Mapping QTL to a phylogenetic tree

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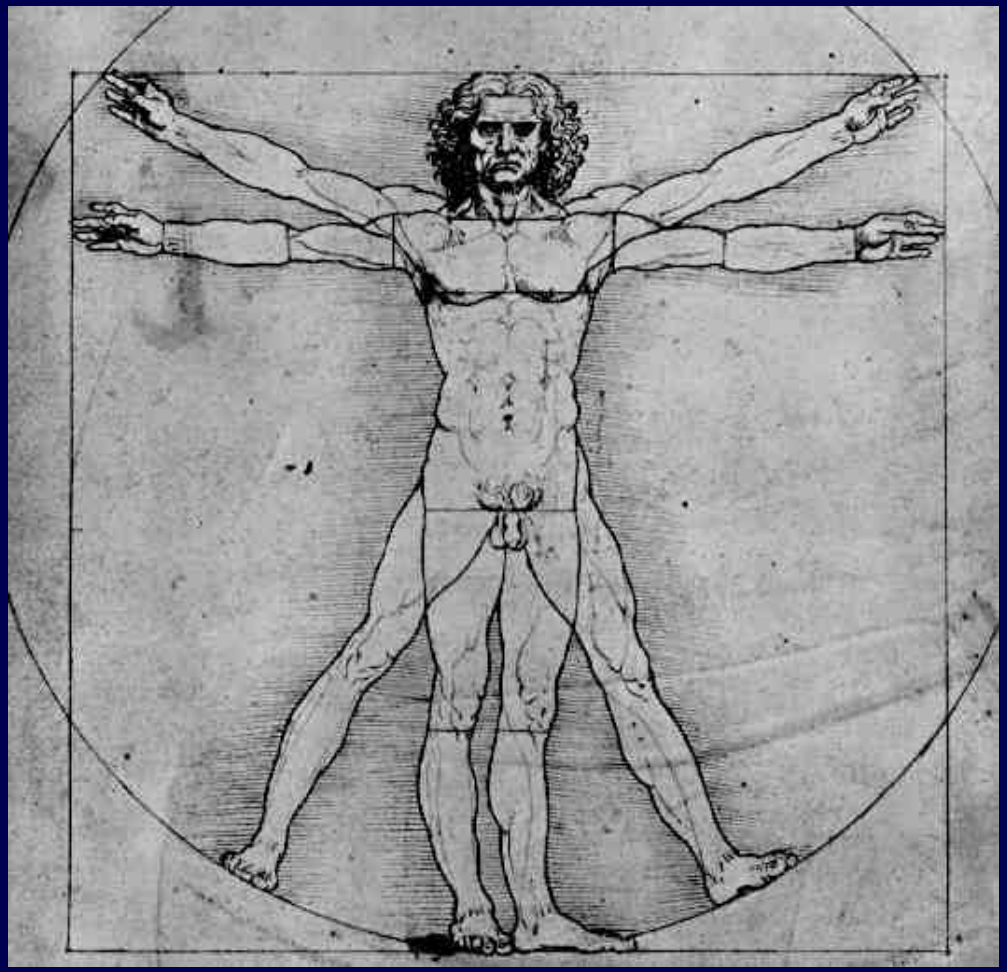
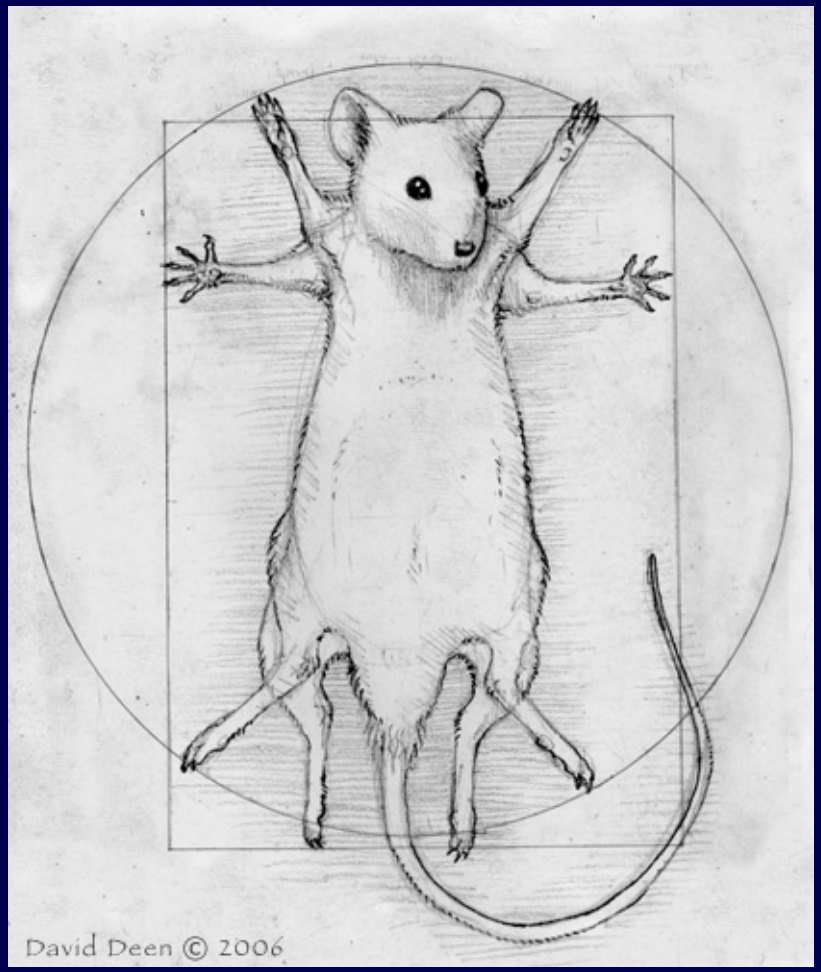
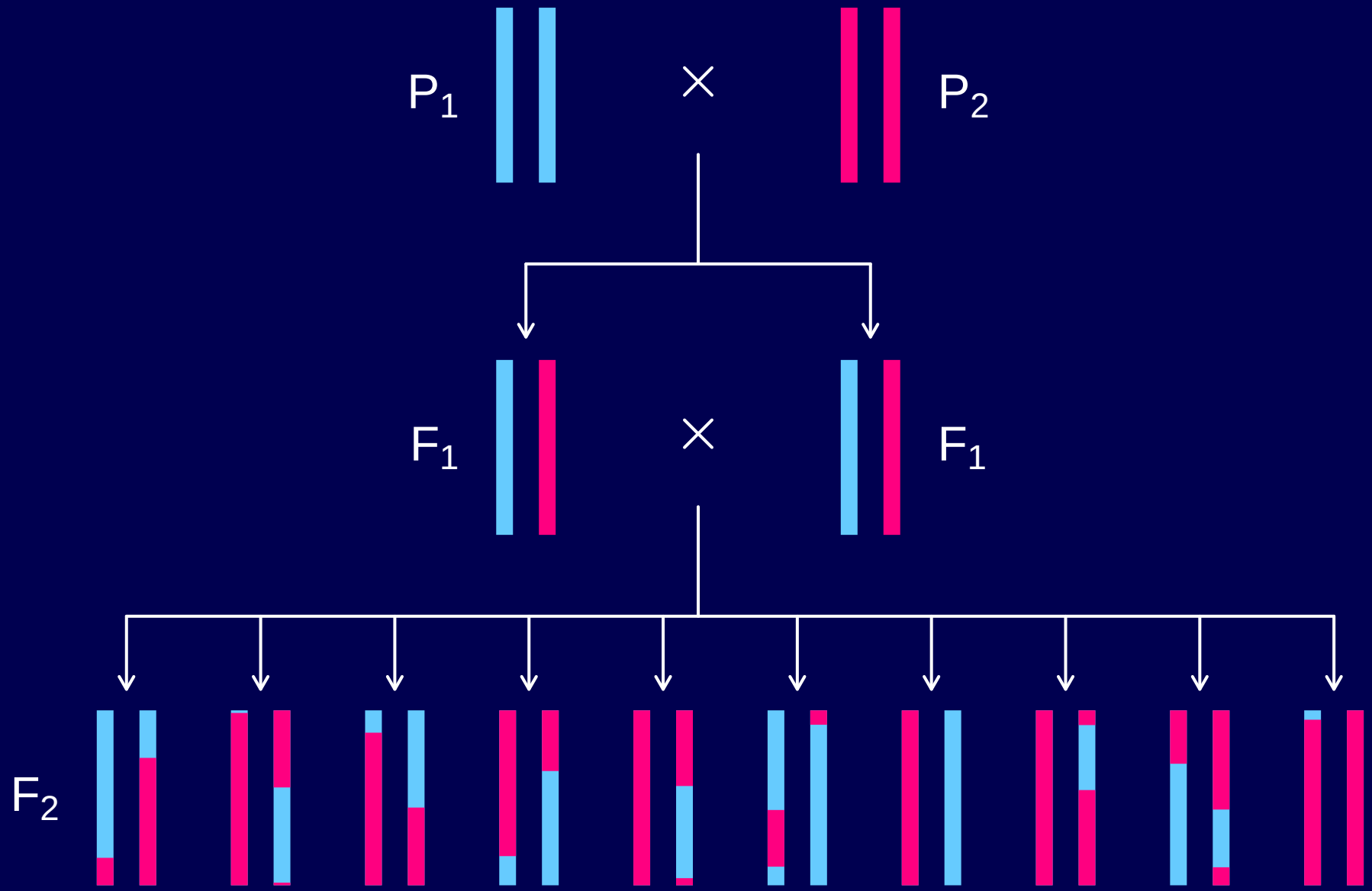
Human vs mouse



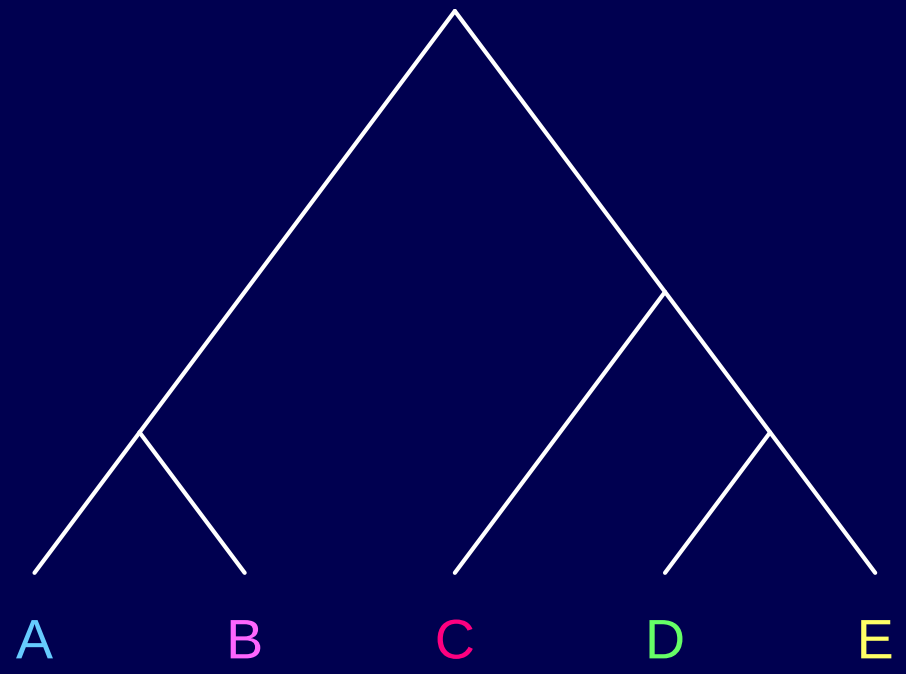


www.daviddeen.com

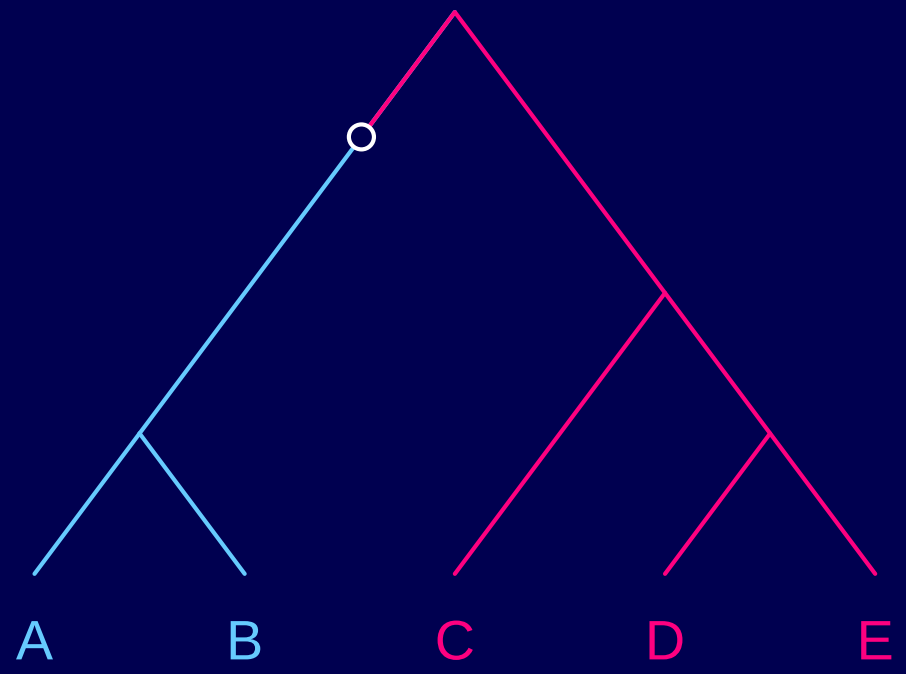
Intercross



A tree



A QTL on a tree



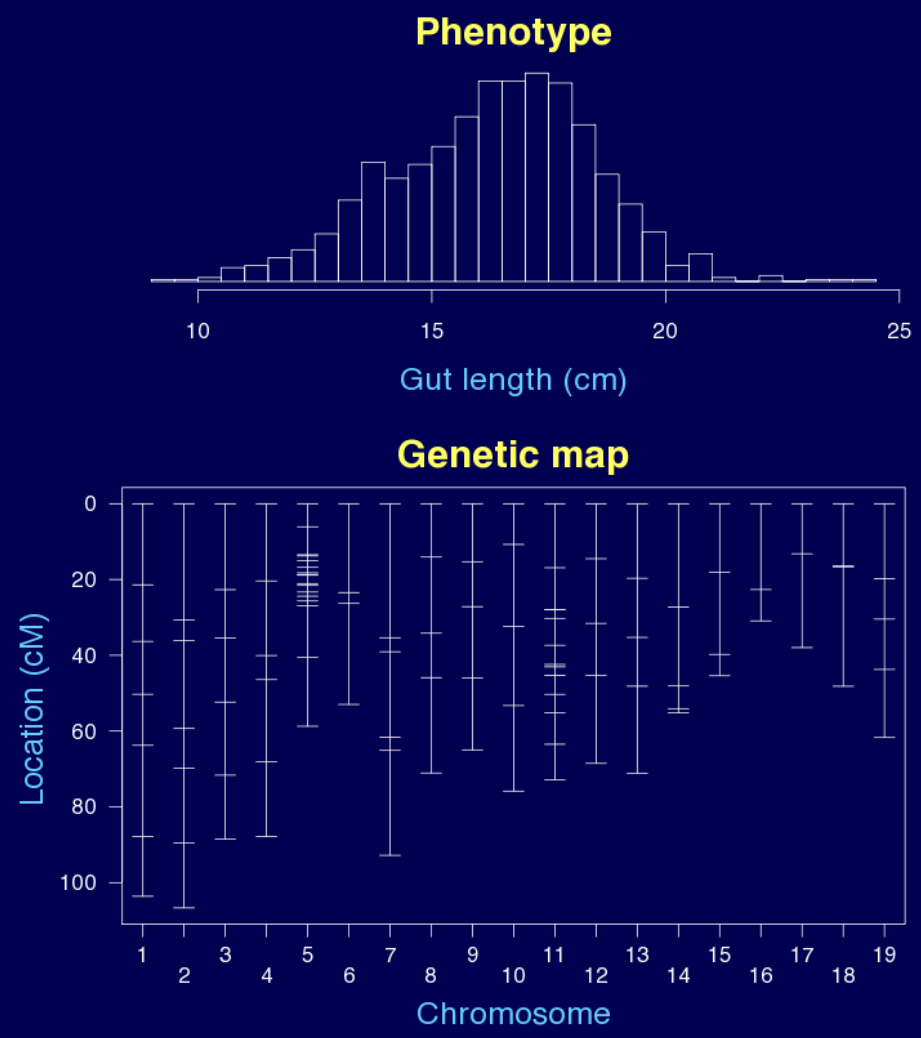
QTL mapping

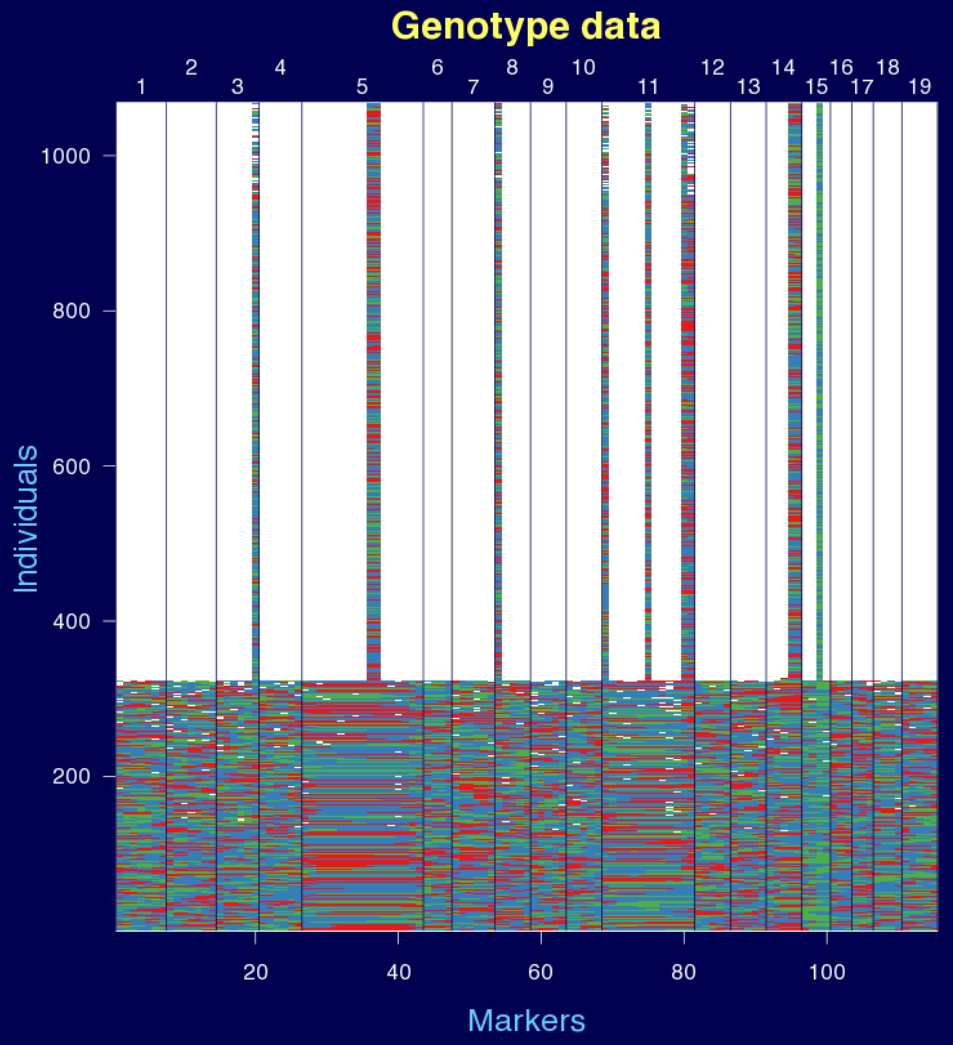
QTL = Quantitative Trait Locus

QTL mapping data:

- Set of intercross individuals
- Quantitative phenotype for each
- Marker genotype data
- Genetic map

QTL mapping data

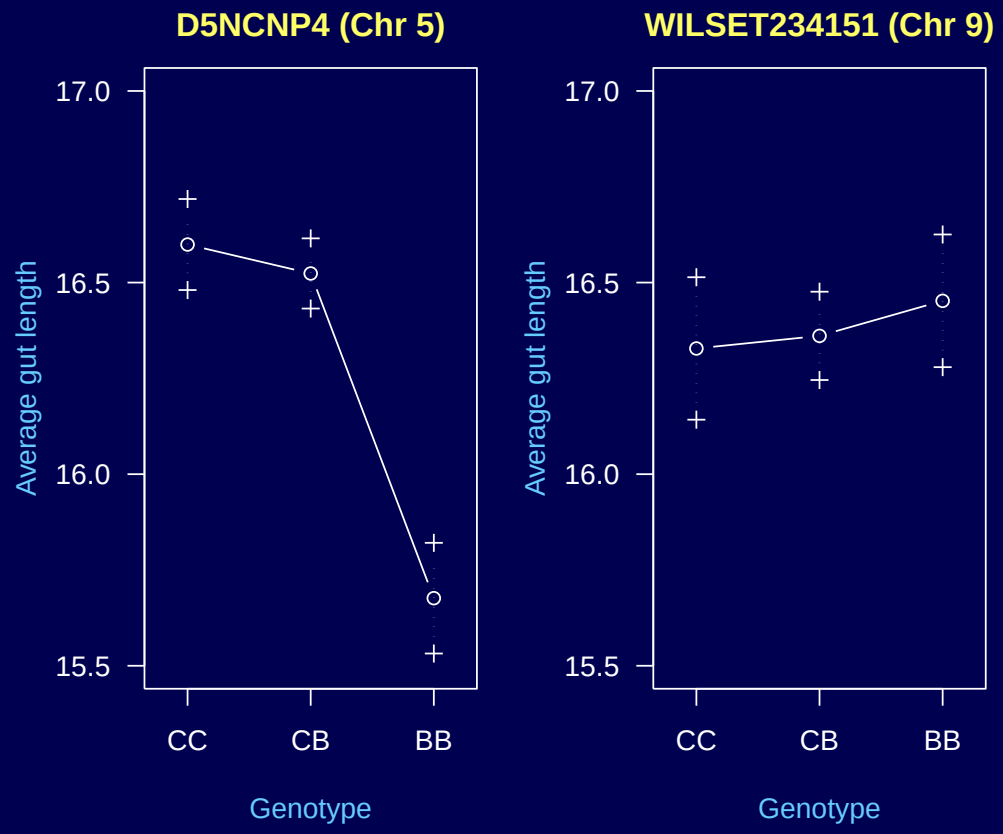




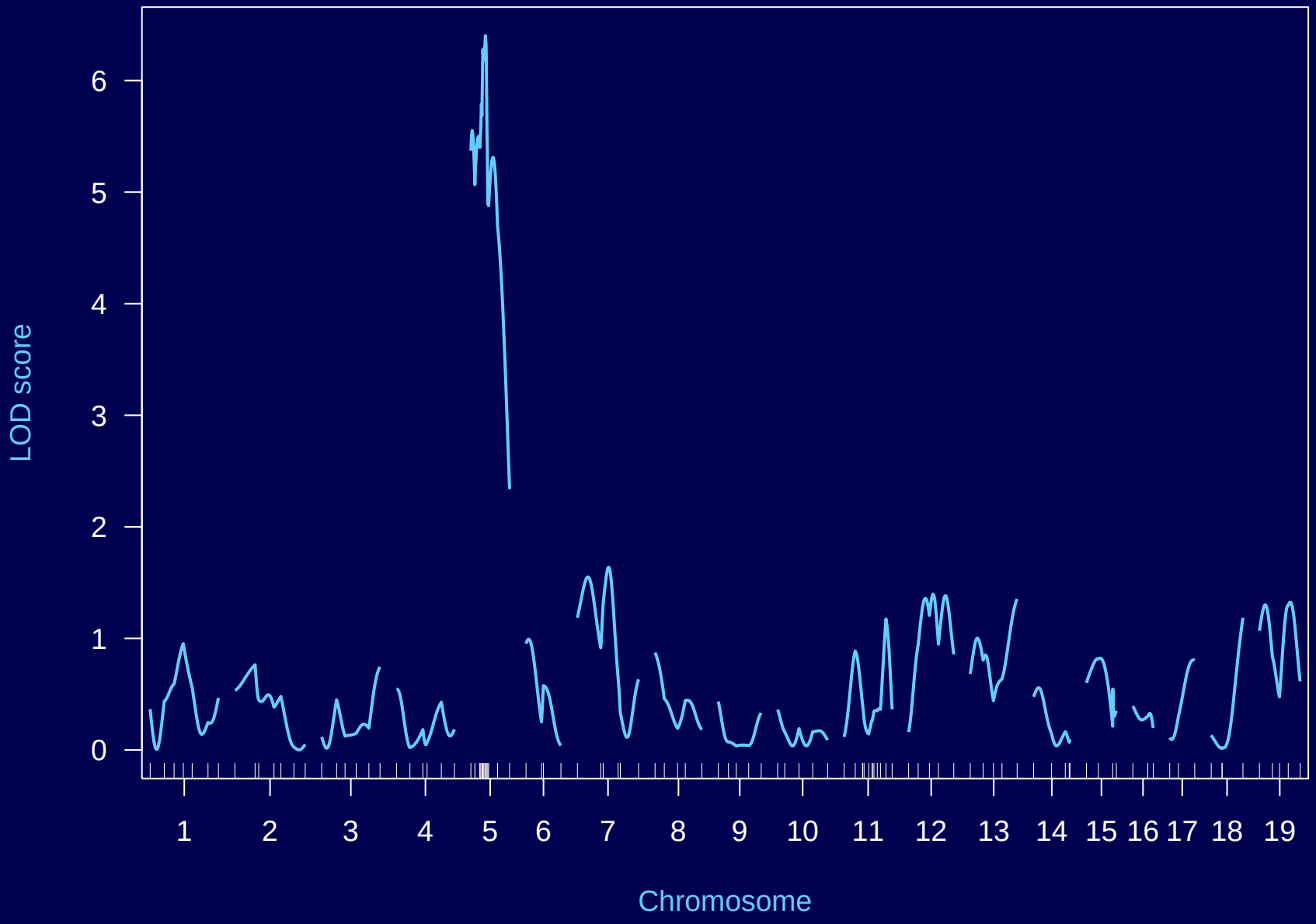
Broman et al., Genetics, 174:2151–2158, 2006
Owens et al., Hum Mol Genet, 14:1549–1558, 2005

ANOVA at marker loci

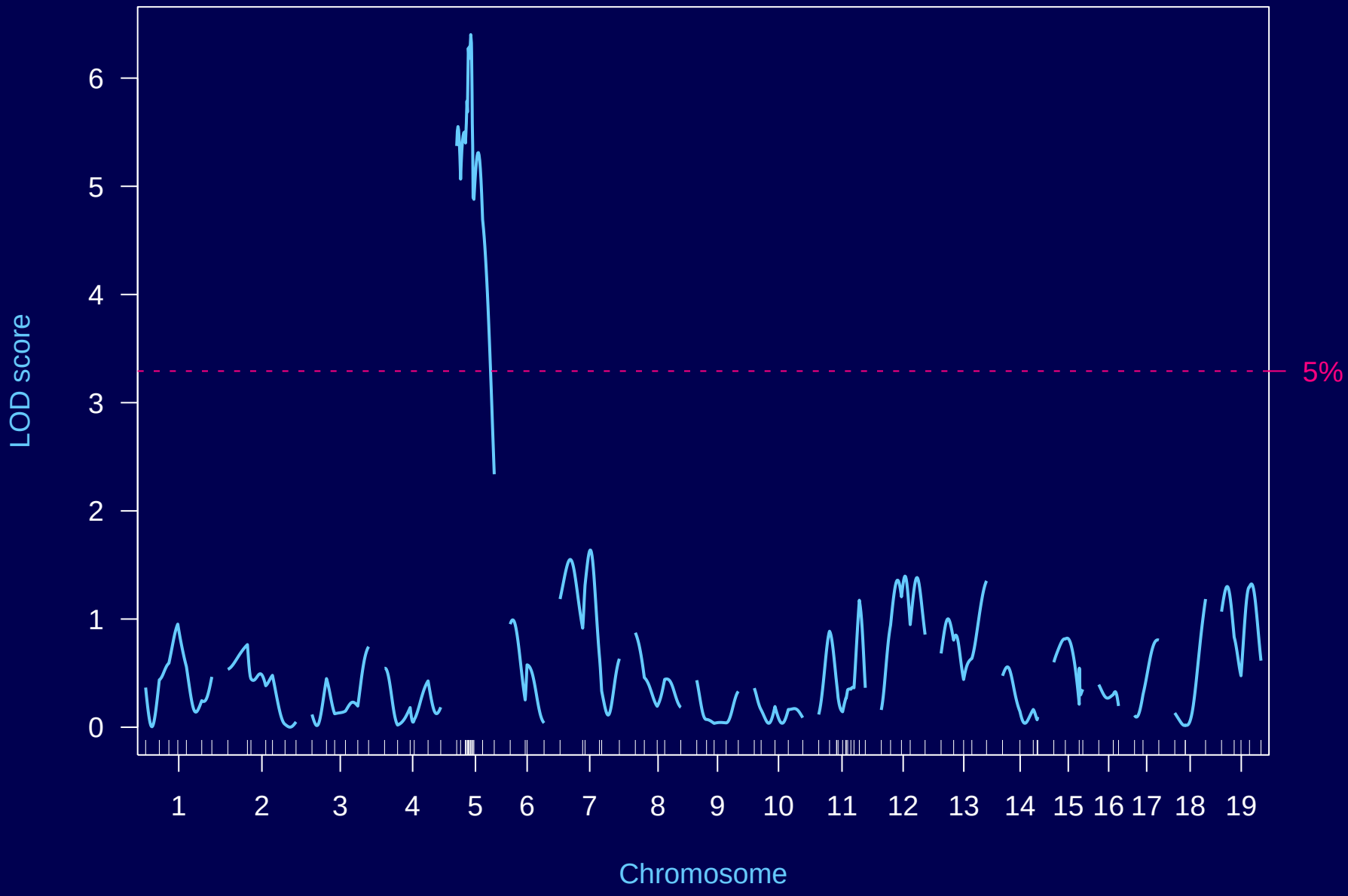
- Split mice into groups according to genotype at a marker.
- Do a t-test / ANOVA.
- Repeat for each marker.



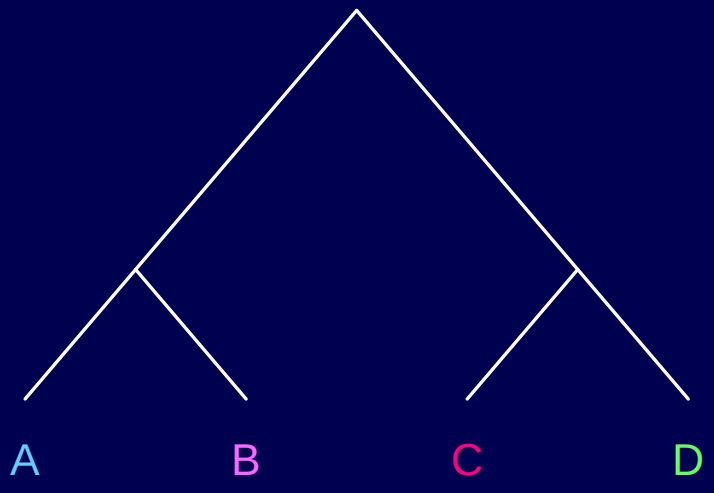
LOD curves


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

LOD curves


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

QTL on a tree



Assumptions

- Single diallelic QTL
- No epistasis or background effects
- No variation in recombination
- Known tree

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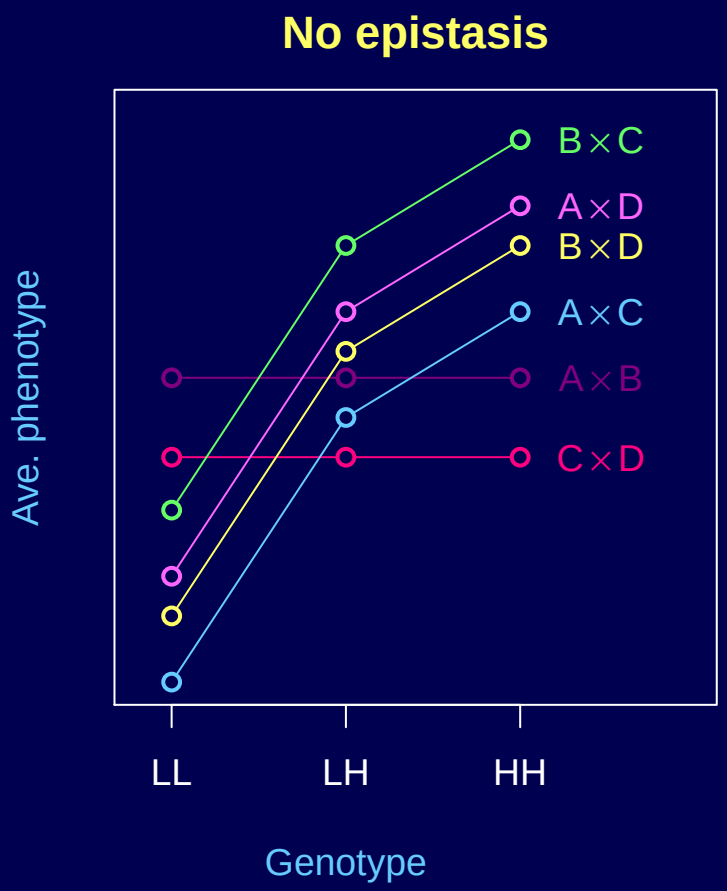

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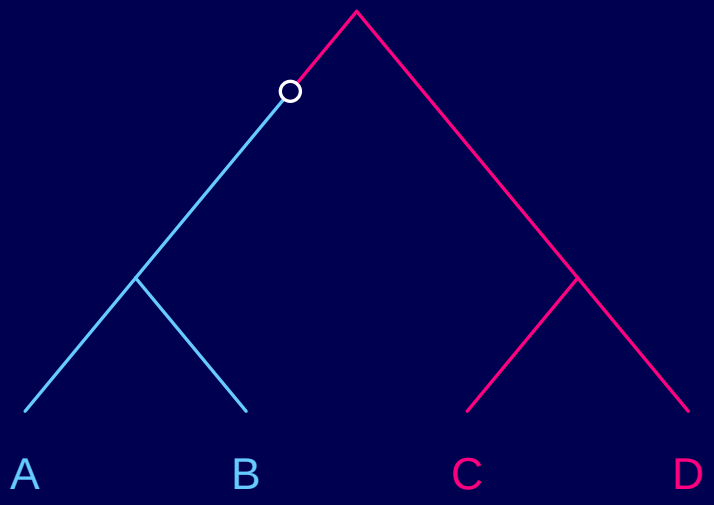

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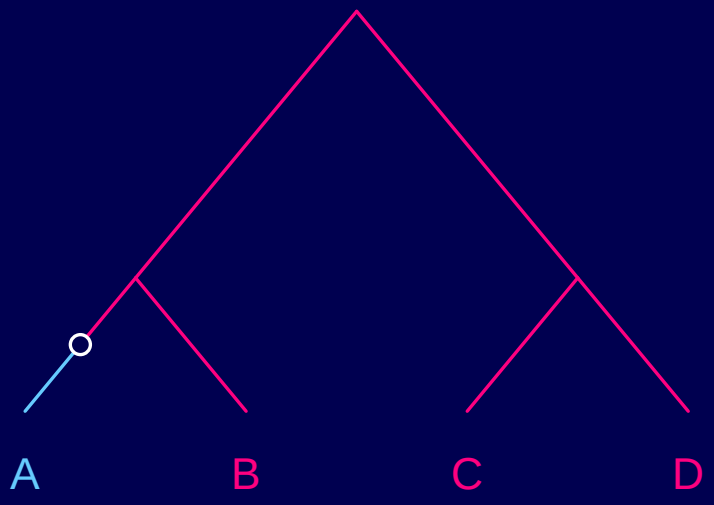

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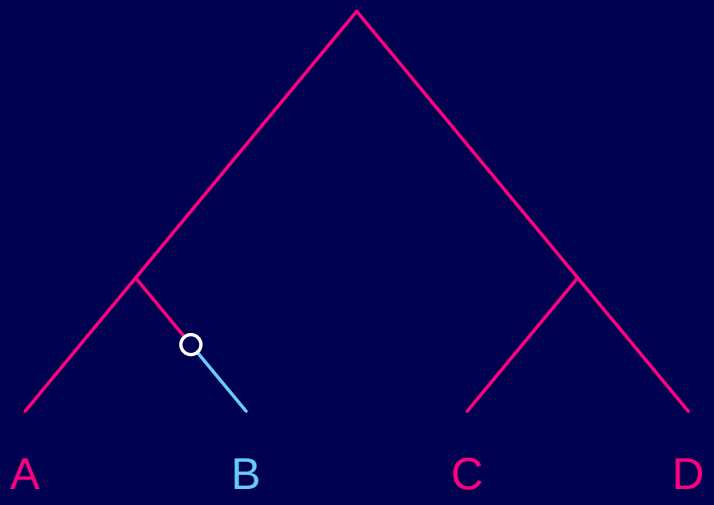

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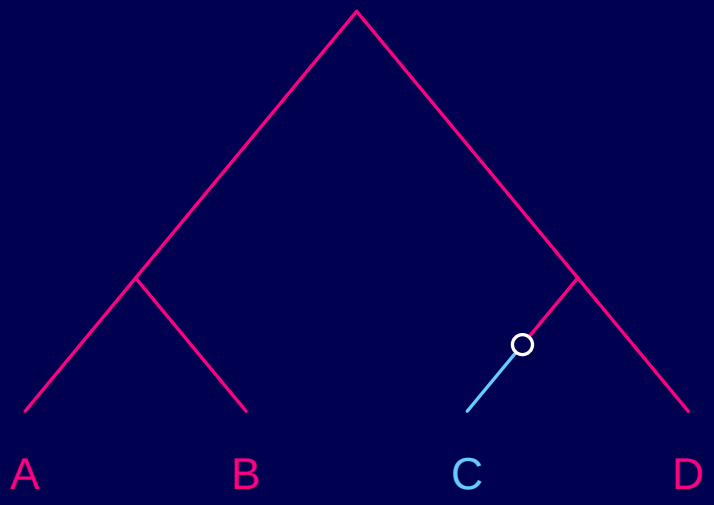

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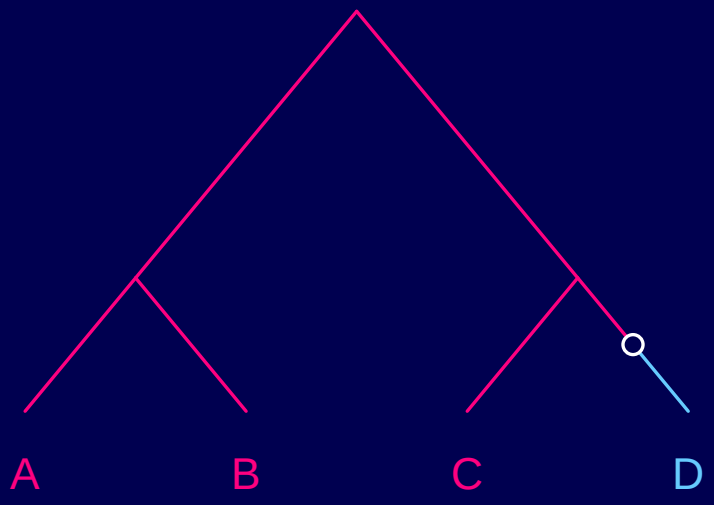

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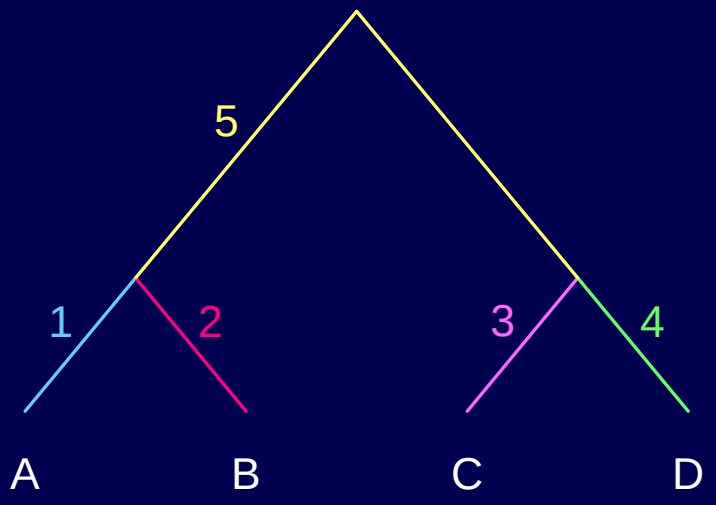

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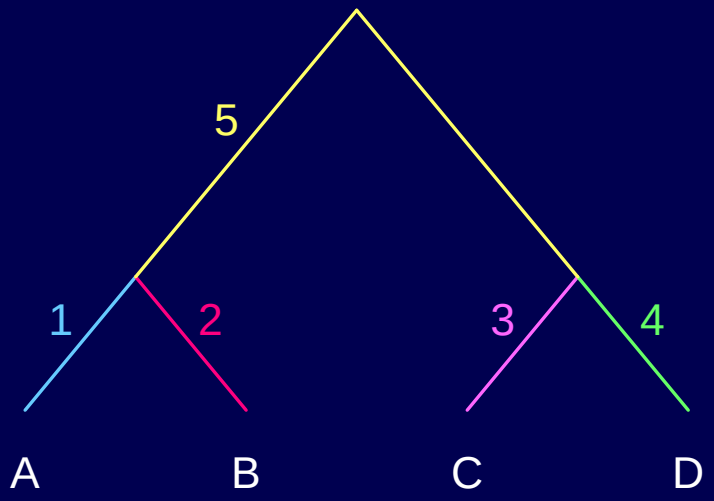
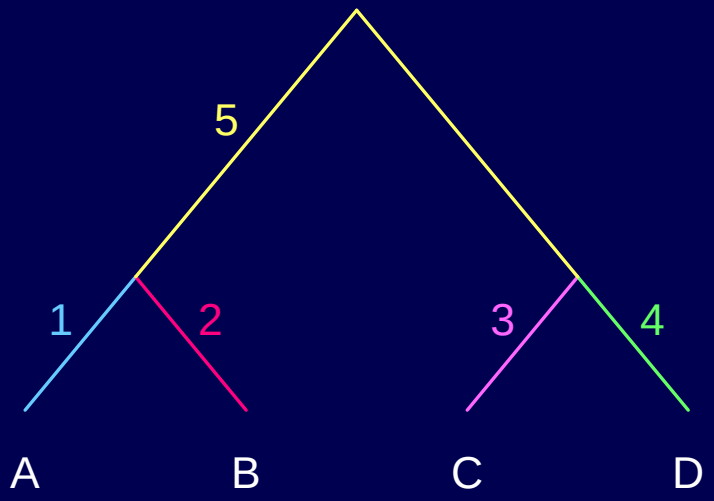


	QTL position (partition of taxa)				
Cross	1 (A|BCD)	2 (B|ACD)	3 (C|ABD)	4 (D|ABC)	5 (AB|CD)
A × B	✓	✓	×	×	×
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

QTL on a tree



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A × B	✓	✓	×	×	×
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

Combining crosses

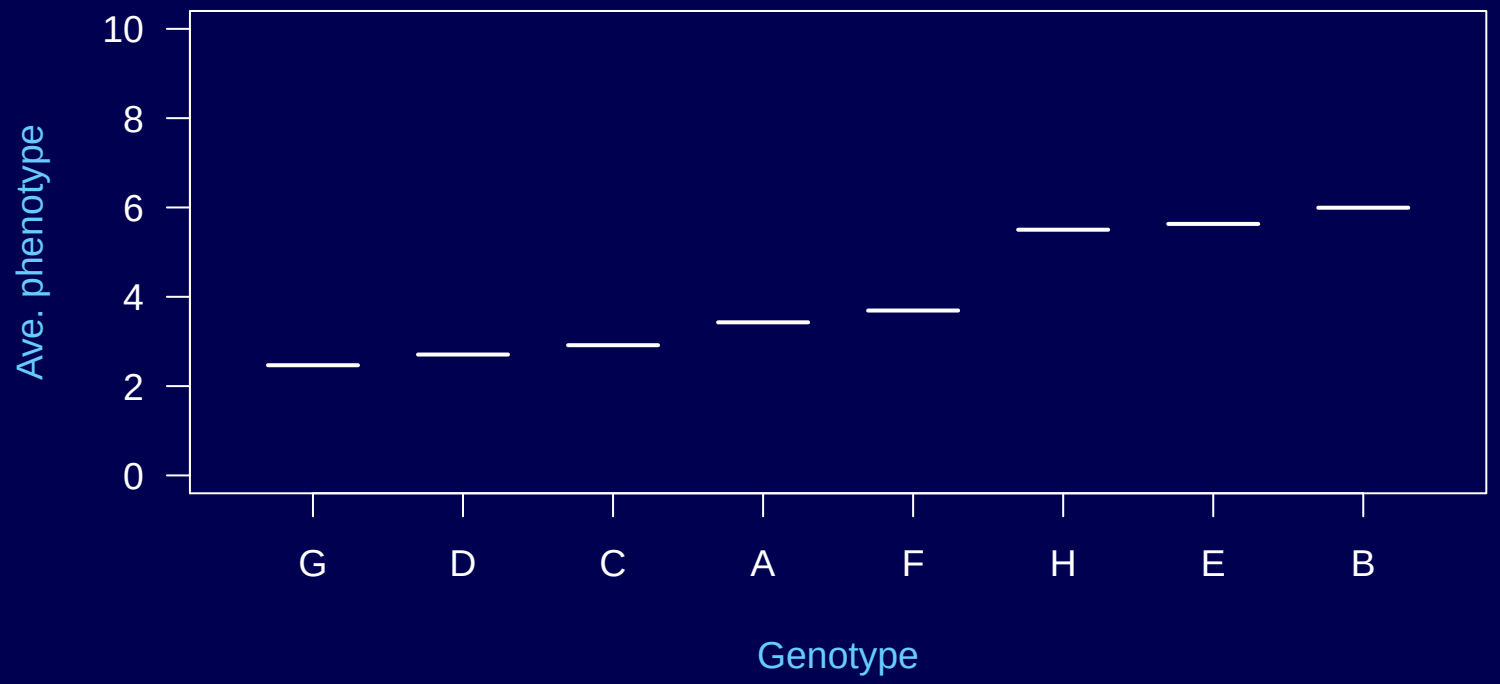
Li et al., Genetics 169:1699–1709, 2005

- Four mouse intercrosses, I×P, P×D, D×C, C×S
- I, D, S have low plasma HDL cholesterol
- P, C have high plasma HDL cholesterol
- Use results from individual crosses to determine partition
- Recode genotypes in each cross to L/H and combine
  (with the goal of increasing mapping precision)

Diallelic QTL

Macdonald and Long, Genetics 176:1261–1281, 2007

- Drosophila recombinant inbred lines (RIL) developed from 8 strains
- Assume an underlying diallelic QTL (that the 8 alleles are of two flavors)
- Approximate method for partitioning the 8 alleles into 2 groups



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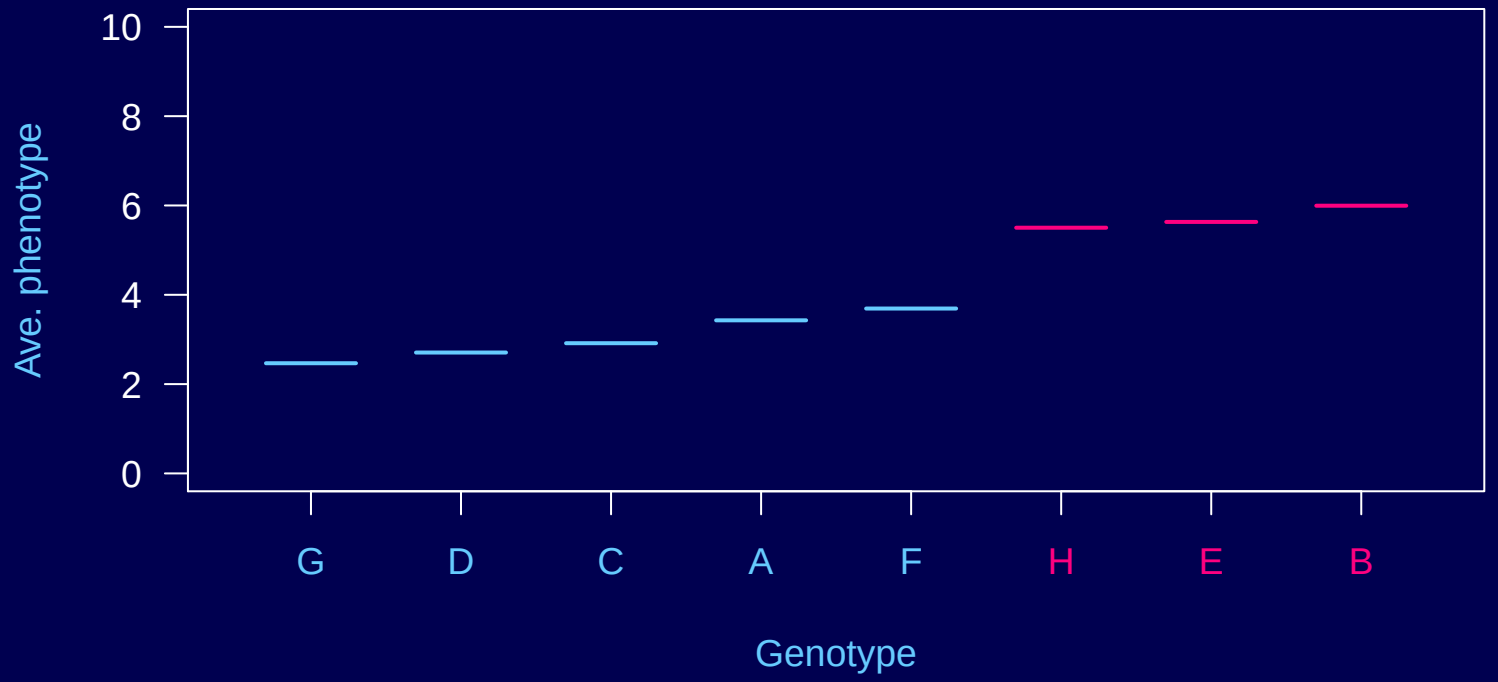
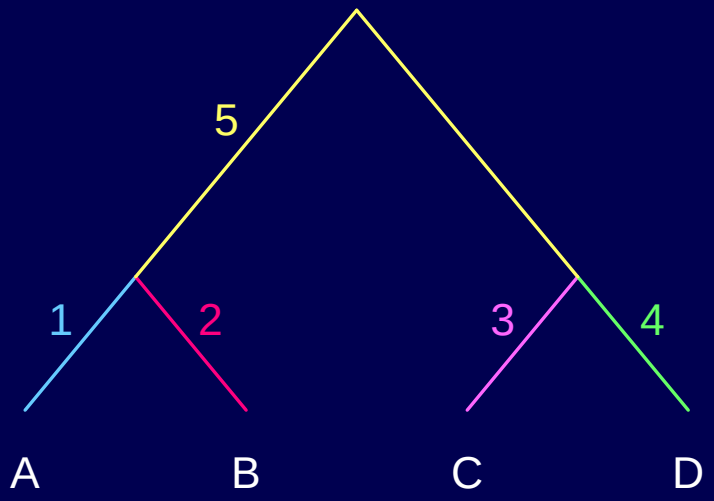


The basic idea



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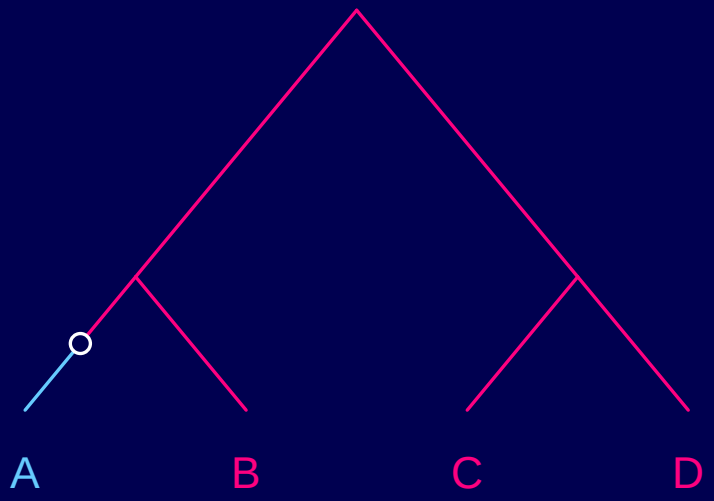
A × B	✓	✓	×	×	×
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

The basic idea



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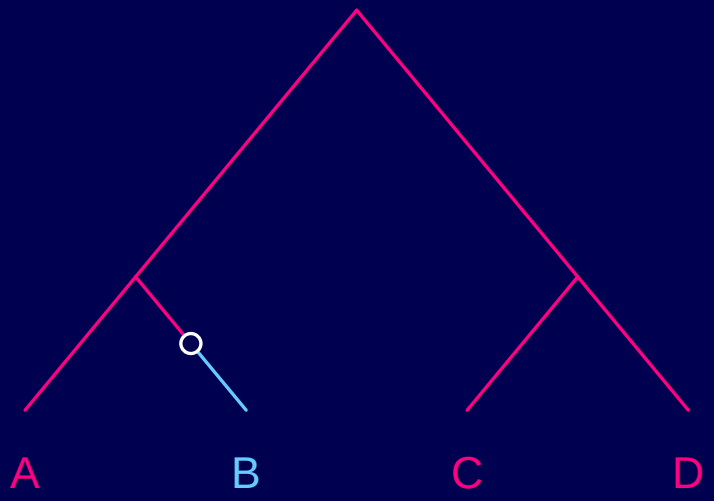
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

The basic idea



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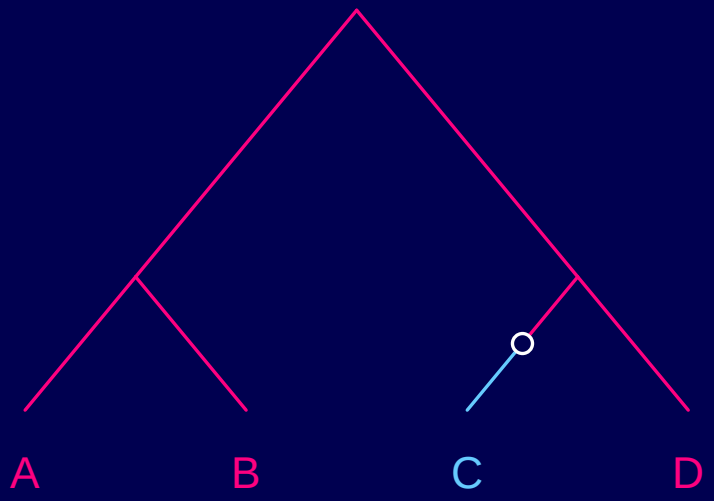
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

The basic idea



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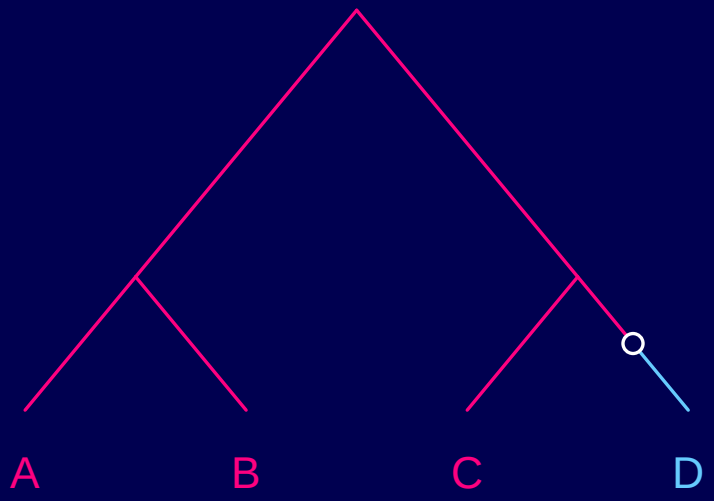
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

The basic idea



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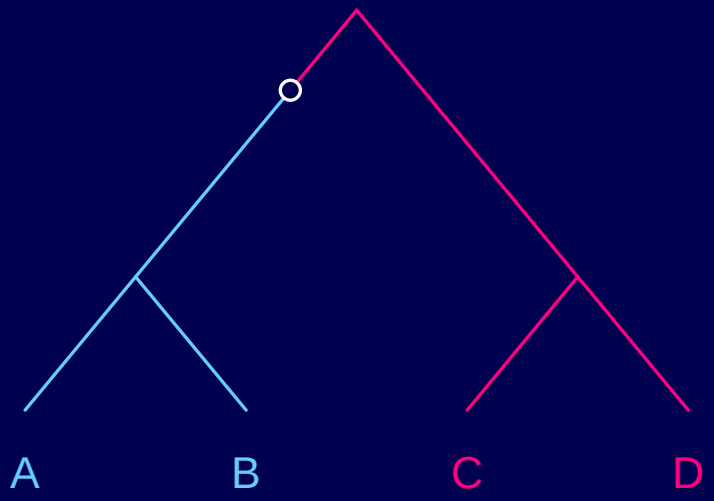
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

The basic idea



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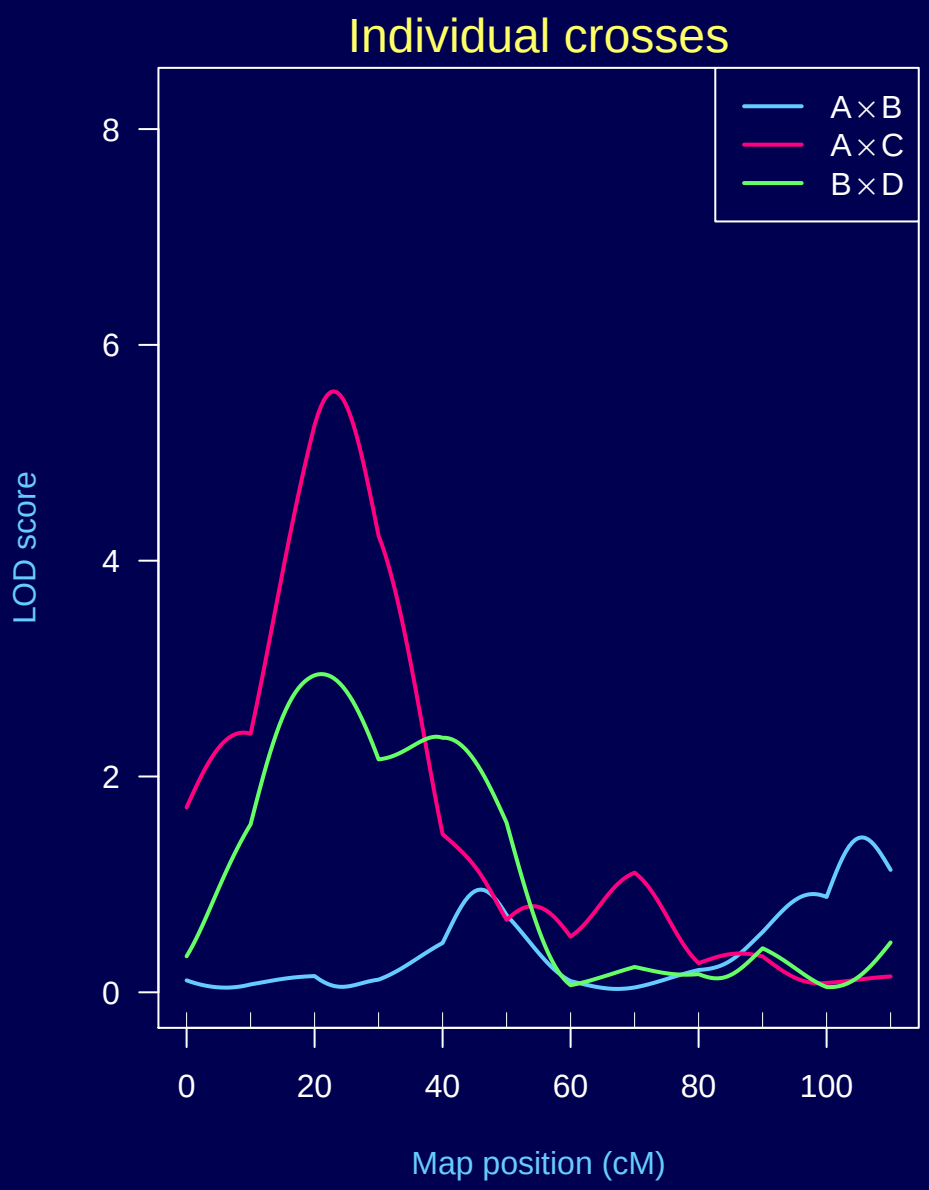
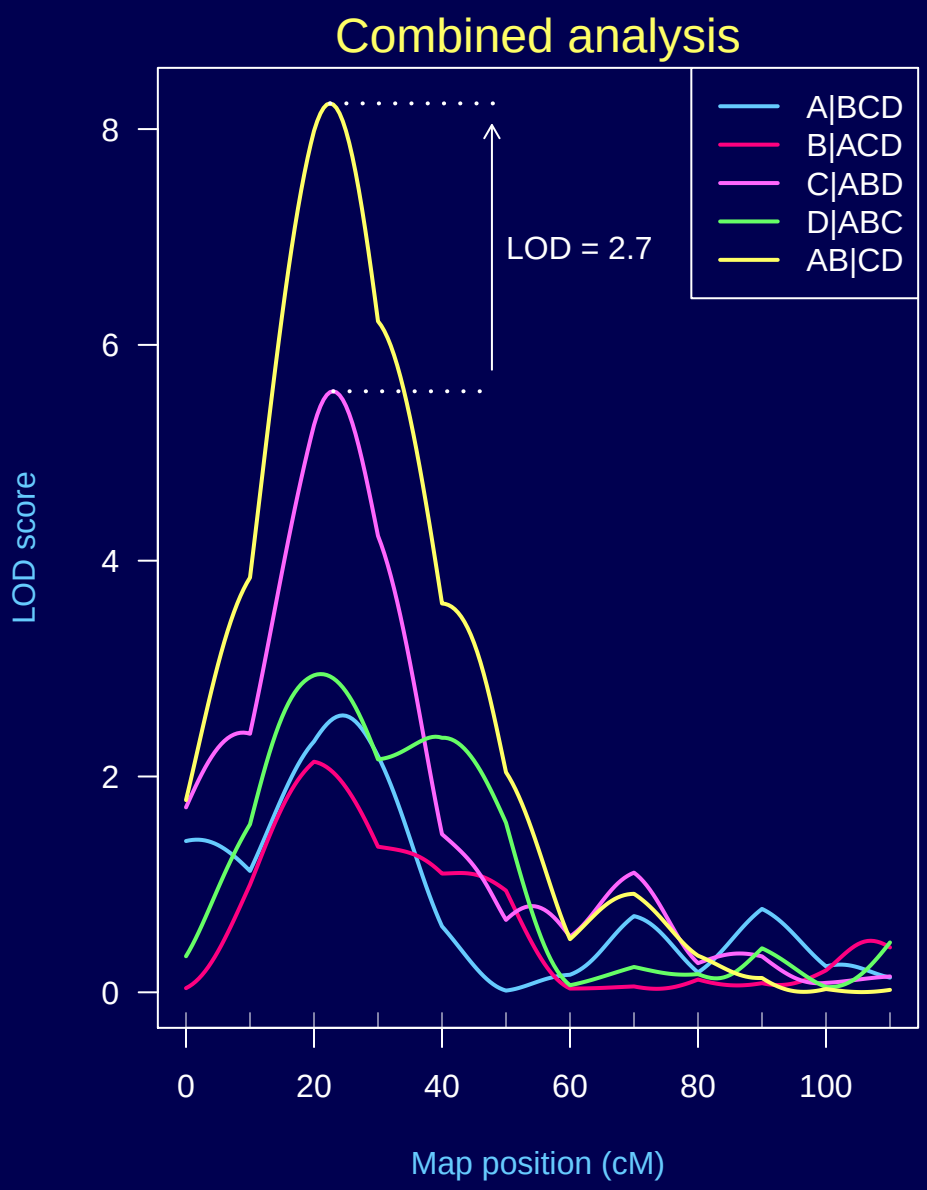
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

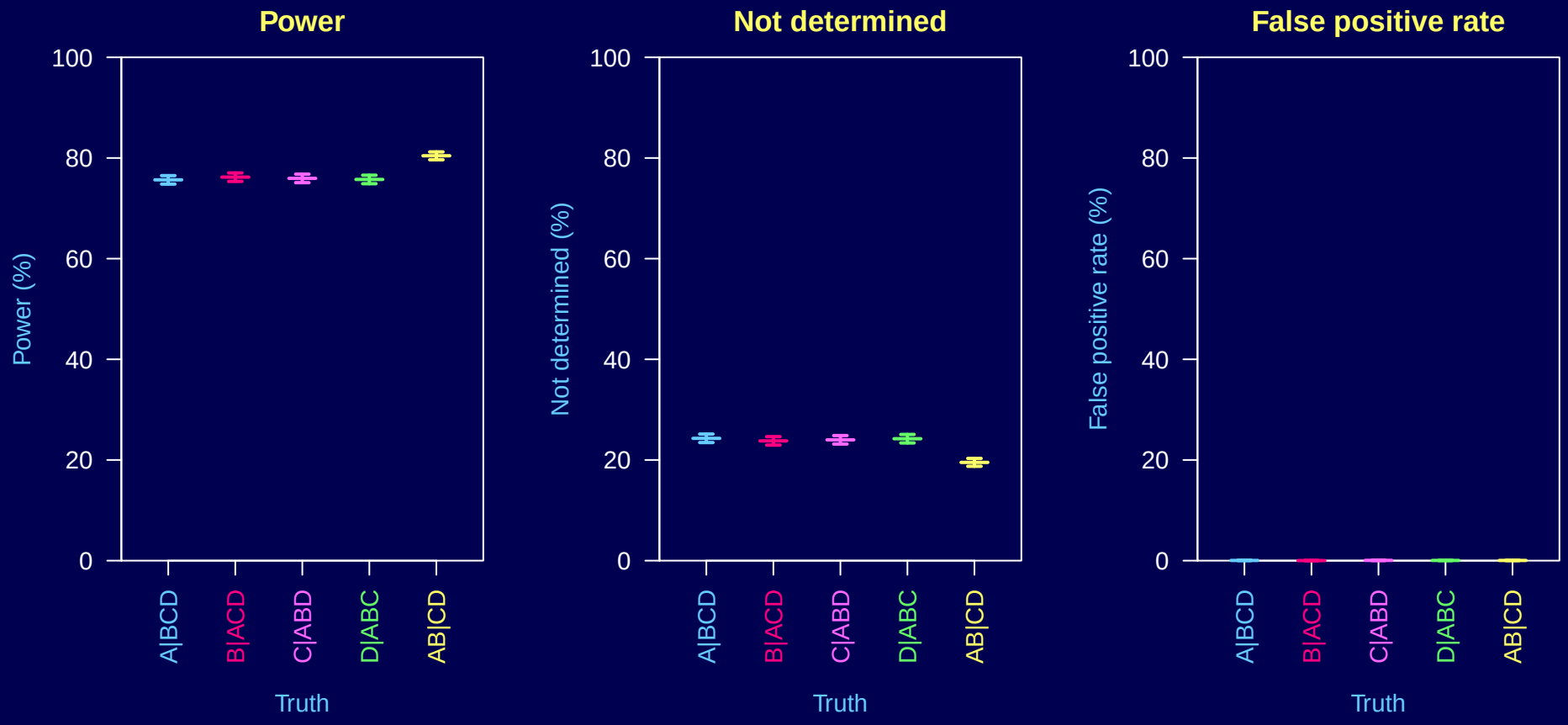
Simulated example





Does it work?

- Four taxa
- One diallelic QTL with h^2 = 10%
- All 6 intercrosses; 100 individuals per cross
- 10,000 simulation replicates



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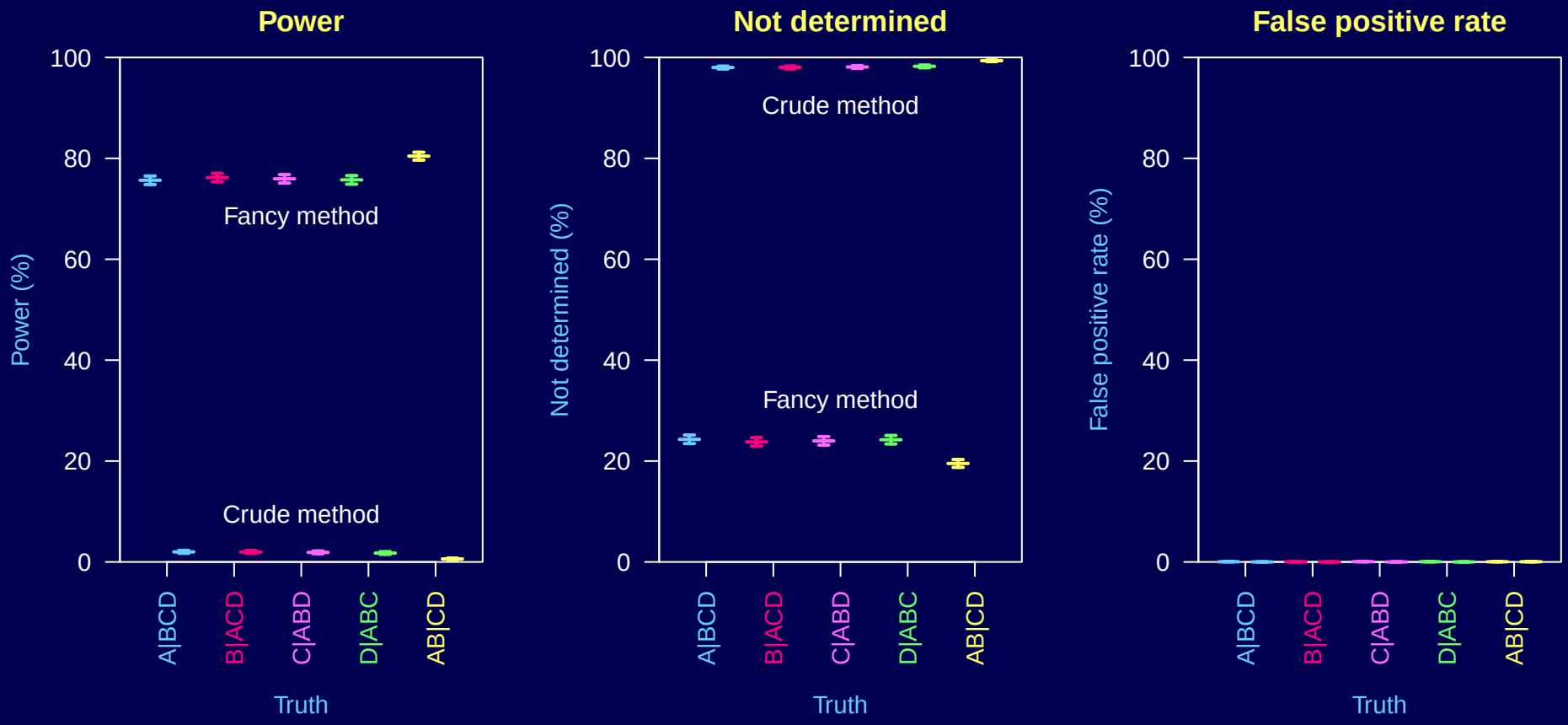

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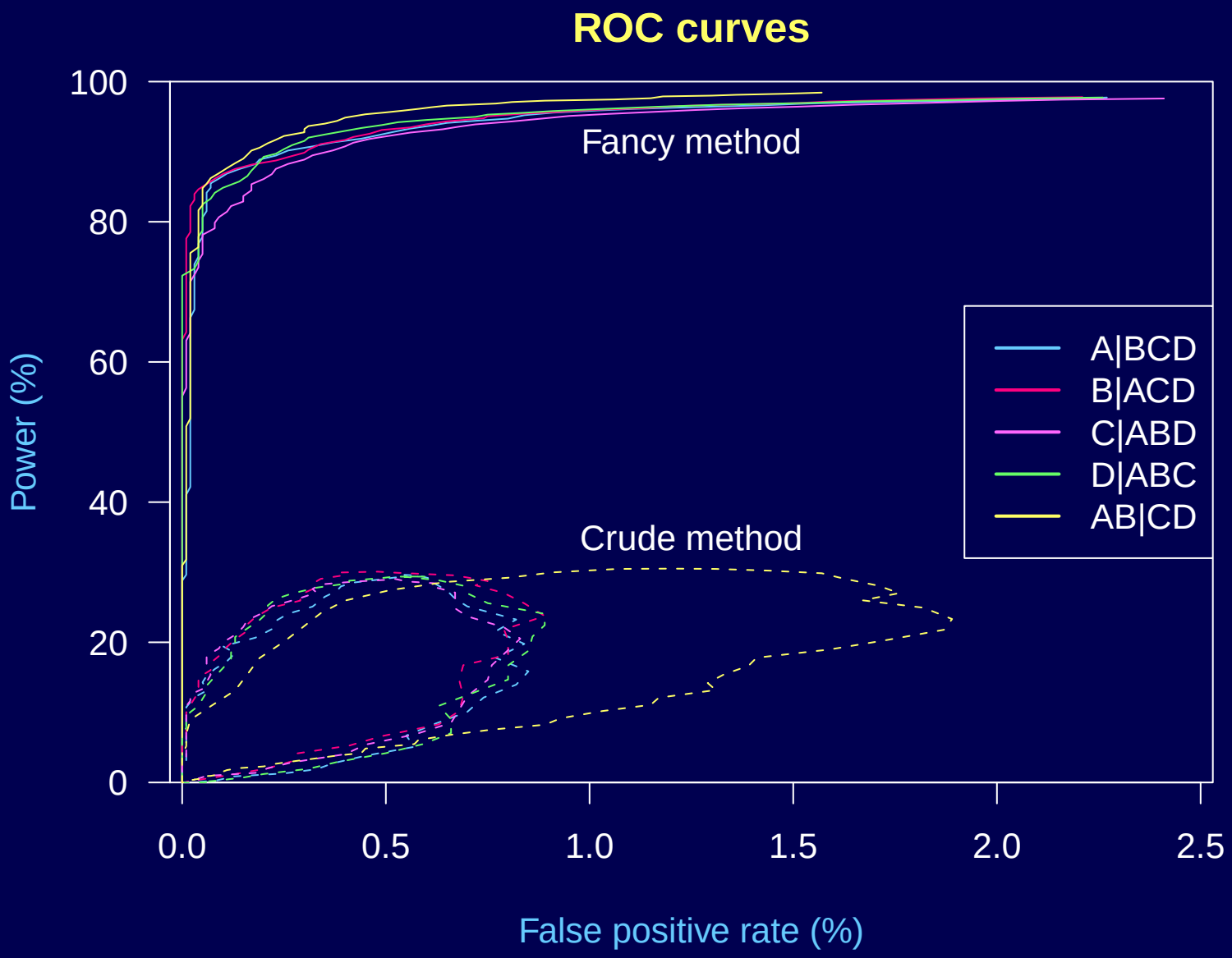
ROC curves
Fancy method
Crude method
A|BCD
B|ACD
C|ABD
D|ABC
AB|CD
Power (%)
False positive rate (%)
0
20
40
60
80
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0.0
0.5
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1.5
2.0
2.5

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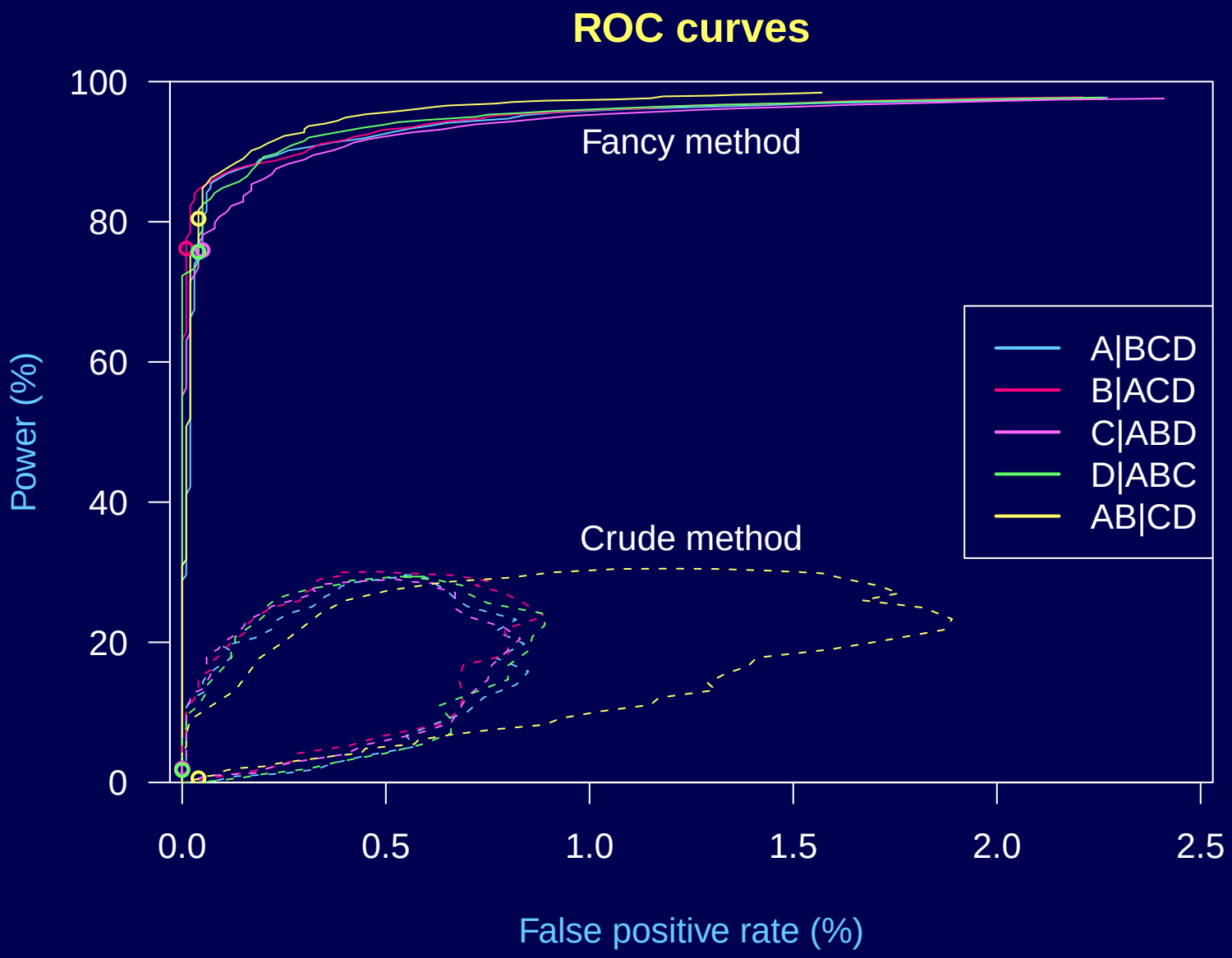
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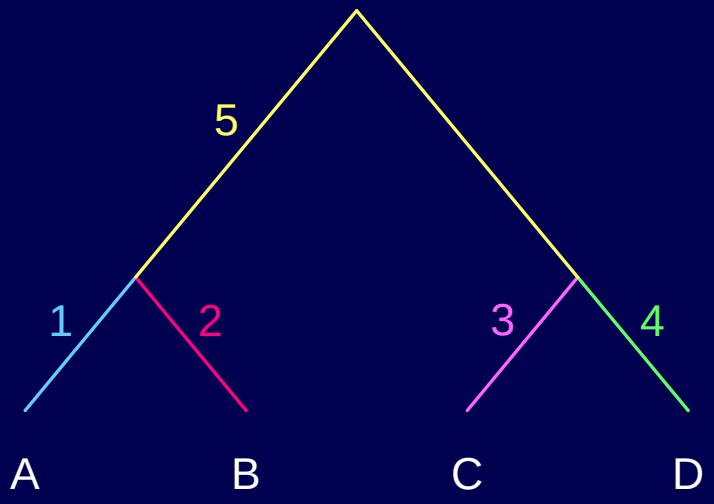
All partitions?



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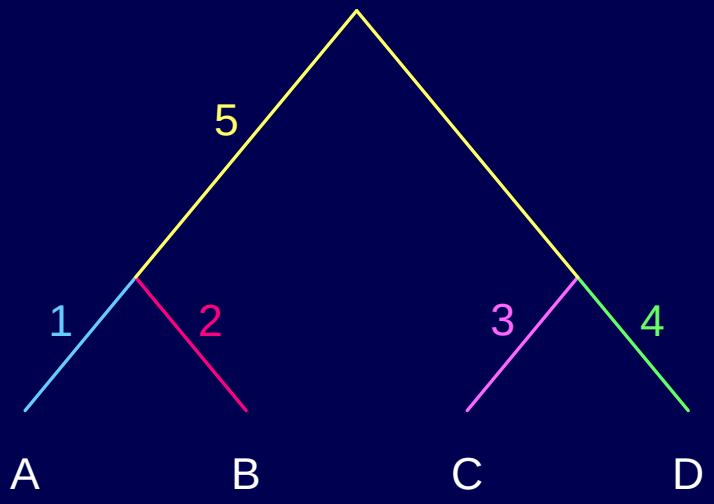
A × B	✓	✓	×	×	×	✓	✓
A × C	✓	×	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓	✓	×
B × C	×	✓	✓	×	✓	✓	×
B × D	×	✓	×	✓	✓	×	✓
C × D	×	×	✓	✓	×	✓	✓

All partitions?



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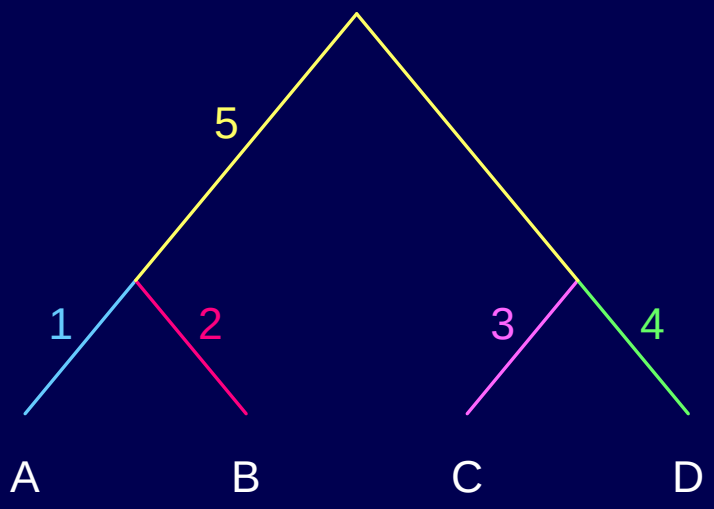
A × C	✓	×	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓	✓	×
B × C	×	✓	✓	×	✓	✓	×
B × D	×	✓	×	✓	✓	×	✓
C × D	×	×	✓	✓	×	✓	✓

Minimal crosses



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A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

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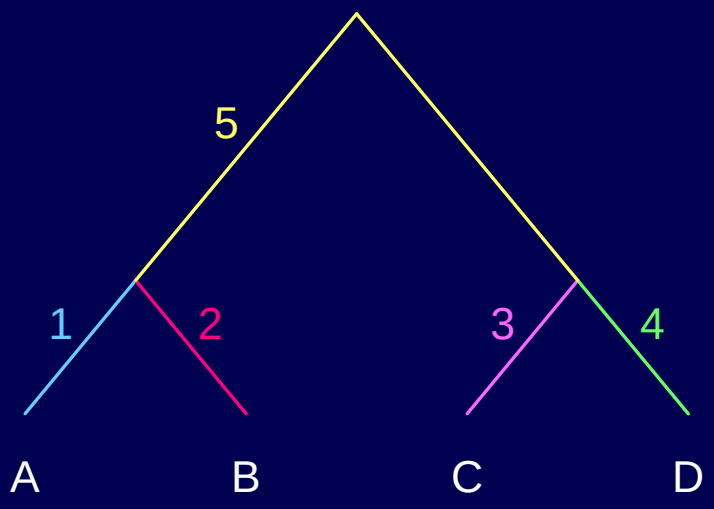

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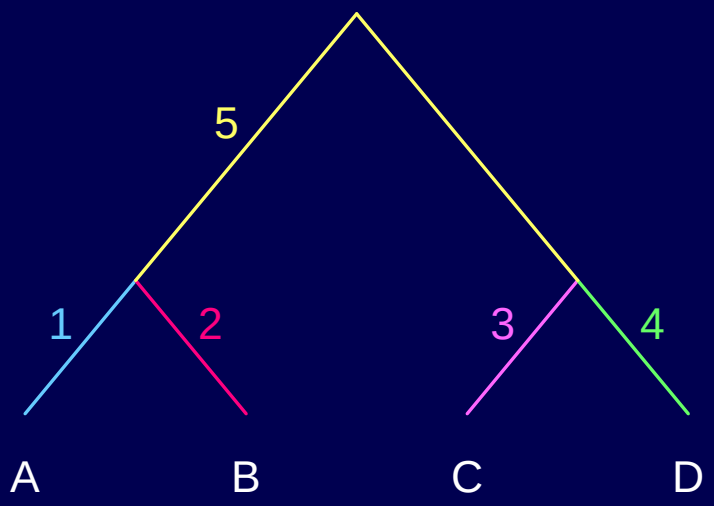
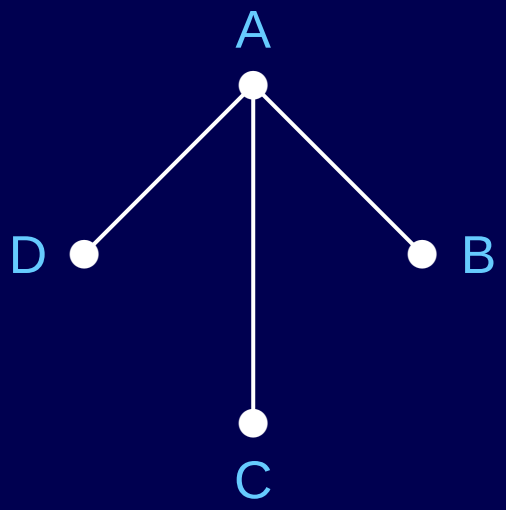
Cross	1 (A|BCD)	2 (B|ACD)	3 (C|ABD)	4 (D|ABC)	5 (AB|CD)
A × B	✓	✓	×	×	×
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

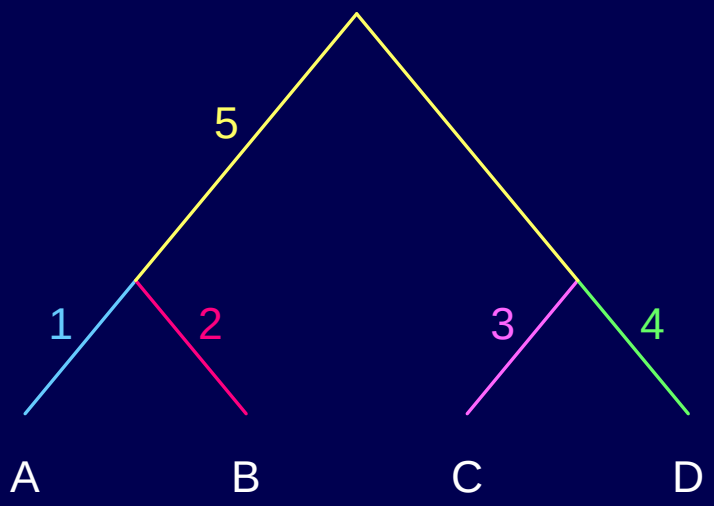
Minimal crosses

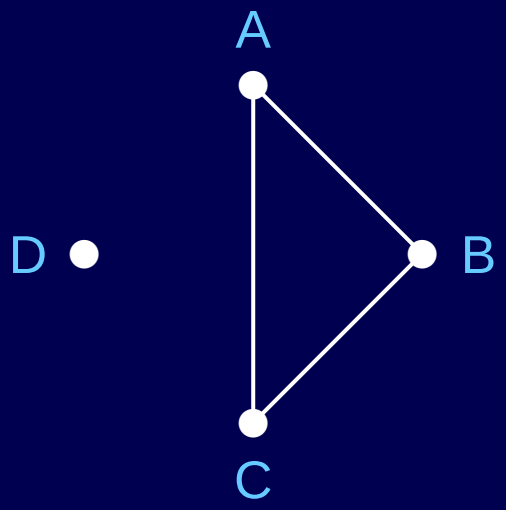




	QTL position (partition of taxa)				
Cross	1 (A|BCD)	2 (B|ACD)	3 (C|ABD)	4 (D|ABC)	5 (AB|CD)
A × B	✓	✓	×	×	×
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

Minimal crosses

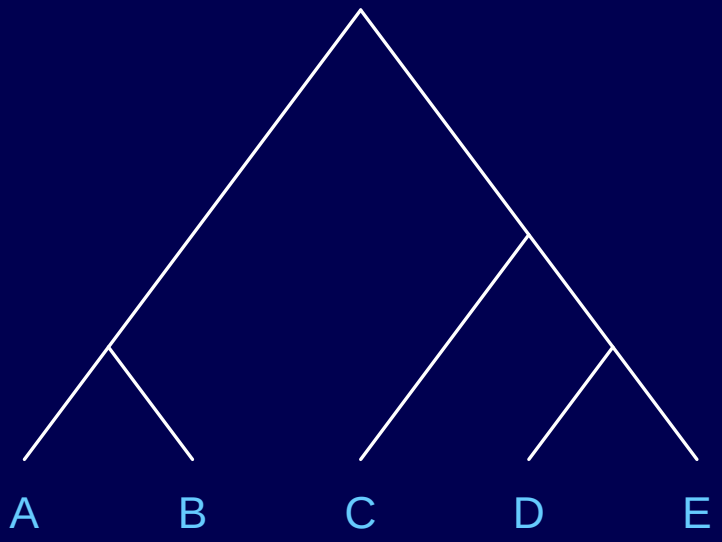




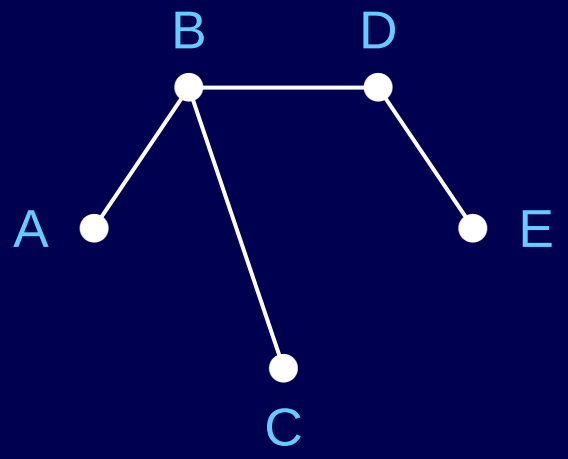
	QTL position (partition of taxa)				
Cross	1 (A|BCD)	2 (B|ACD)	3 (C|ABD)	4 (D|ABC)	5 (AB|CD)
A × B	✓	✓	×	×	×
A × C	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓
B × C	×	✓	✓	×	✓
B × D	×	✓	×	✓	✓
C × D	×	×	✓	✓	×

Minimal crosses

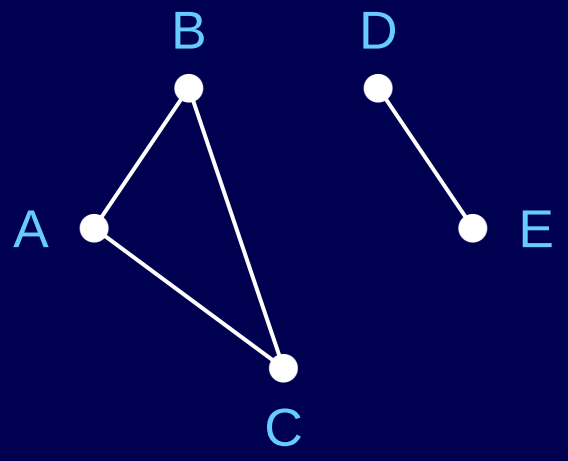
Tree



Crosses



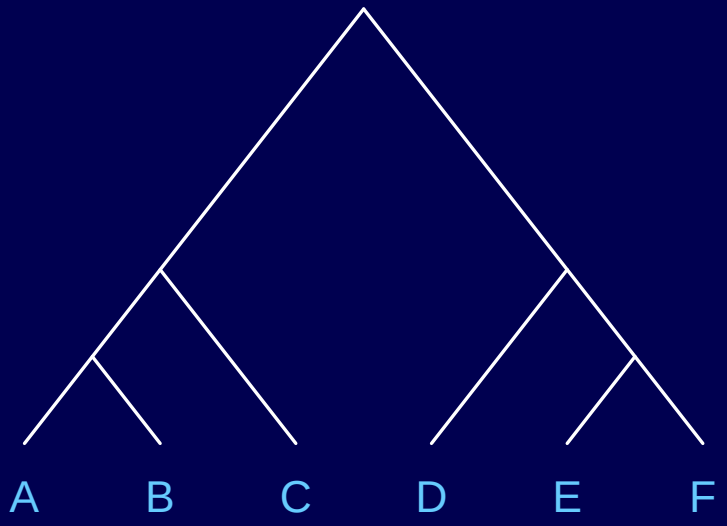
works



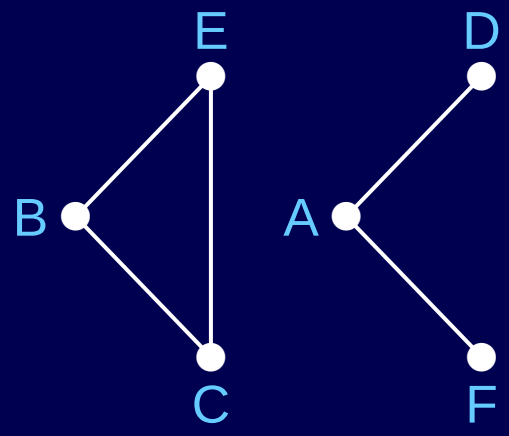
doesn't work

Minimal crosses

Tree



Crosses

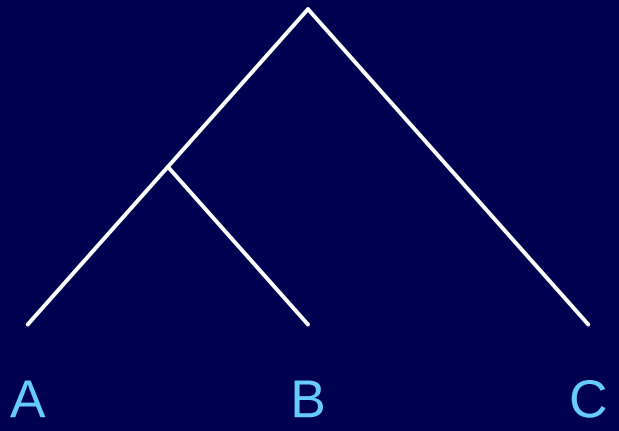


works (sort of)

Minimal crosses

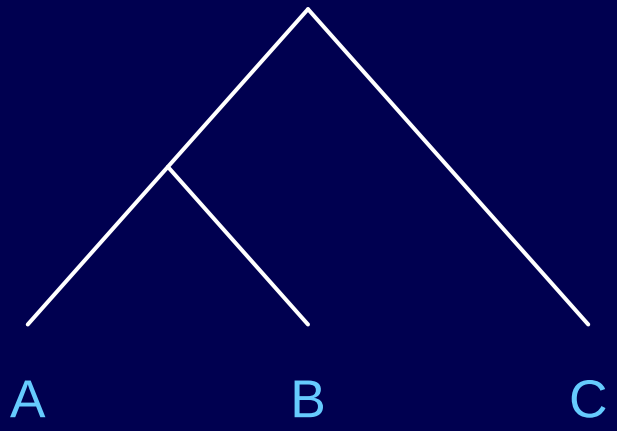
- For n taxa, you need at least n – 1 crosses
- Crosses should involve all taxa
- Crosses should connect all taxa
  (if you consider all possible partitions)

All or some crosses?

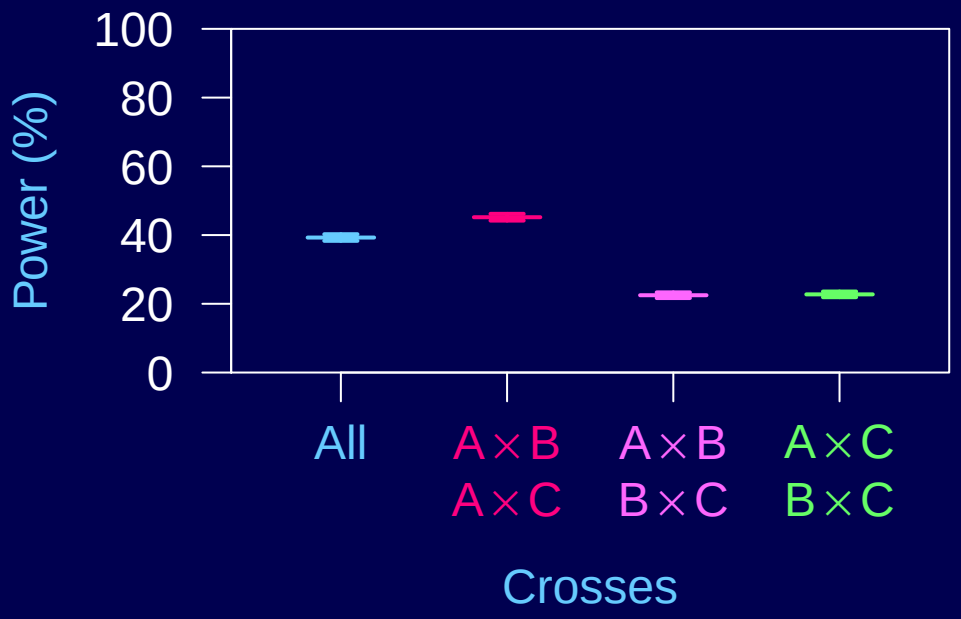


- 3 taxa
- All crosses, 100 individuals each,
  or 2 crosses, 150 individuals each?
- QTL with 10% heritability; A|BC pattern

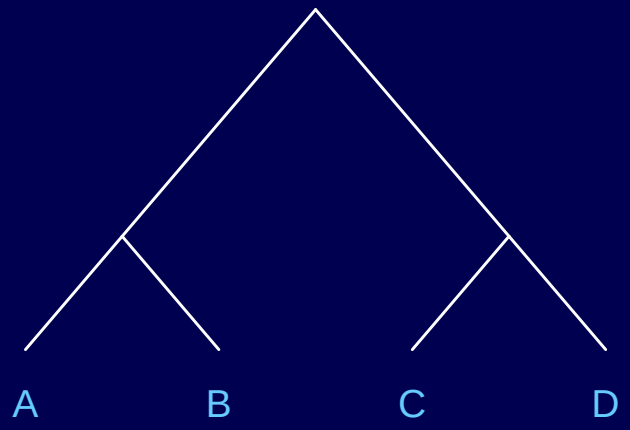
All or some crosses?



- 3 taxa
- All crosses, 100 individuals each,
  or 2 crosses, 150 individuals each?
- QTL with 10% heritability; A|BC pattern

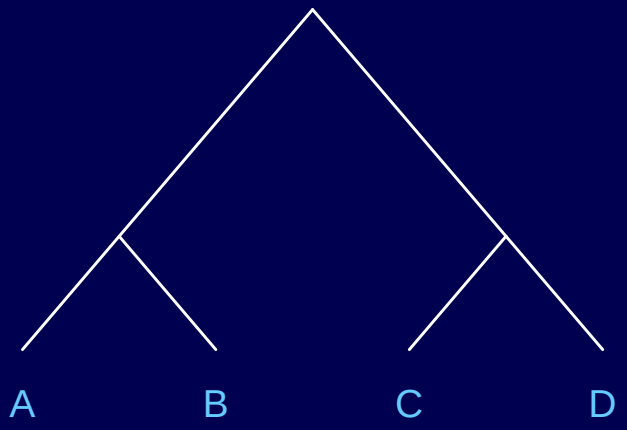


All or some crosses?

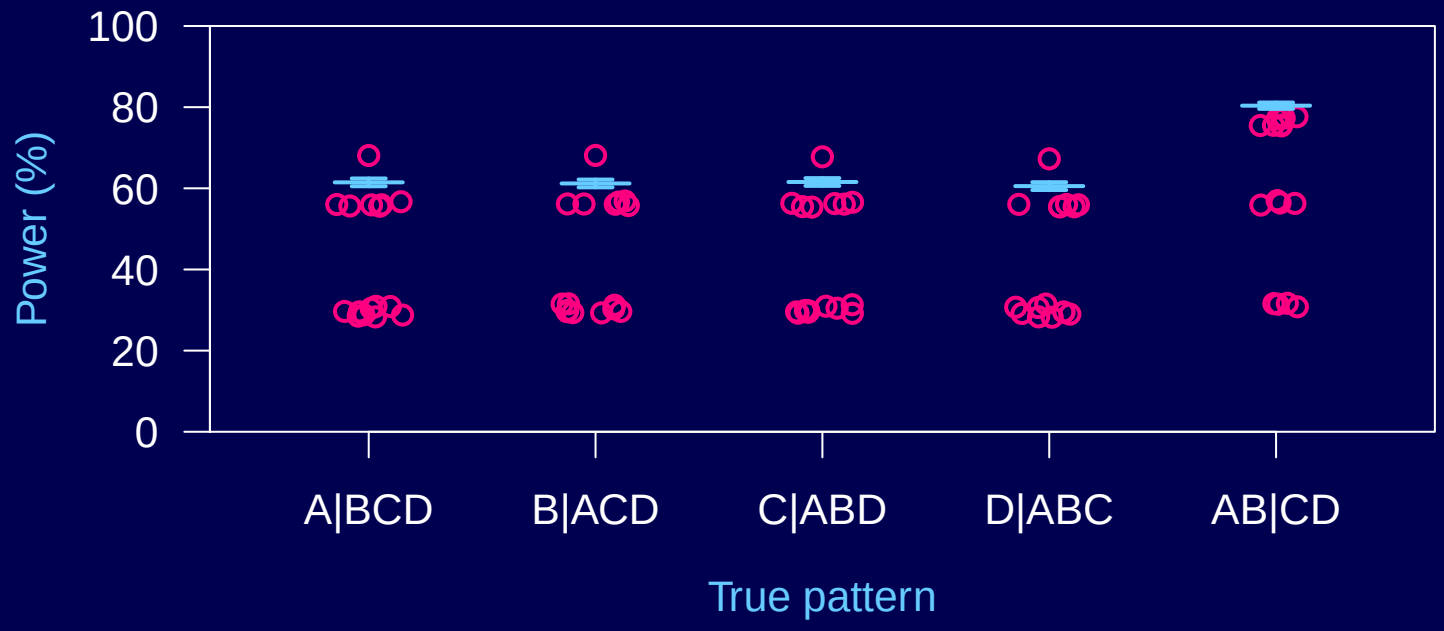


- 4 taxa
- All crosses, 100 individuals each, or 3 crosses, 200 individuals each?
- QTL with 10% heritability

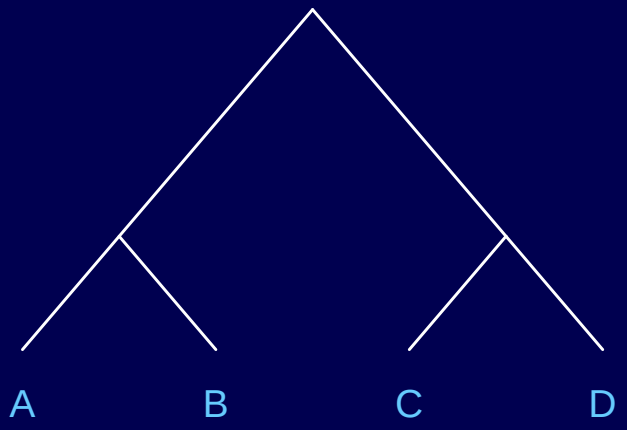
All or some crosses?



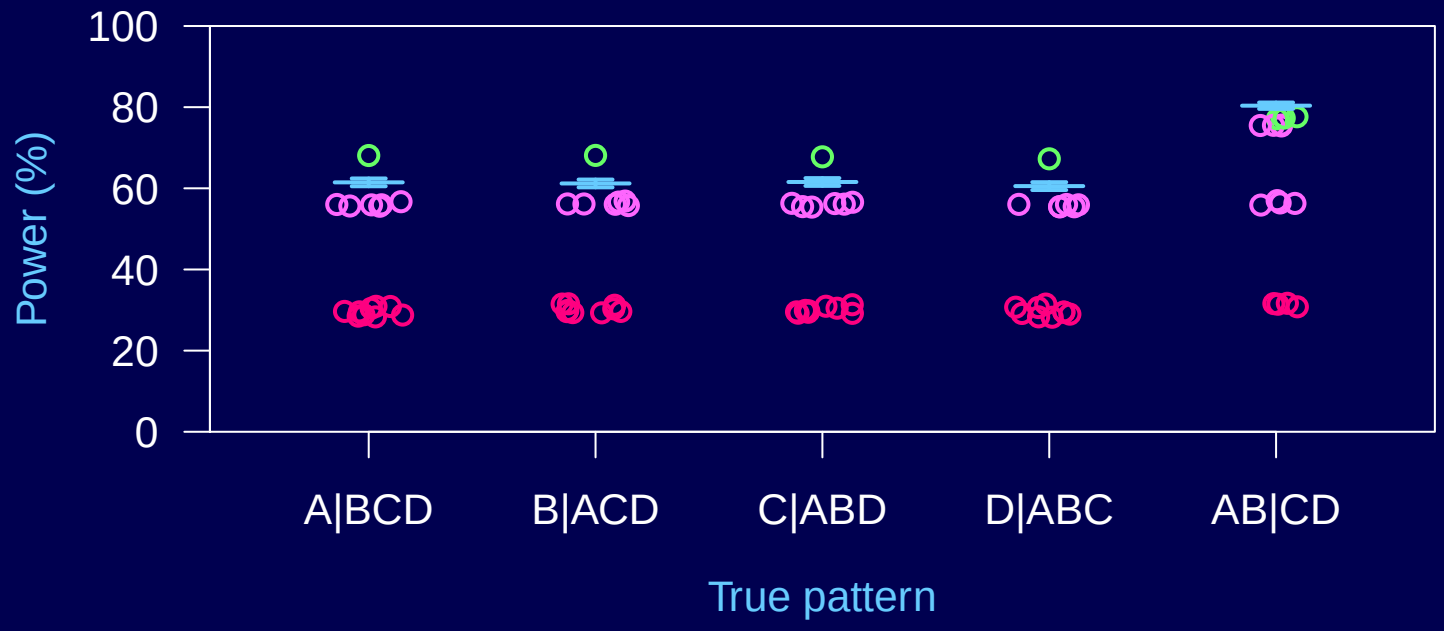
- 4 taxa
- All crosses, 100 individuals each, or 3 crosses, 200 individuals each?
- QTL with 10% heritability



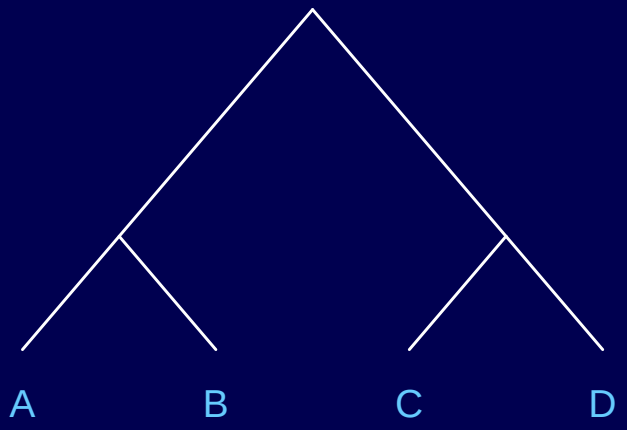
All or some crosses?



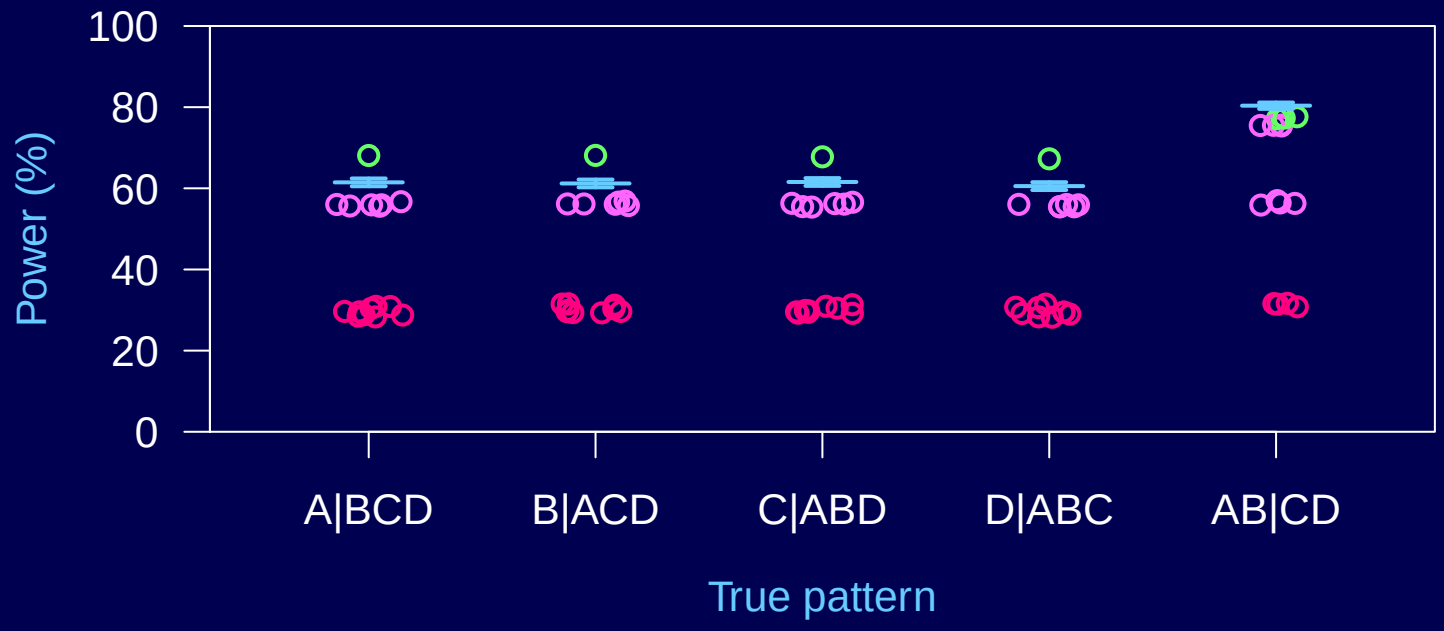
- 4 taxa
- All crosses, 100 individuals each, or 3 crosses, 200 individuals each?
- QTL with 10% heritability



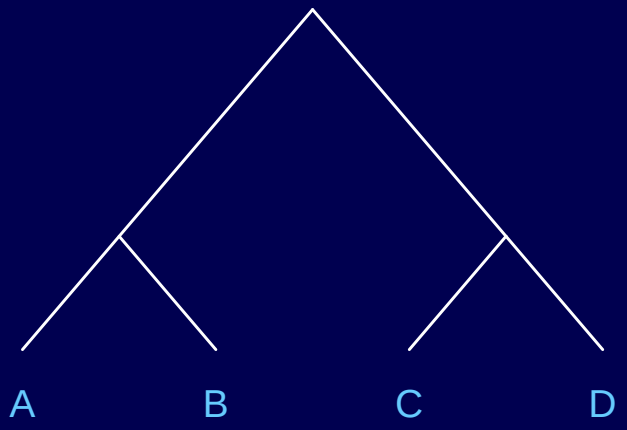
All or some crosses?



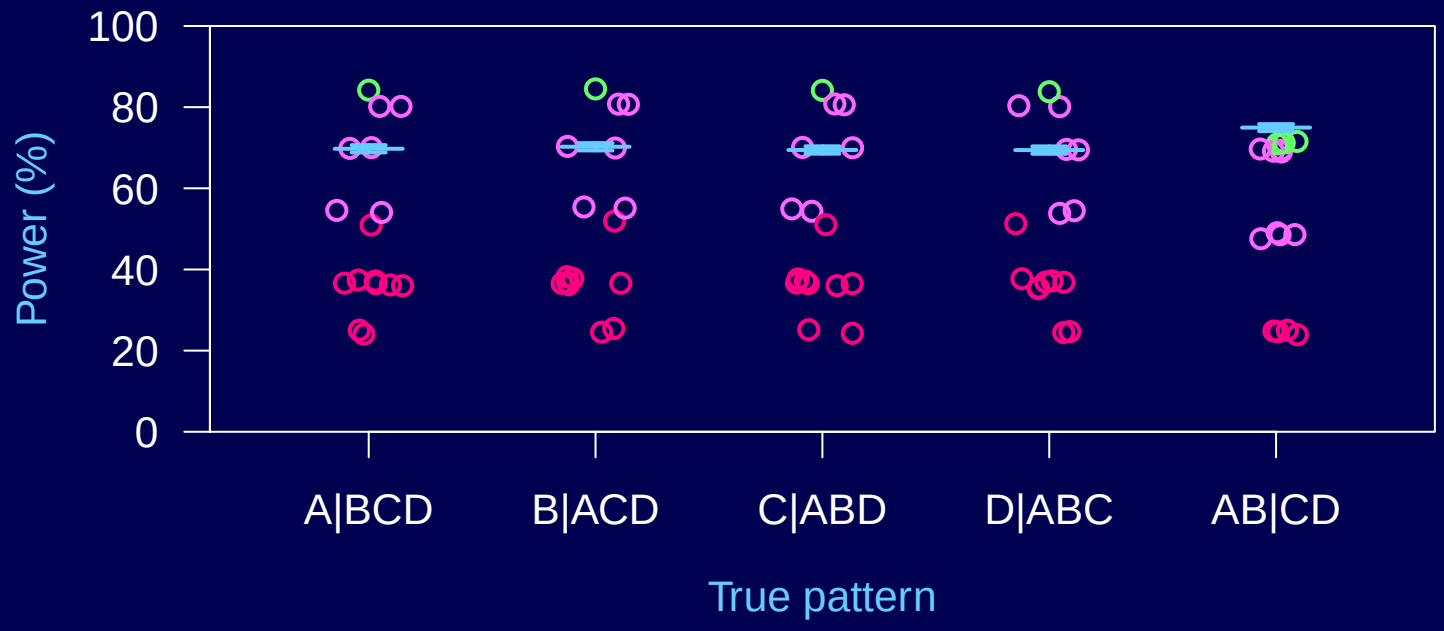
- 4 taxa
- All crosses, 100 individuals each, or 3 crosses, 200 individuals each?
- QTL with 10% heritability
- Consider all 7 partitions



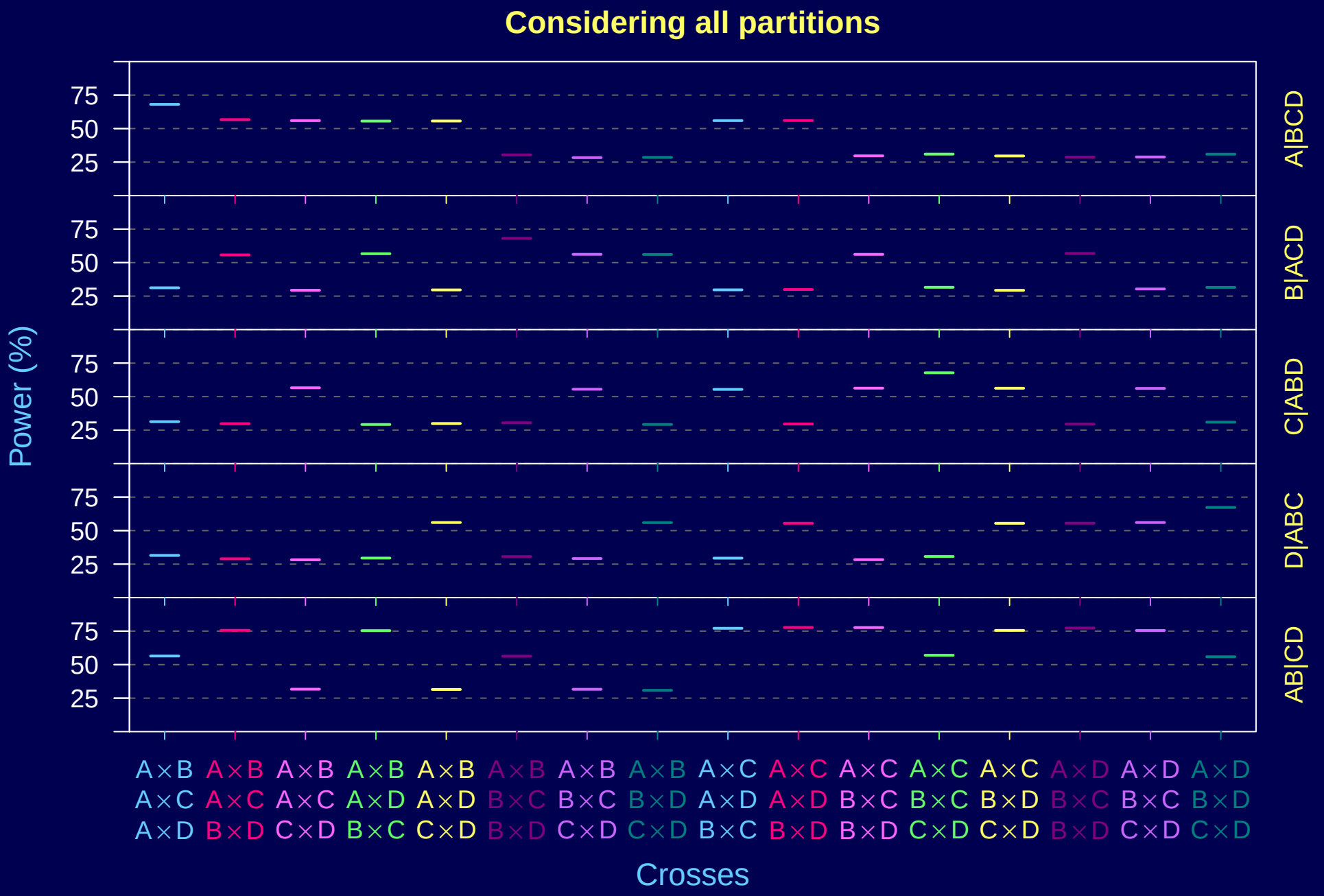
All or some crosses?



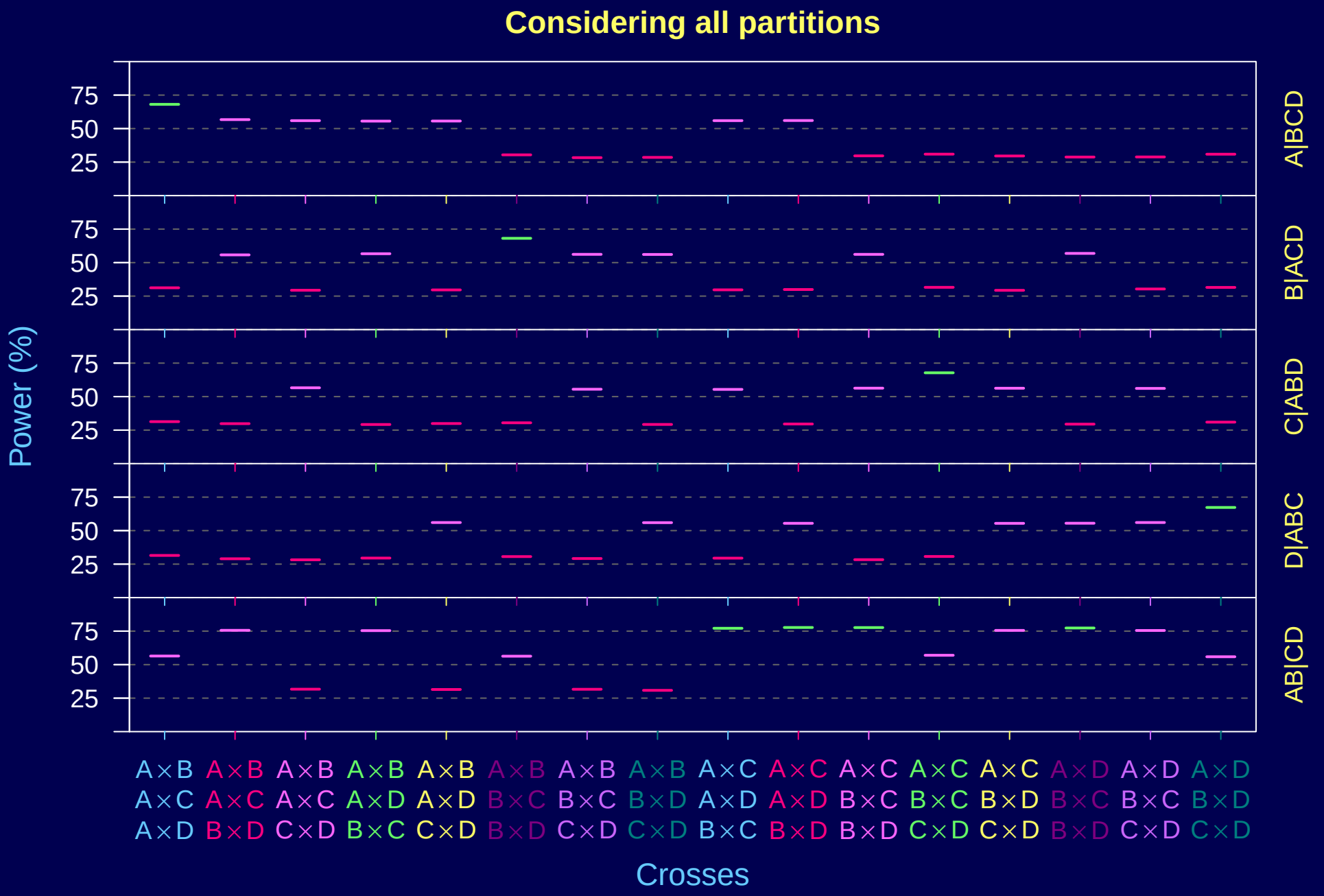
- 4 taxa
- All crosses, 100 individuals each, or 3 crosses, 200 individuals each?
- QTL with 10% heritability
- Consider the 5 partitions induced by the tree



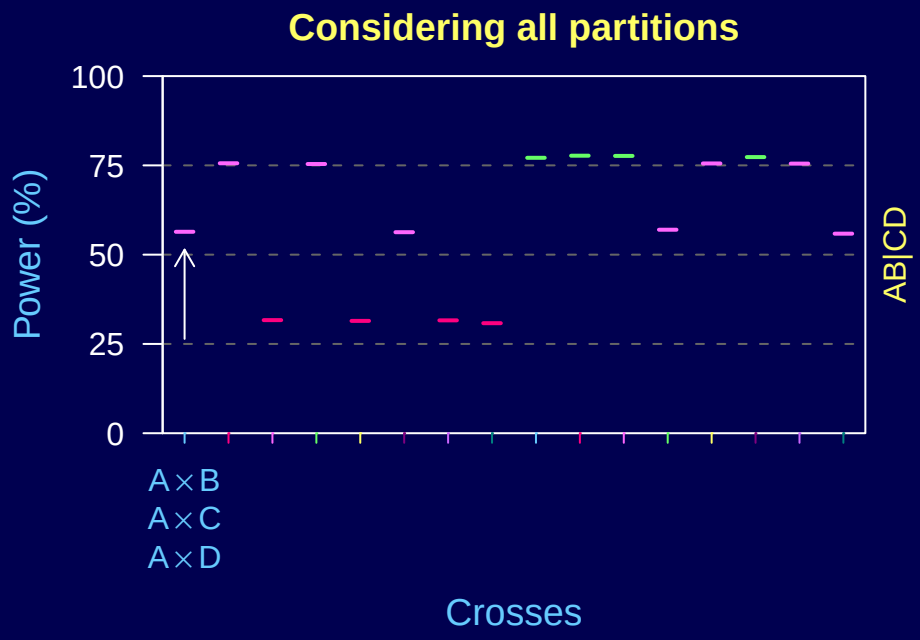
Which crosses?

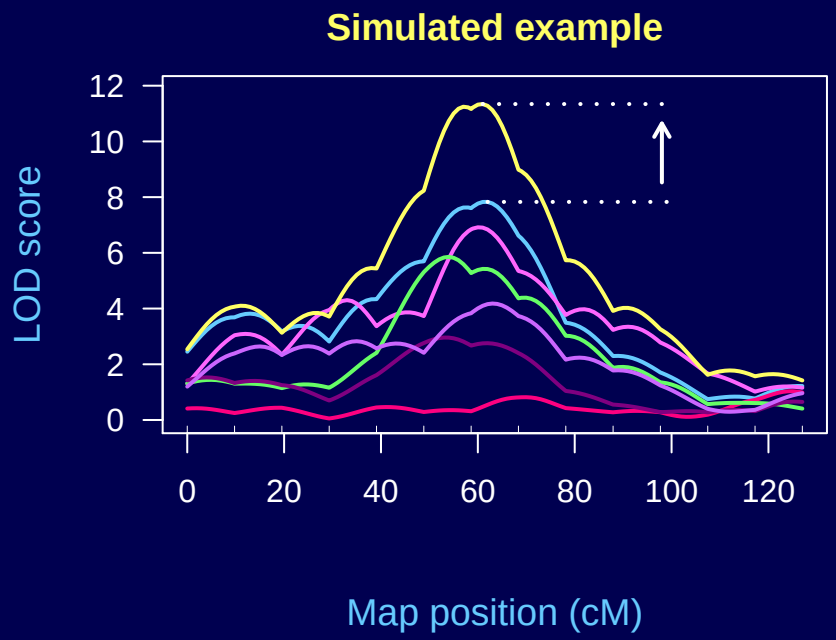


Which crosses?



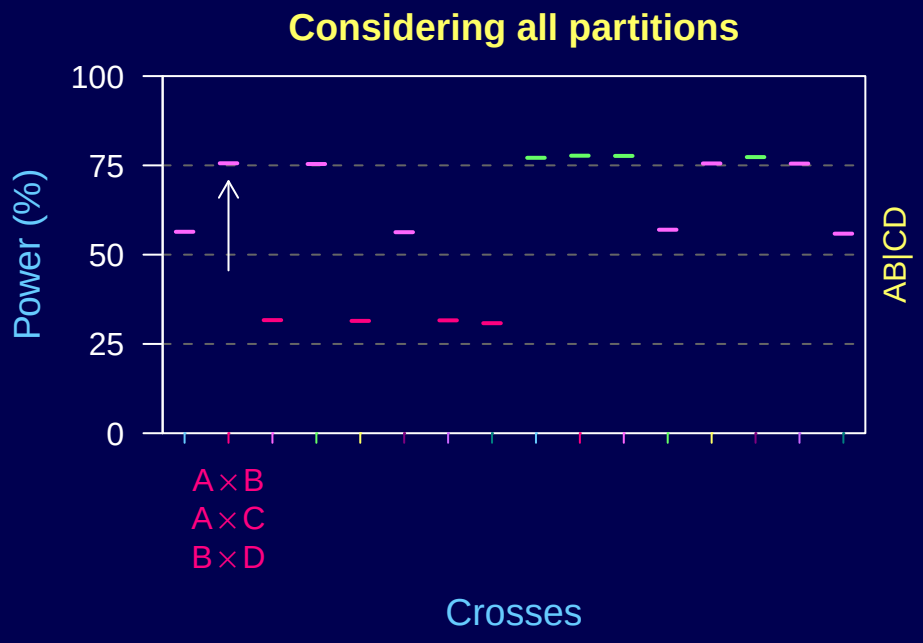
Which crosses?

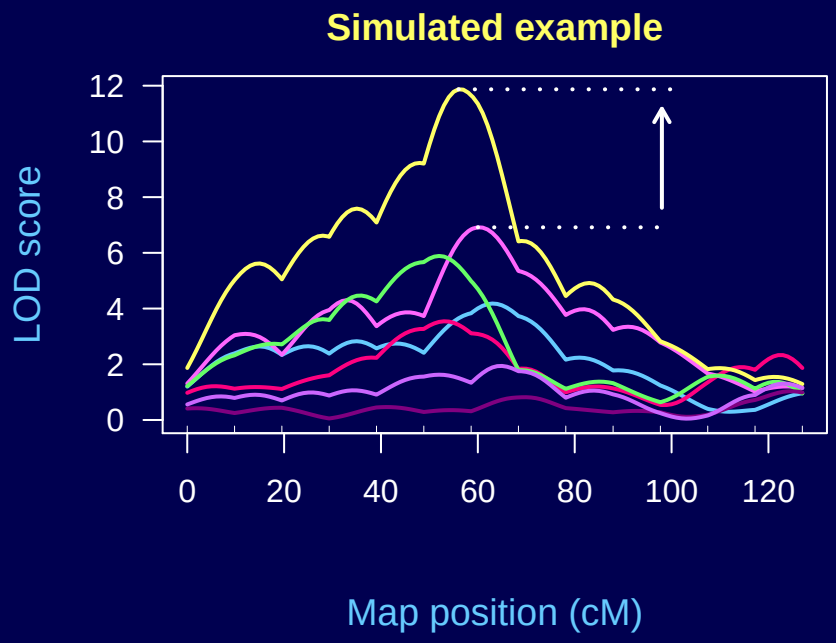




	Partition of taxa						
Cross	A|BCD	B|ACD	C|ABD	D|ABC	AB|CD	AC|BD	AD|BC
A × B	✓	✓	×	×	×	✓	✓
A × C	✓	×	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓	✓	×
B × C	×	✓	✓	×	✓	✓	×
B × D	×	✓	×	✓	✓	×	✓
C × D	×	×	✓	✓	×	✓	✓

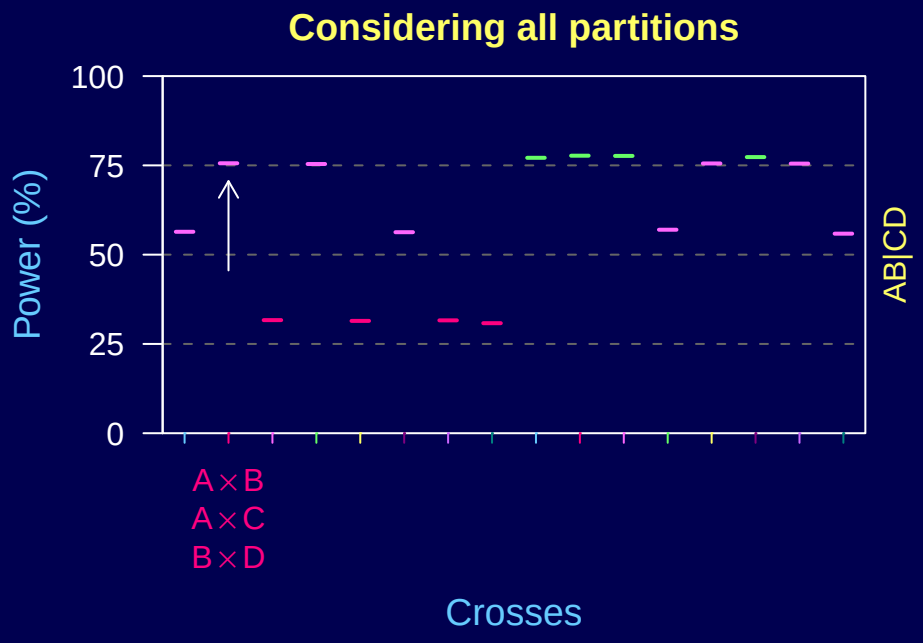
Which crosses?

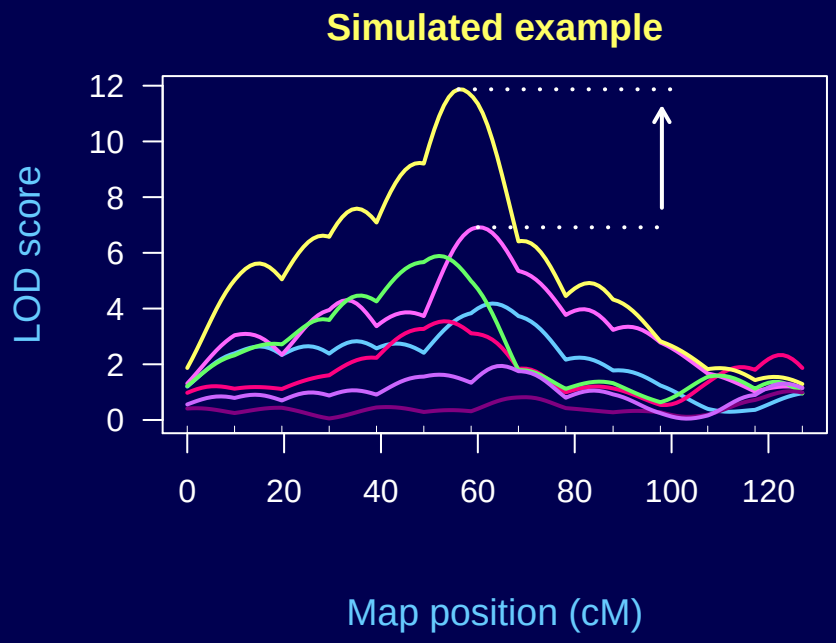




	Partition of taxa						
Cross	A|BCD	B|ACD	C|ABD	D|ABC	AB|CD	AC|BD	AD|BC
A × B	✓	✓	×	×	×	✓	✓
A × C	✓	×	✓	×	✓	×	✓
A × D	✓	×	×	✓	✓	✓	×
B × C	×	✓	✓	×	✓	✓	×
B × D	×	✓	×	✓	✓	×	✓
C × D	×	×	✓	✓	×	✓	✓

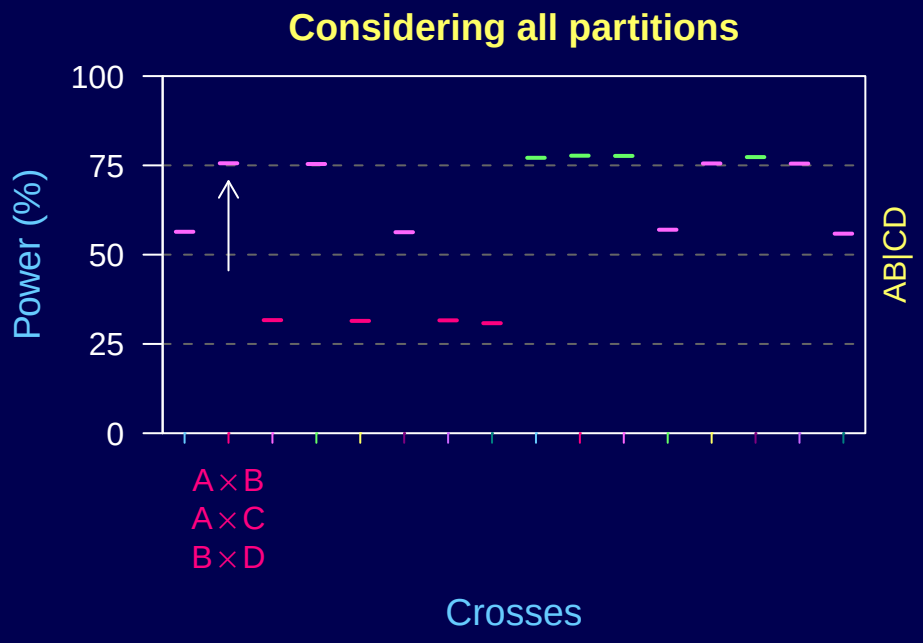
Which crosses?

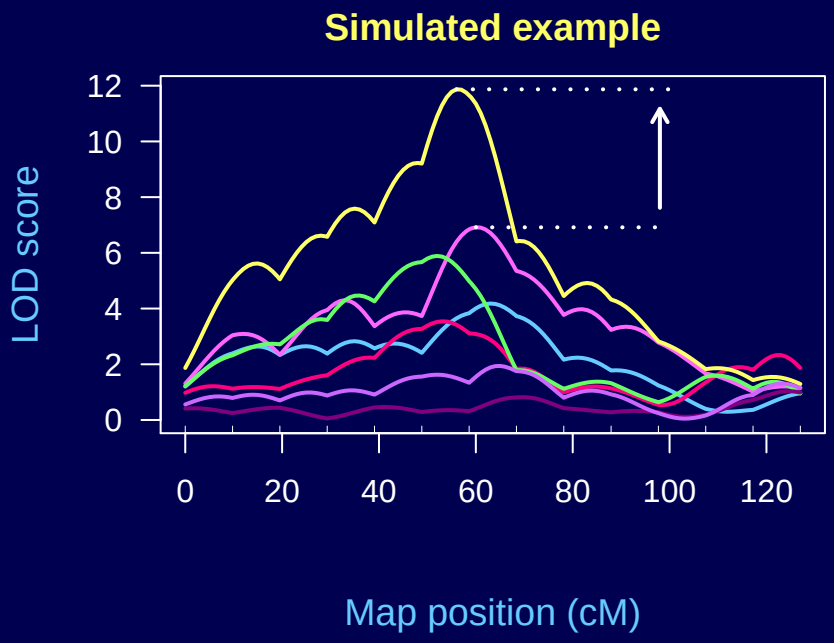




	Partition of taxa						
Cross	A|BCD	B|ACD	C|ABD	D|ABC	AB|CD	AC|BD	AD|BC
A × B	+	−	0	0	0	+	+
A × C	+	0	−	0	+	0	+
A × D	+	0	0	−	+	+	0
B × C	0	+	−	0	+	−	0
B × D	0	+	0	−	+	0	−
C × D	0	0	+	−	0	+	−

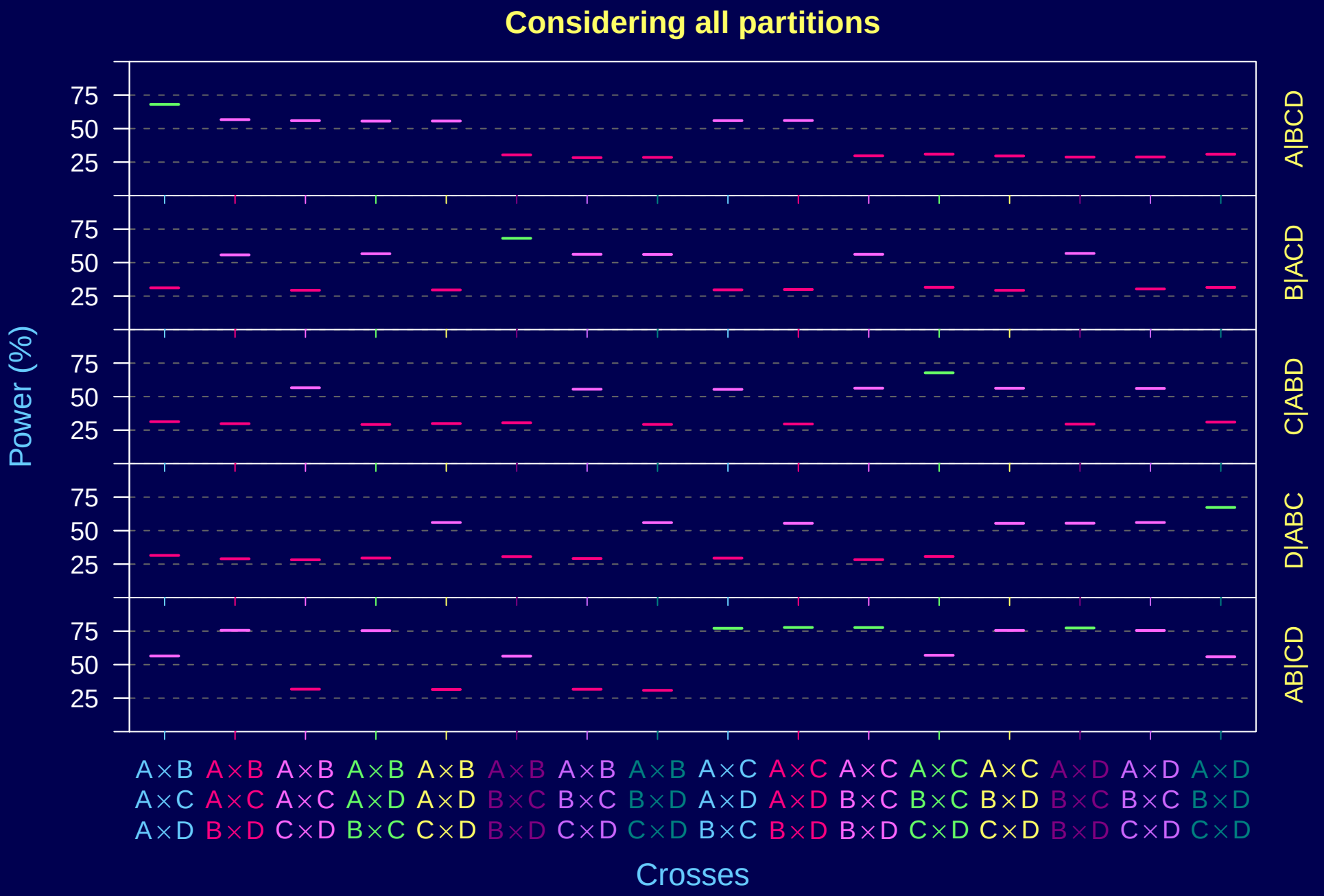
Which crosses?



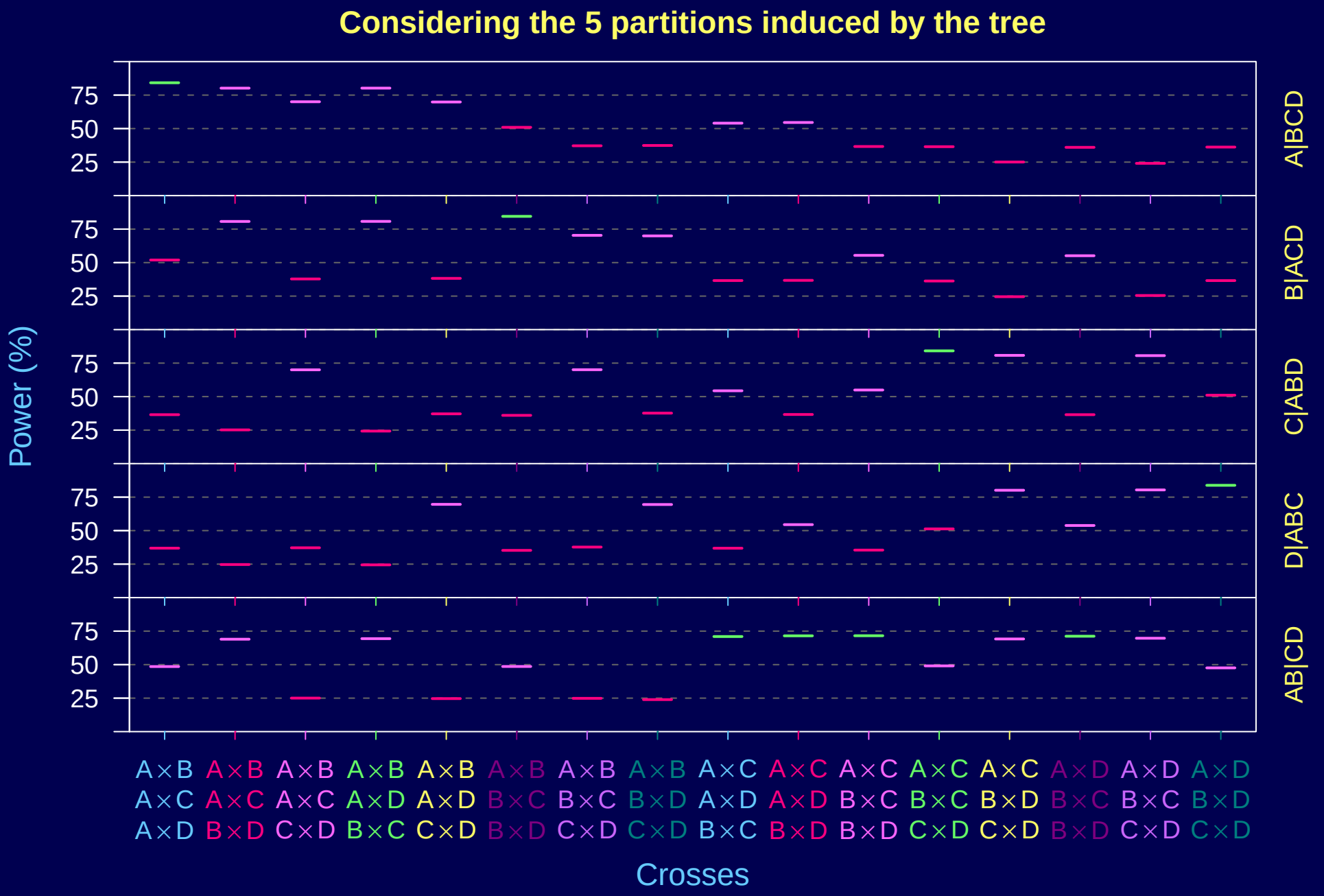


	Partition of taxa						
Cross	A|BCD	B|ACD	C|ABD	D|ABC	AB|CD	AC|BD	AD|BC
A × B	+	−	0	0	0	+	+
A × C	+	0	−	0	+	0	+
A × D	+	0	0	−	+	+	0
B × C	0	+	−	0	+	−	0
B × D	0	+	0	−	+	0	−
C × D	0	0	+	−	0	+	−

Which crosses?



Which crosses?



Caveats

- Epistasis
- Multiple linked QTL
- More than two alleles

Future work

- Software
- Application
- Paper
- Sensitivity to departures from assumptions
- Multiple linked loci
- Jointly consider multiple unlinked regions

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