69$ $\quad T_i^H = 2.62$ $\quad T_i^L = 1.19$ $\quad T_m + T_i^H = 5.31$ $\quad T_m + T_i^L = 3.88$ $\quad 2T_m = 5.38$

Add an interaction?



$T_m = 2.69$ $T_i^H = 2.62$ $T_i^L = 1.19$ $T_m + T_i^H = 5.31$ $T_m + T_i^L = 3.88$ $2T_m = 5.38$

Add an interaction?

$T_m = 2.69$ $T_i^H = 2.62$ $T_i^L = 1.19$ $T_m + T_i^H = 5.31$ $T_m + T_i^L = 3.88$ $2T_m = 5.38$

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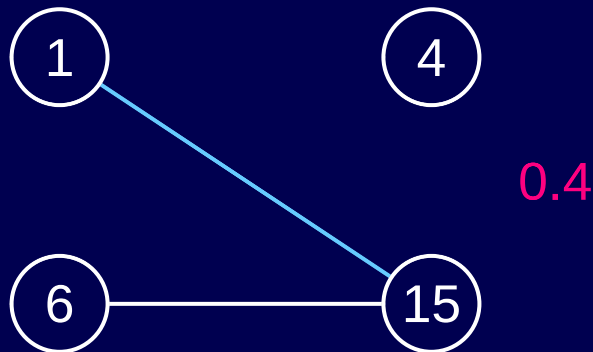

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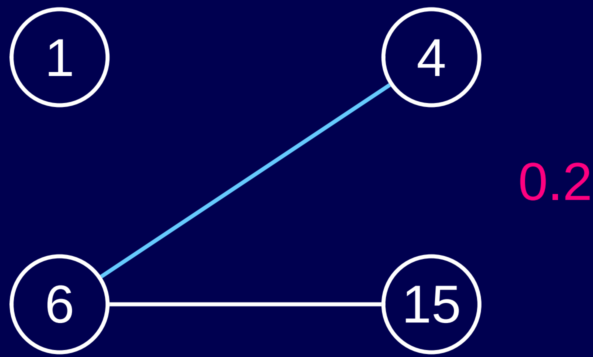

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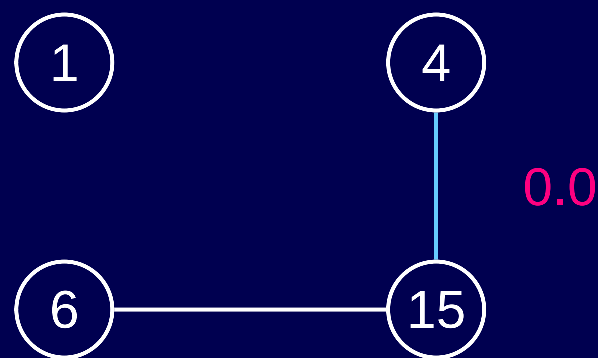

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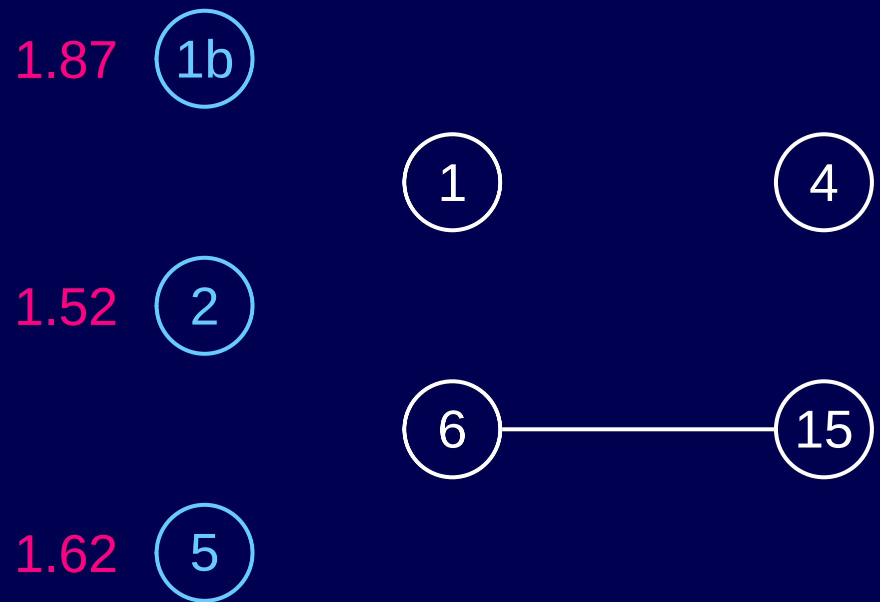
Add another QTL?



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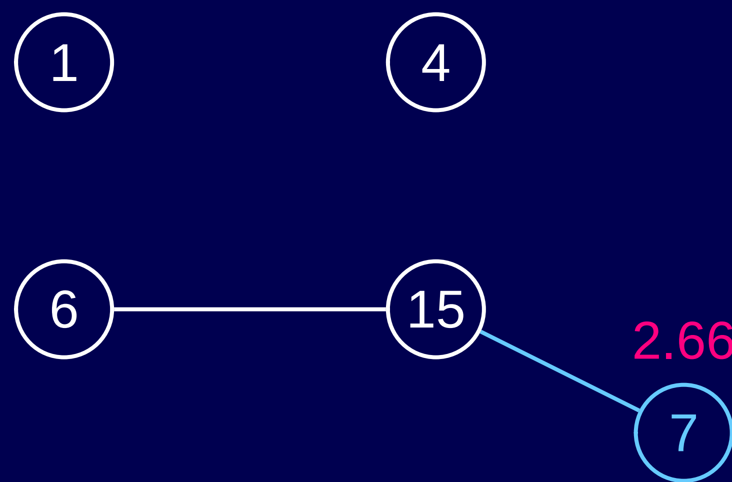

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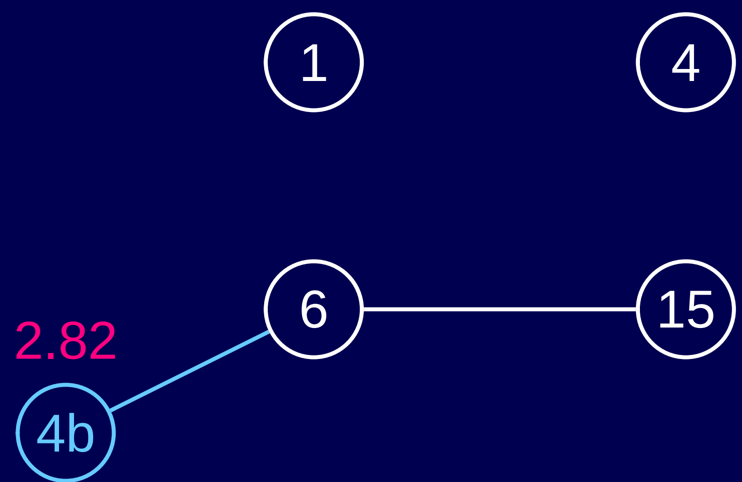
Add another QTL?



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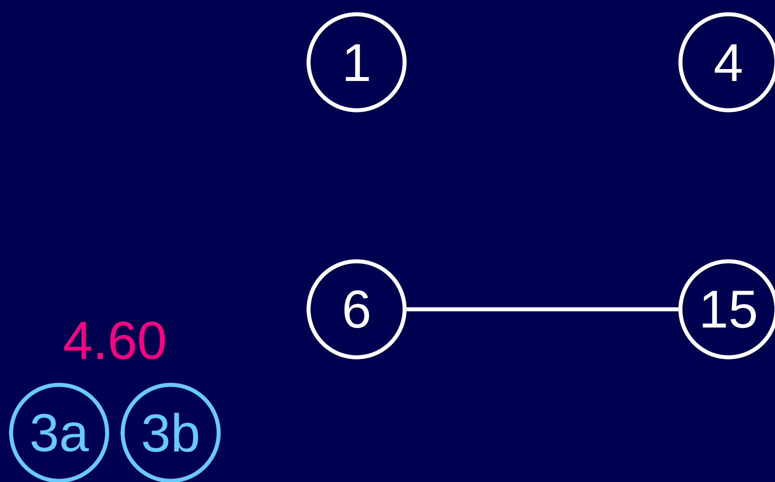
Add a pair of QTL?



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To do

- Improve search procedures
- X chromosome
- QTL $\times$ covariate interactions
- Measuring model uncertainty
- Measuring uncertainty in QTL location

Summary

- QTL mapping is a model selection problem
- The criterion for comparing models is most important
- We're focusing on a penalized likelihood method and believe we have a practical solution

Manichaikul A, Moon JY, Sen Ś, Yandell BS, Broman KW (2009) A model selection approach for the identification of quantitative trait loci in experimental crosses, allowing epistasis. *Genetics* 181:1077–1086

Acknowledgments

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