The X chromosome in QTL mapping: What a pain in the @$$!

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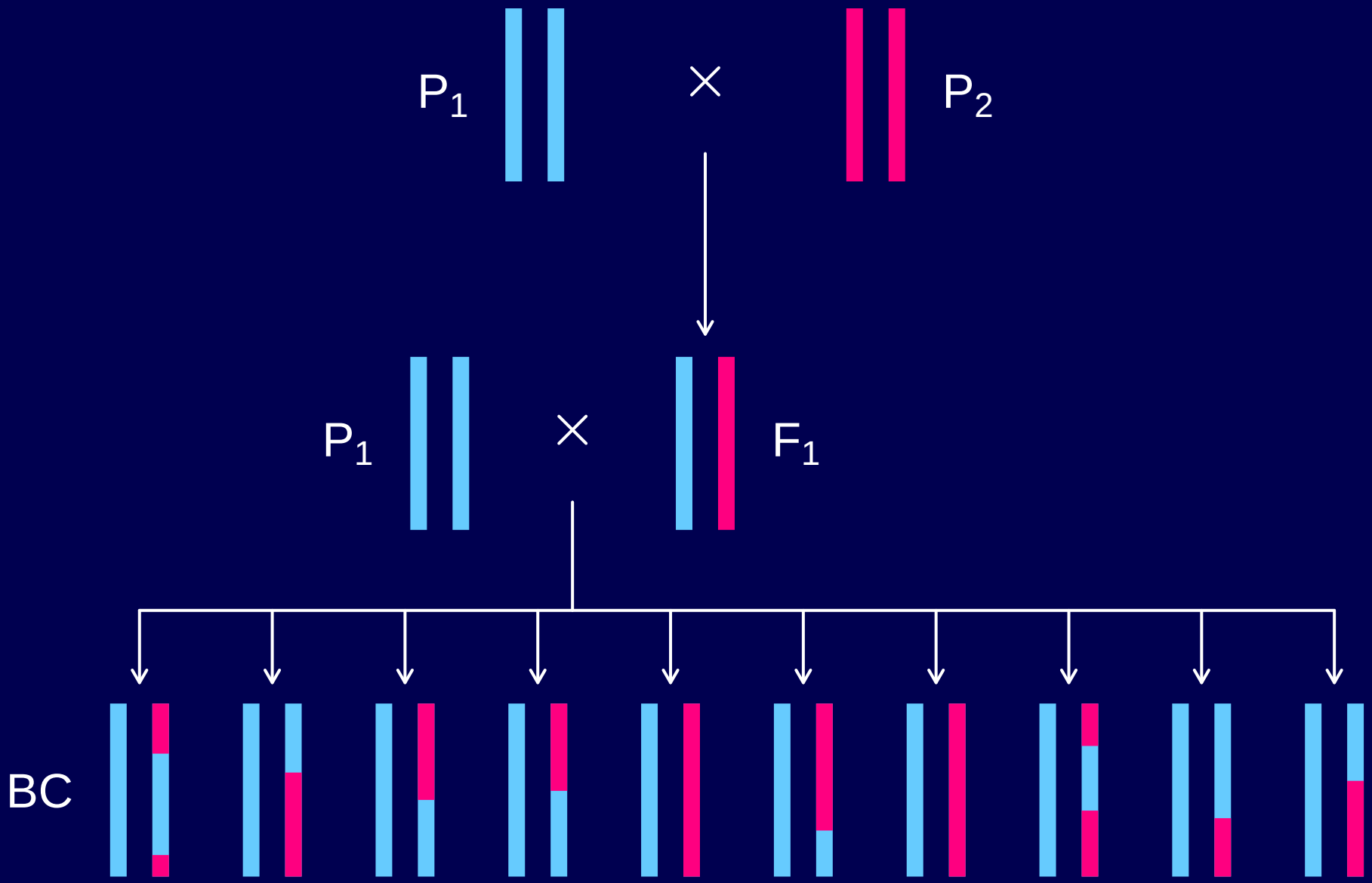
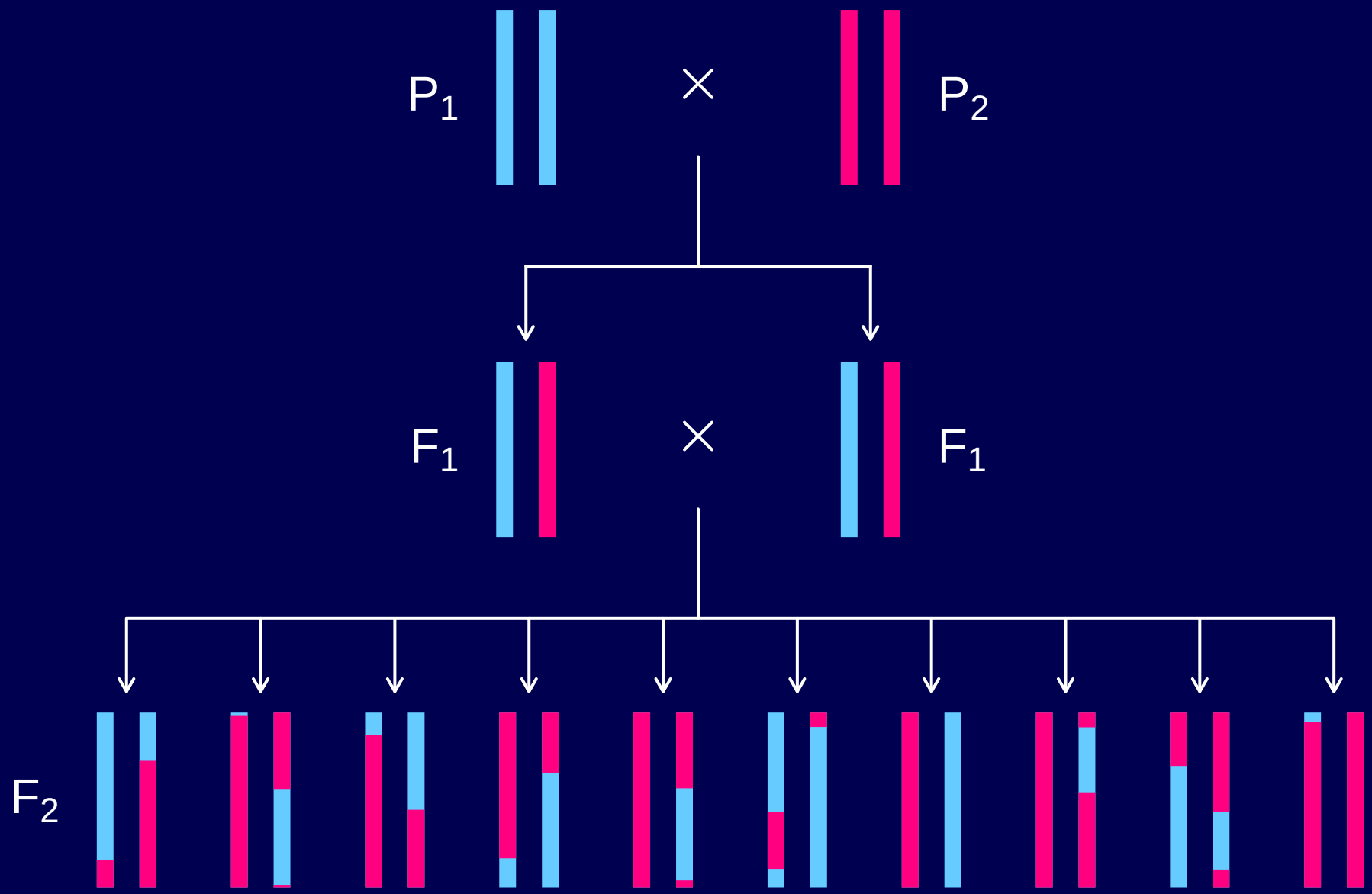
C57BL/6

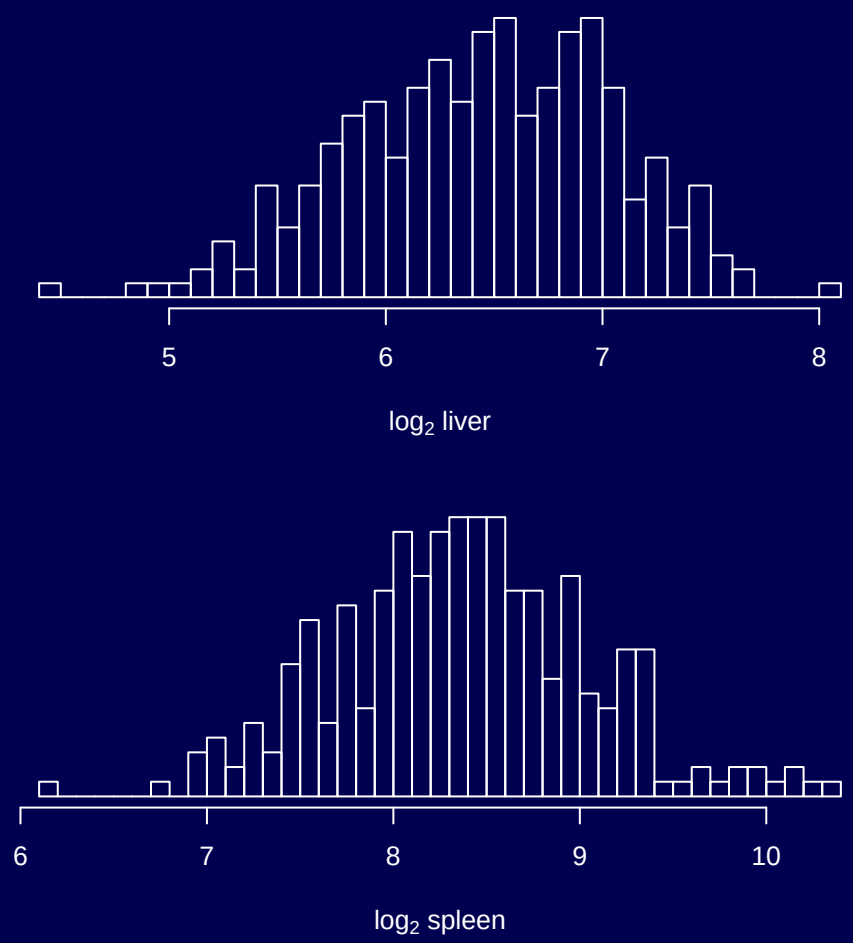
Backcross

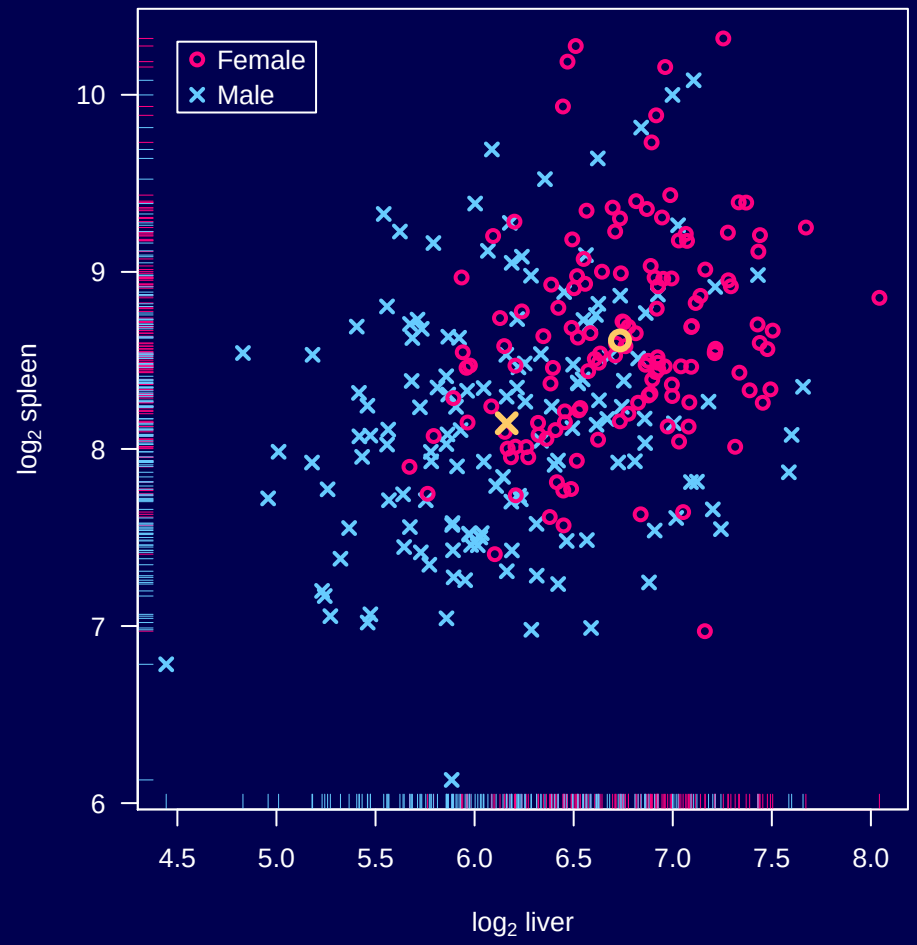


Intercross

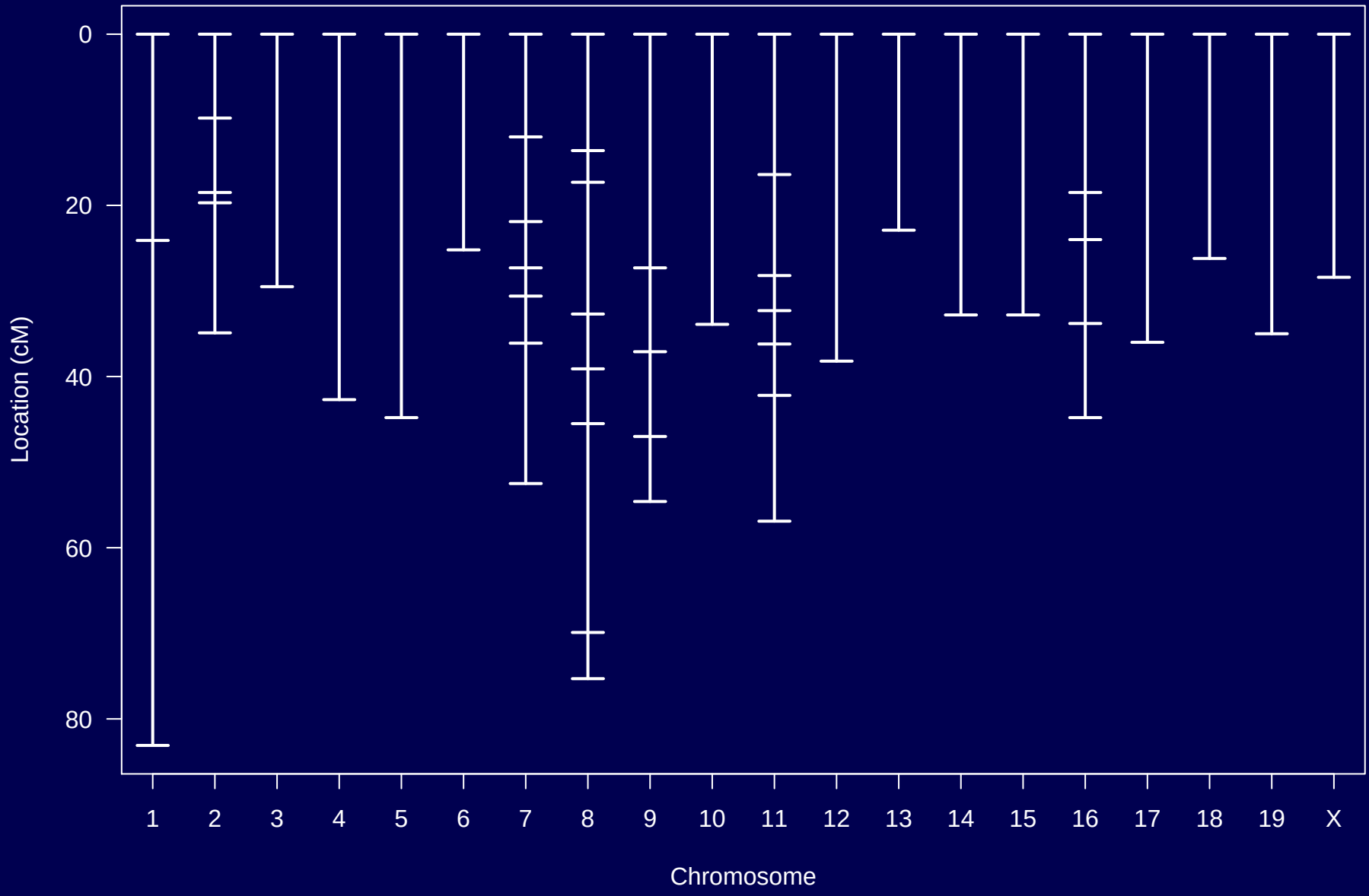


Phenotype data

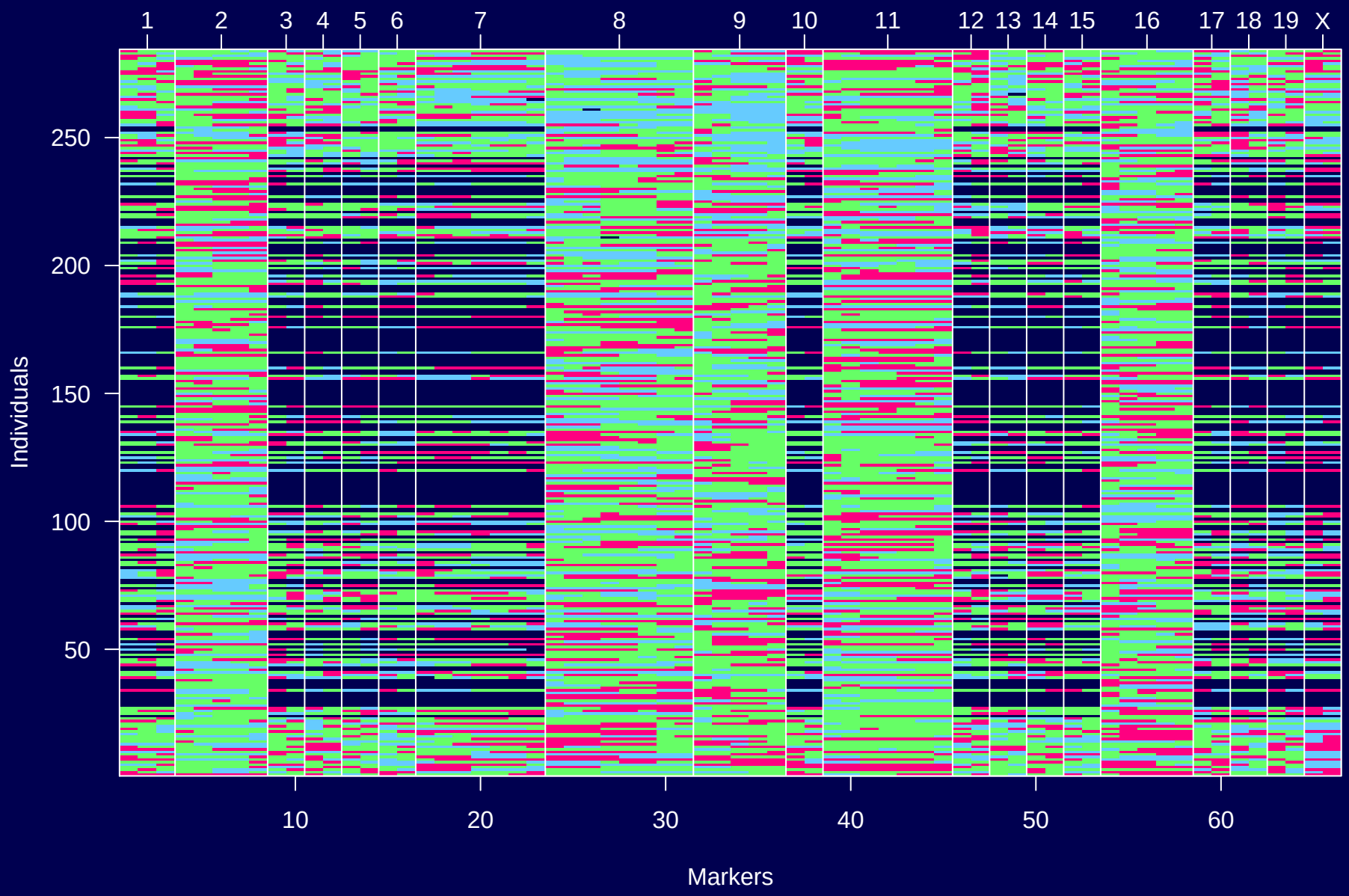




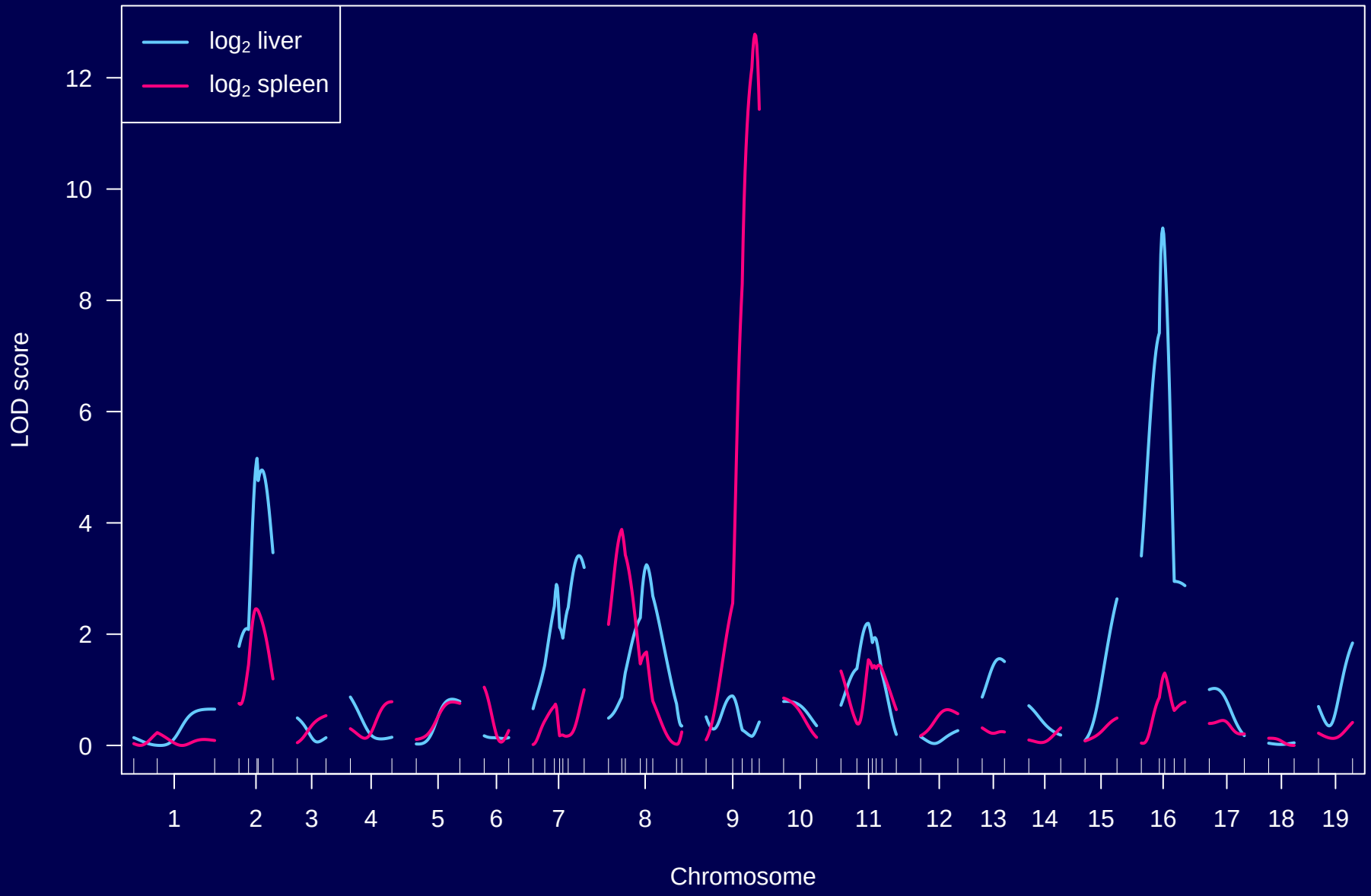
Genetic map


0
20
40
60
80
Location (cM)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

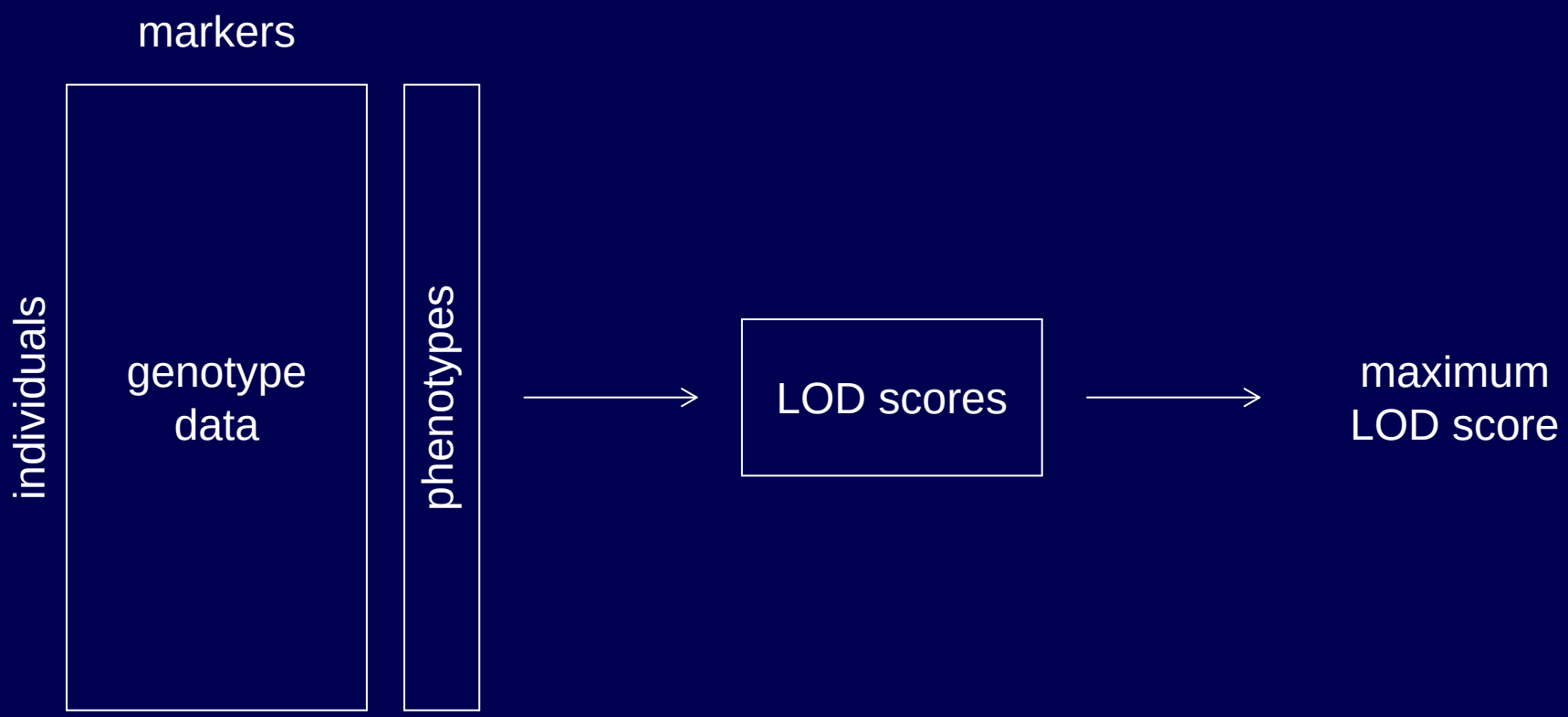
Genotype data



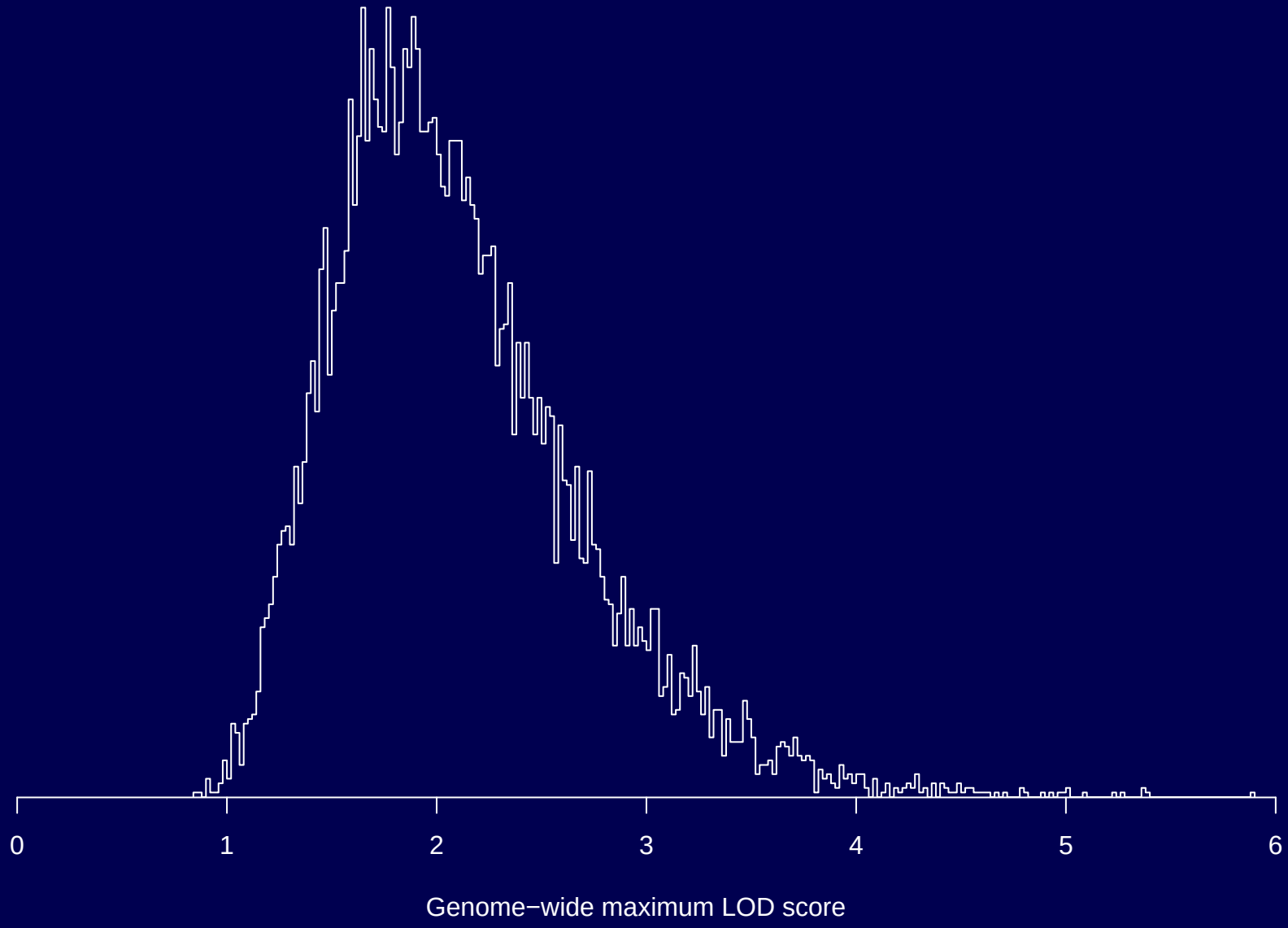
LOD curves


log2 liver
log2 spleen
LOD score
0
2
4
6
8
10
12
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Chromosome

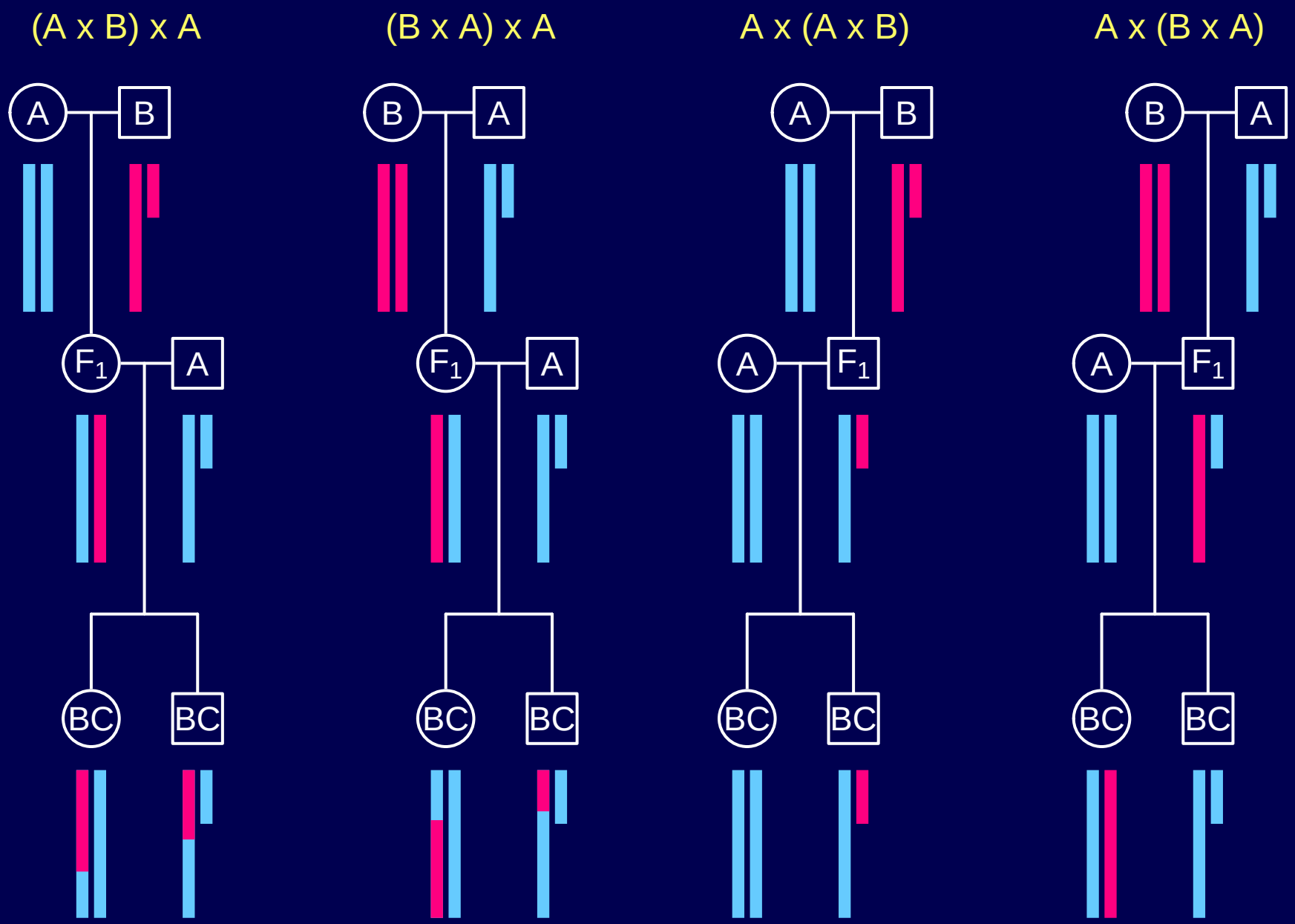
Permutation test



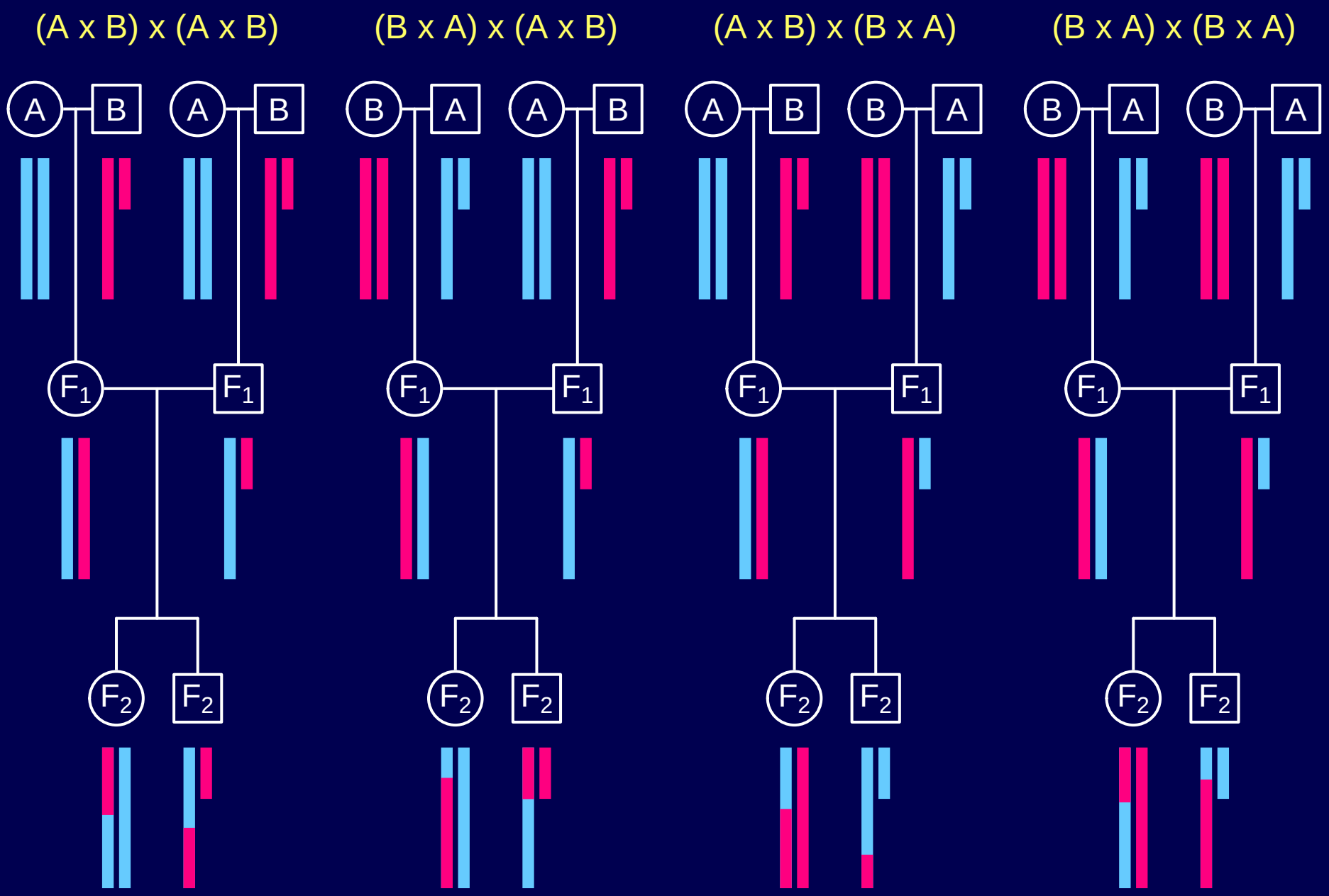
Permutation results



X chr in backcross



X chr in intercross



Example

Intercross: both dir, both sexes

- ♀ forward AA or AB
- ♀ reverse AB or BB
- ♂ forward AY or BY
- ♂ reverse AY or BY

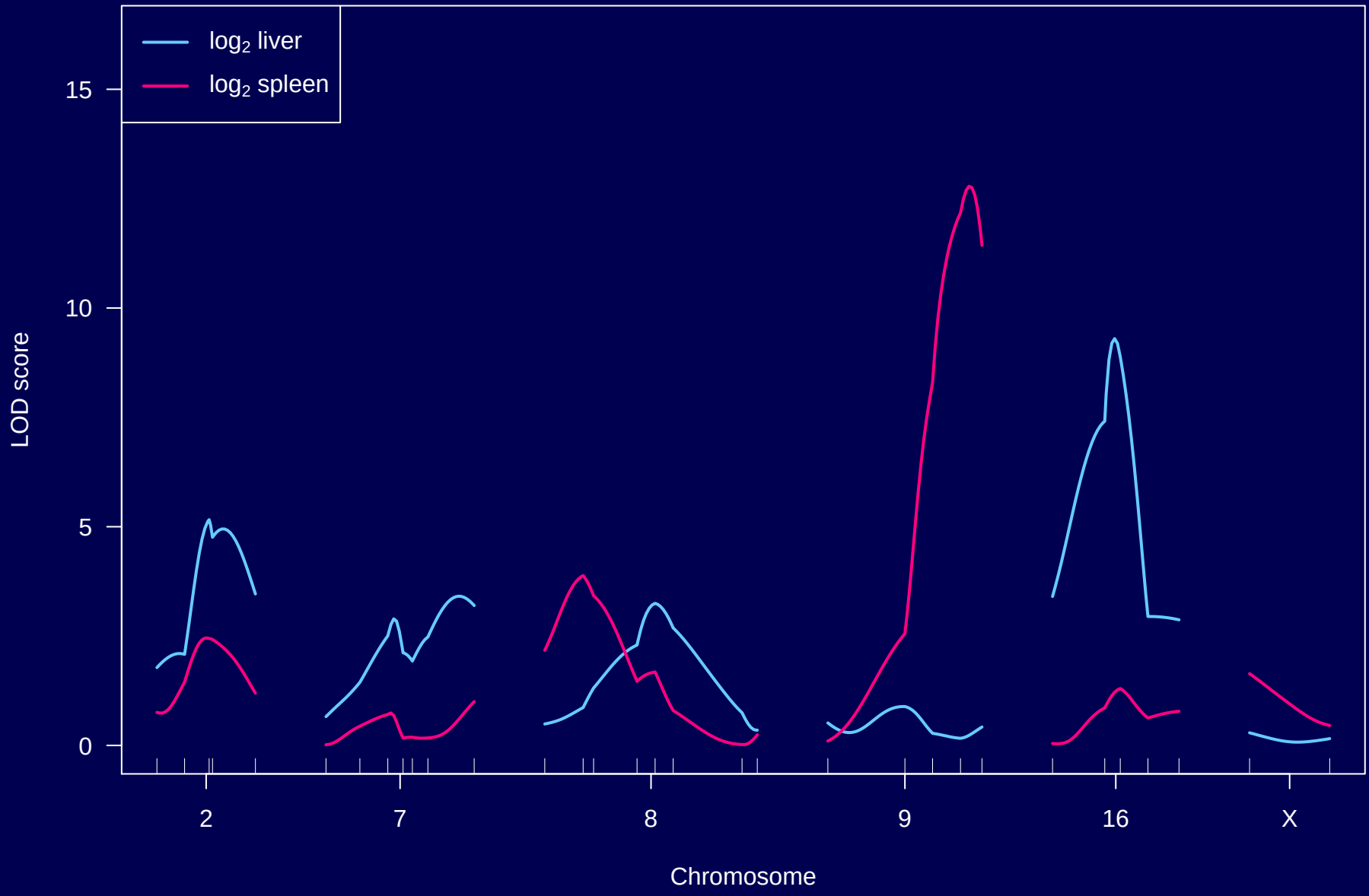
Principles

- Sex- or cross-direction-difference in the phenotype shouldn't lead to spurious linkage on the X chromosome
- Simple as possible
- Null nested within alternative

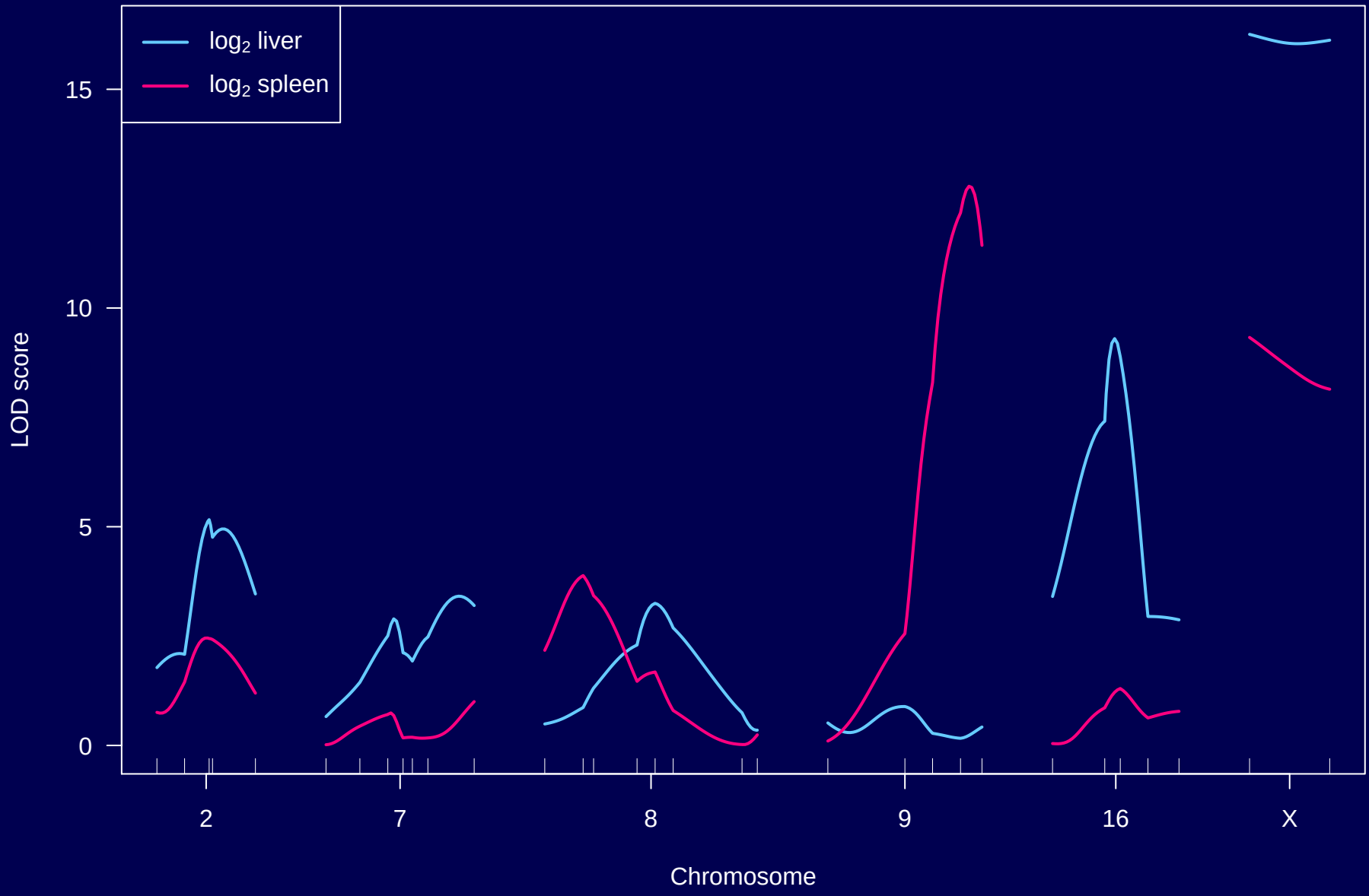
Approach

Cross	Direction	Sexes	Contrasts	H_0	df
BC		both	AA:AB:AY:BY	♀:♂	2
BC		♀	AA:AB	grand mean	1
BC		♂	AY:BY	grand mean	1
F_2	both	both	AA:ABf:ABr:BB:AY:BY	$♀_f$:$♀_r$:♂	3
F_2	both	♀	AA:ABf:ABr:BB	$♀_f$:$♀_r$	2
F_2	both	♂	AY:BY	grand mean	1
F_2	one	both	AA:AB:AY:BY	♀:♂	2
F_2	one	♀	AA:AB	grand mean	1
F_2	one	♂	AY:BY	grand mean	1

Results


log2 liver
log2 spleen
LOD score
15
10
5
0
2
7
8
9
16
X
Chromosome

Bad Results


log2 liver
log2 spleen
LOD score
15
10
5
0
2
7
8
9
16
X
Chromosome

Chromosome-specific thresholds

Let α_i = false positive rate for chromosome i.

We need $1 - \alpha = \prod(1 - \alpha_i)$

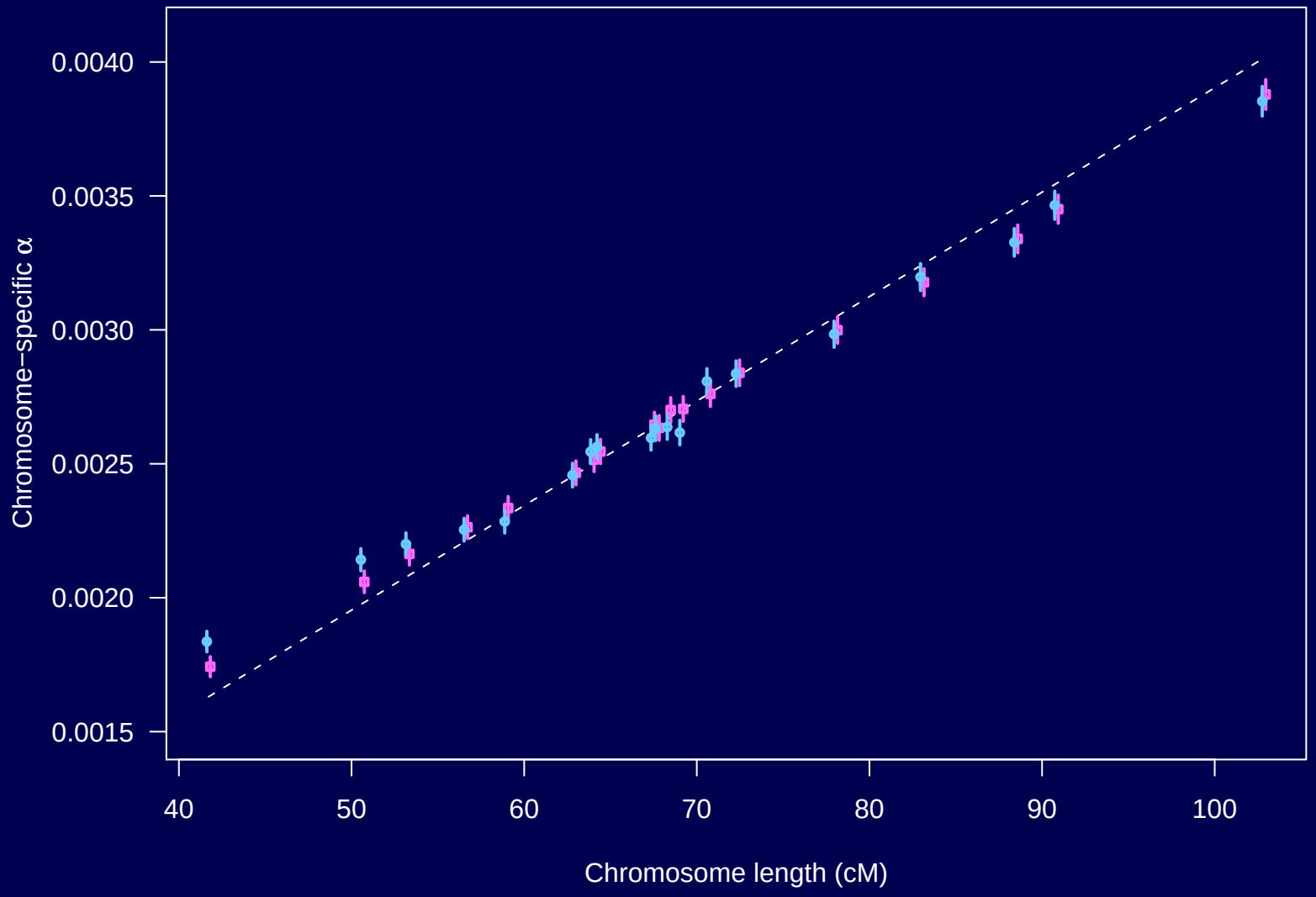
For example, $\alpha_1 = \alpha$ and $\alpha_j = 0$ for $j \neq 1$

The usual method: constant LOD threshold
(i.e., constant power)

My approach: $\alpha_i \propto L_i$ where L_i = length of chr i

Similar and more convenient: $\alpha_i = (1 - \alpha)^{L_i/L}$

Simulation results



A- and X-specific permutations

- Do separate permutations within autosomes and X chromosome.

- $M^\star_{Ai}$ = maximum LOD across autosomes in replicate i.
  $M^\star_{Xi}$ = maximum LOD across X chromosome in replicate i.

- $T_A = (1-\alpha)^{L_A/L}$ quantile of $M^\star_{Ai}$
  $T_X = (1-\alpha)^{L_X/L}$ quantile of $M^\star_{Xi}$

- Genome-scan-adjusted p-values
  M_X = observed maximum LOD on X
  $p_{\text{unadj}} = \text{Prop}(M^\star_{Xi} \geq M_X)$
  $p_{\text{adj}} = 1 - (1 - p_{\text{unadj}})^{L/L_X}$

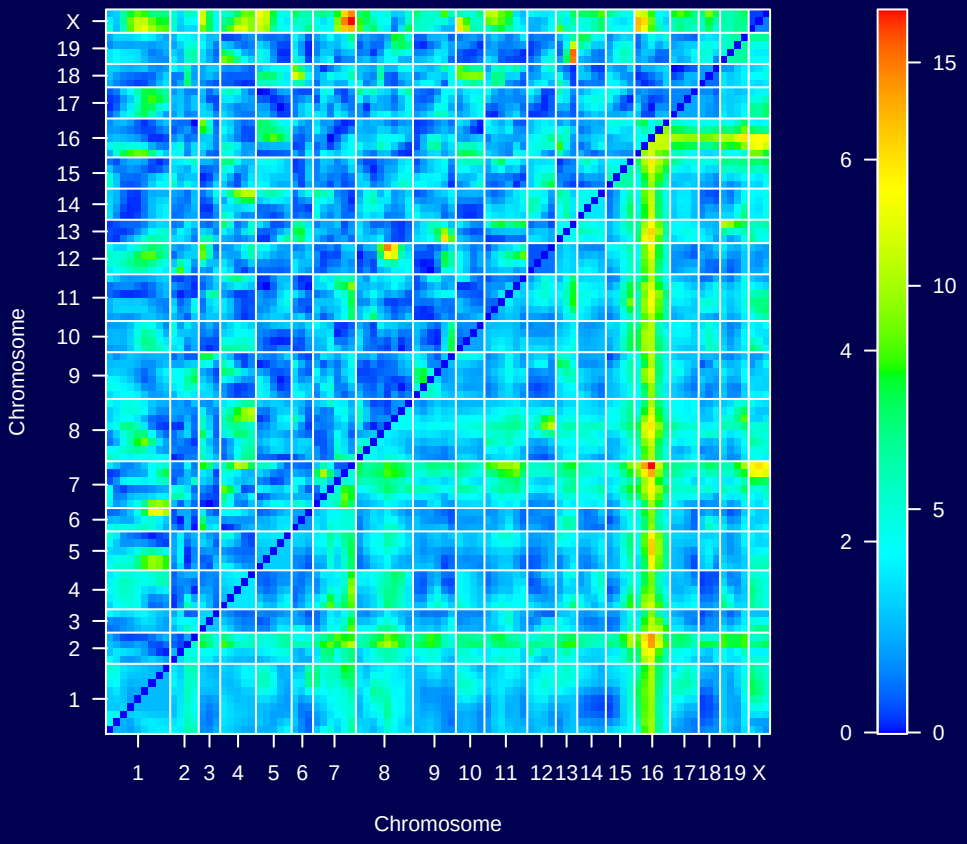
- Let n_A = no. permutation replicates for autosomes
  We want $n_X = n_A \times L_A/L_X$ to get equivalent precision.
  (This doubles the computation time.)

LOD thresholds for the example

	$\log_2$ liver		$\log_2$ spleen	
	5%	20%	5%	20%
autosomes	3.32	2.62	3.33	2.59
X chromosome	4.66	3.78	4.55	3.70

Note: 1100 permutations on autosomes
31,075 on X chromosome

2d scans



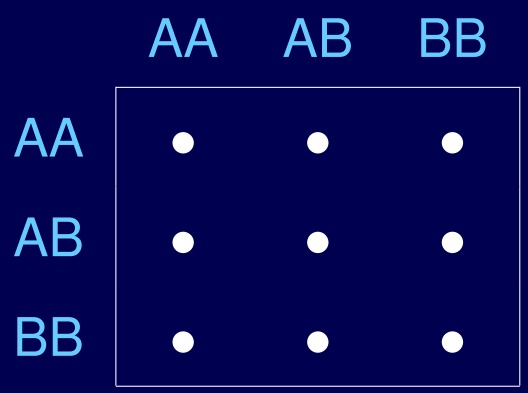
Full: $Q_1 + Q_2 + Q_1 : Q_2$

Add: $Q_1 + Q_2$

One: Q_1

Null: $\varnothing$

A vs. A



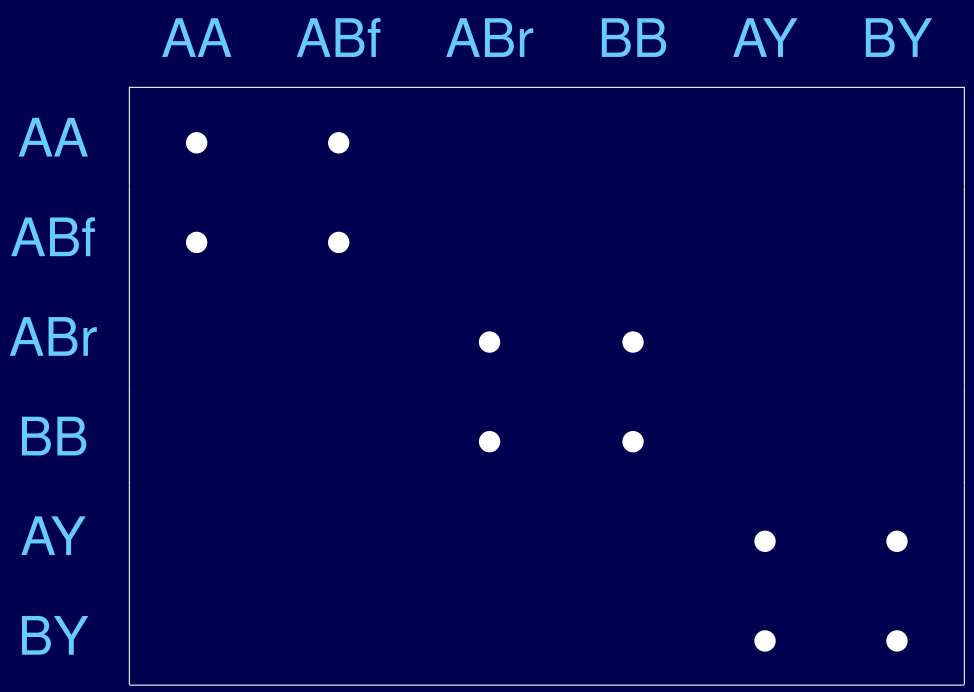
full: 9 param

add: 5 param

} int: 4 df

null: 1 param

X vs. X



full: 12 param

add: 9 param

} int: 3 df

null: 3 param

A vs. X

full: 18 param

add: 8 param

} int: 10 df

null: 3 param

Summary

- The X chromosome is a pain in the @$$!
- Must take care regarding contrasts and null hypothesis
- Need for autosome- and X-chr-specific permutations
- 2d scan requires great care; odd degrees of freedom