The genetic dissection of complex traits

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The goal

Identify genes that contribute to complex diseases

Complex disease = one that's hard to figure out

- Many genes + environment + other stuff

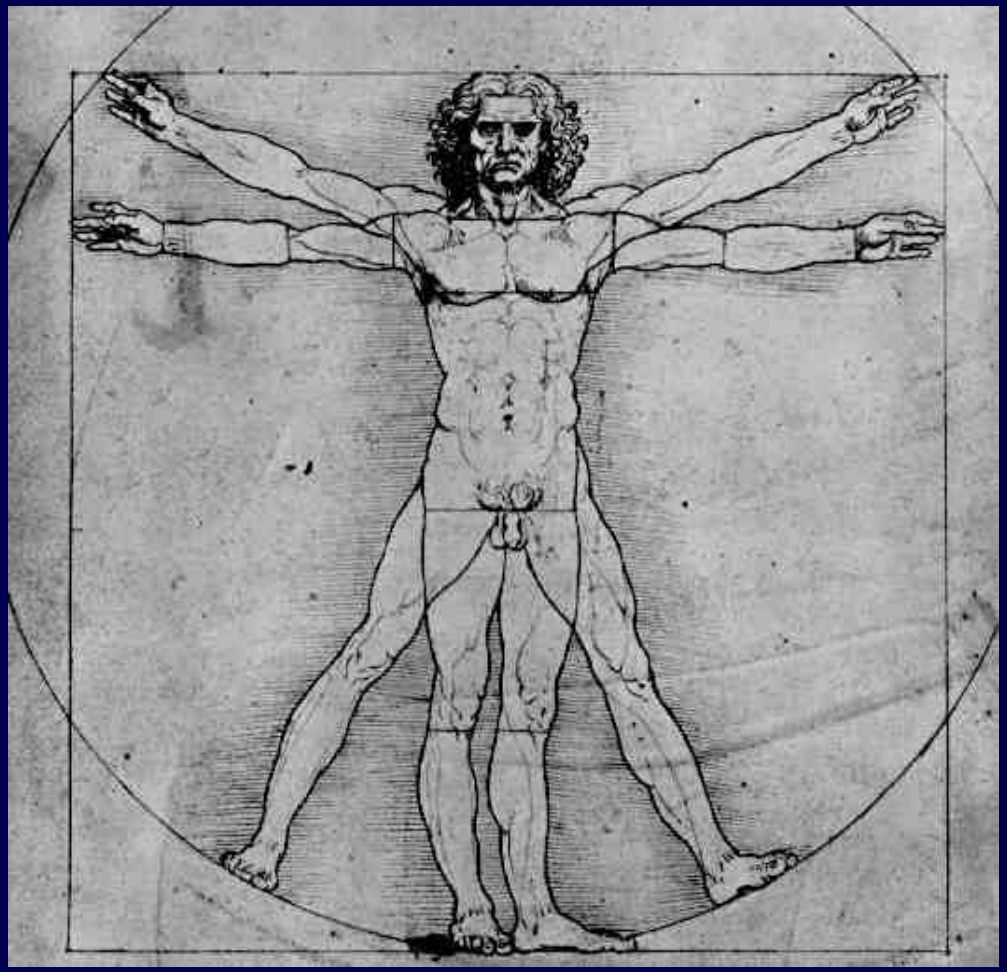
The genetic approach

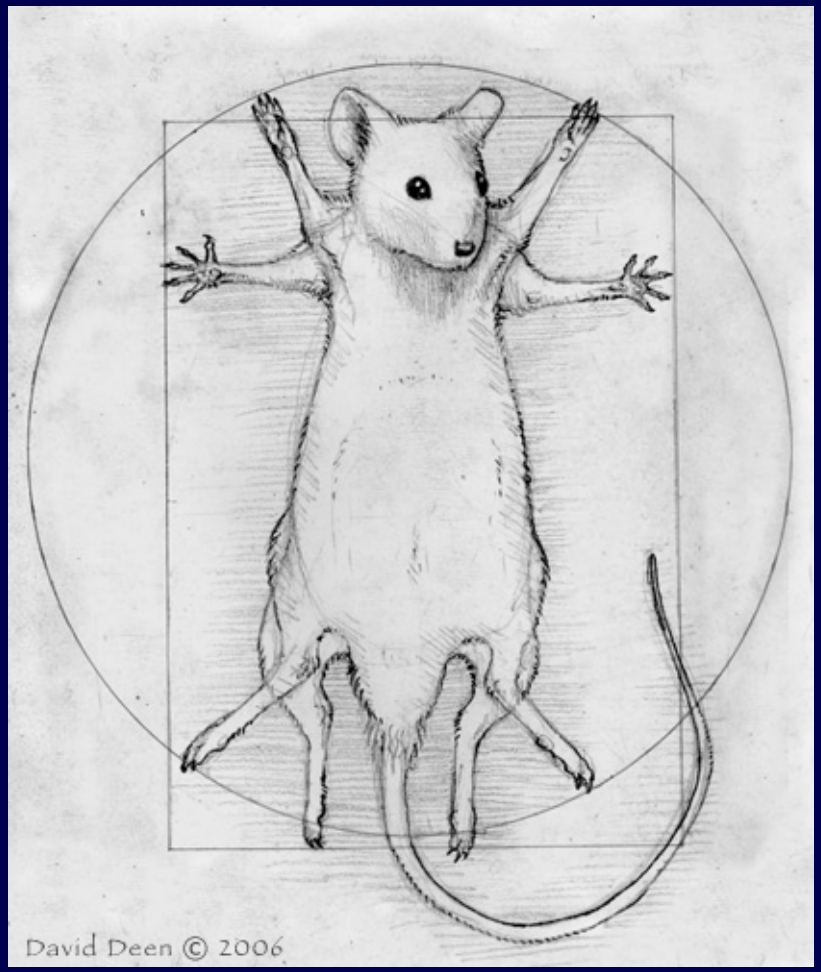
- Start with the trait; find genes that influence it
  - Allelic differences at the gene result in phenotypic differences
- Value: Need not know anything in advance
- Goal
  - Understand the disease etiology (pathways/mechanisms)
  - Prediction/prevention
  - Identify possible drug targets

Approaches

- Experimental crosses in model organisms
- Mutagenesis in model organisms
- Association analysis with inbred strains
- Linkage analysis in human pedigrees
  - A few large pedigrees
  - Many small families (e.g., sib pairs)
- Association analysis in human populations
  - Candidate genes vs. whole genome

Human vs mouse





www.daviddeen.com

Mutagenesis

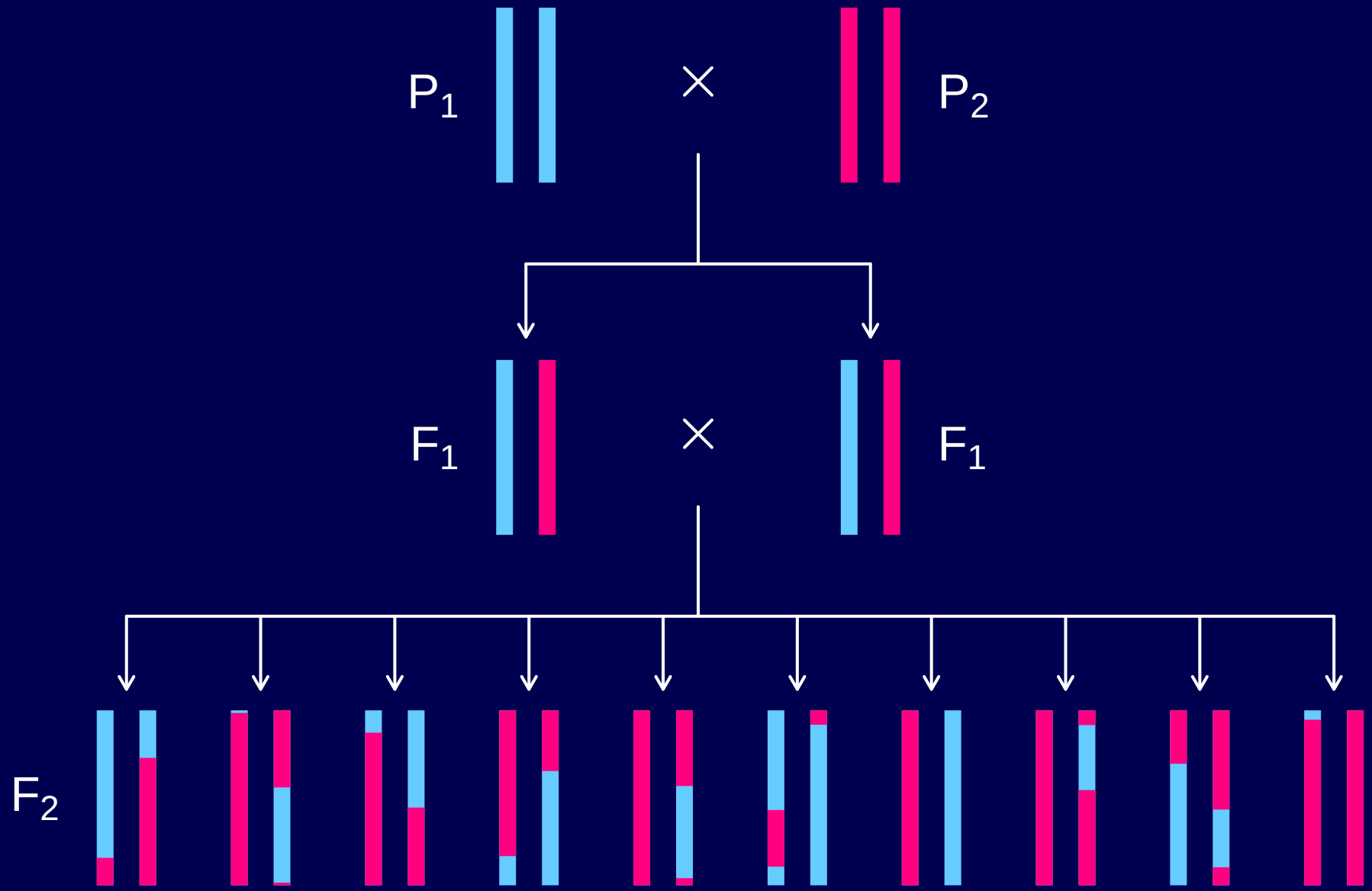
Advantages

+ Can find things
+ At the gene

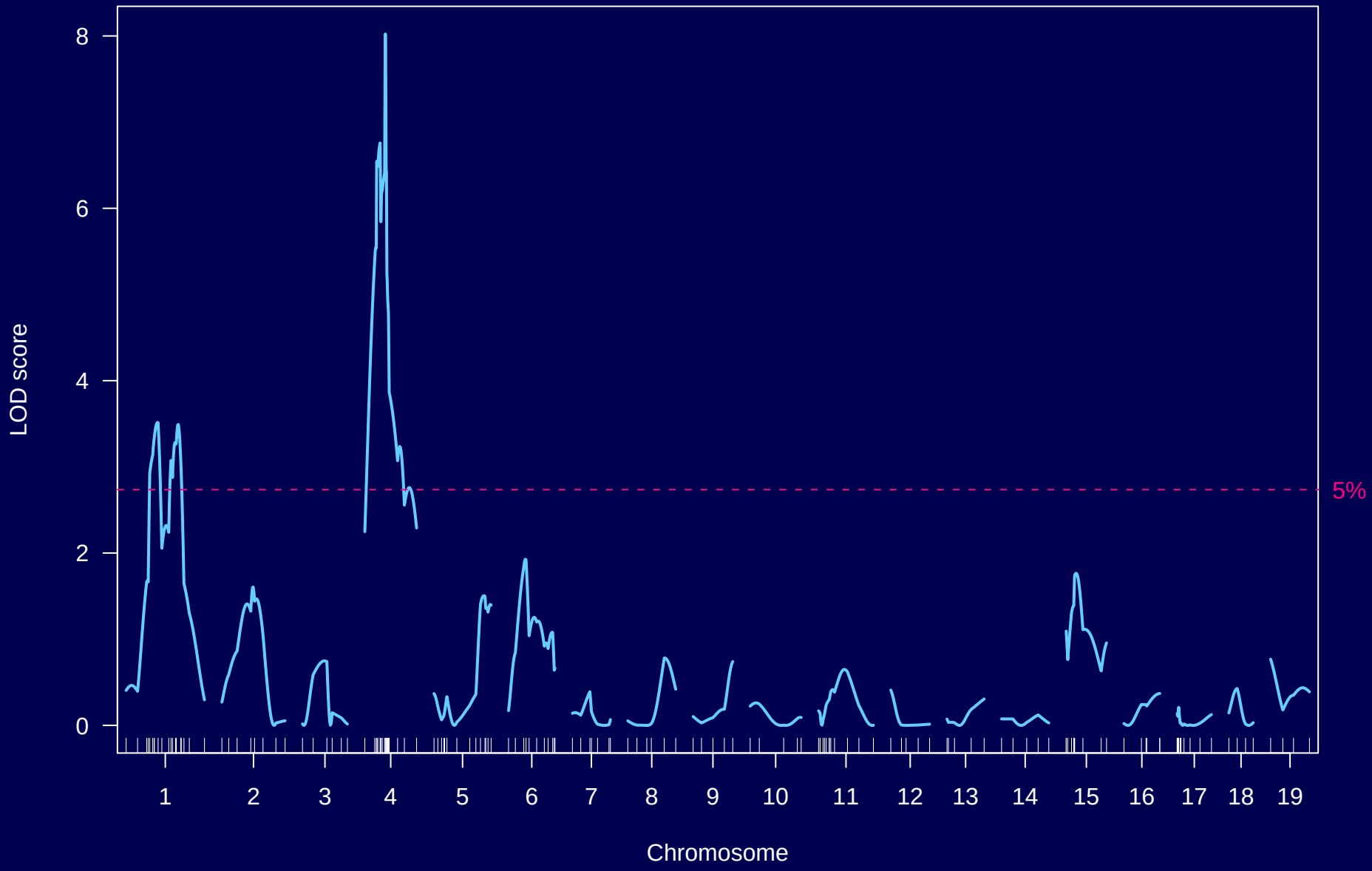
Disadvantages

– Need cheap phenotype screen
– Mutations must have large effect
– Genes found may be irrelevant
– Still need to map the mutation
– Recessive mutations are hard to see

Intercross



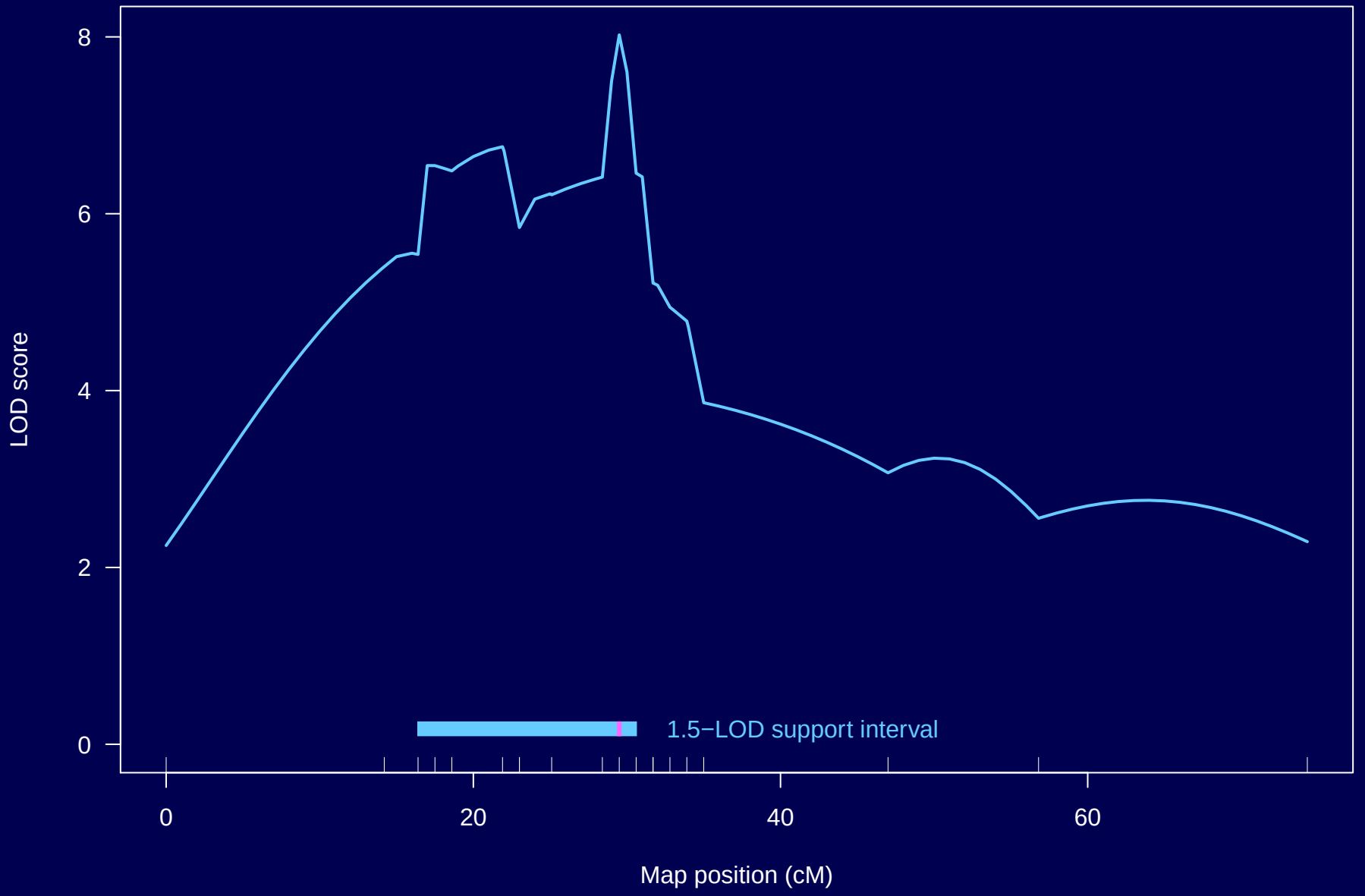
LOD curves


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

Joys of QTL mapping

- Genotype $\longrightarrow$ phenotype
- Recombination is cool
- Simple correlation structure
- Lots of opportunity for collaboration
- Lots of open problems
- Not many competitors

Chromosome 4



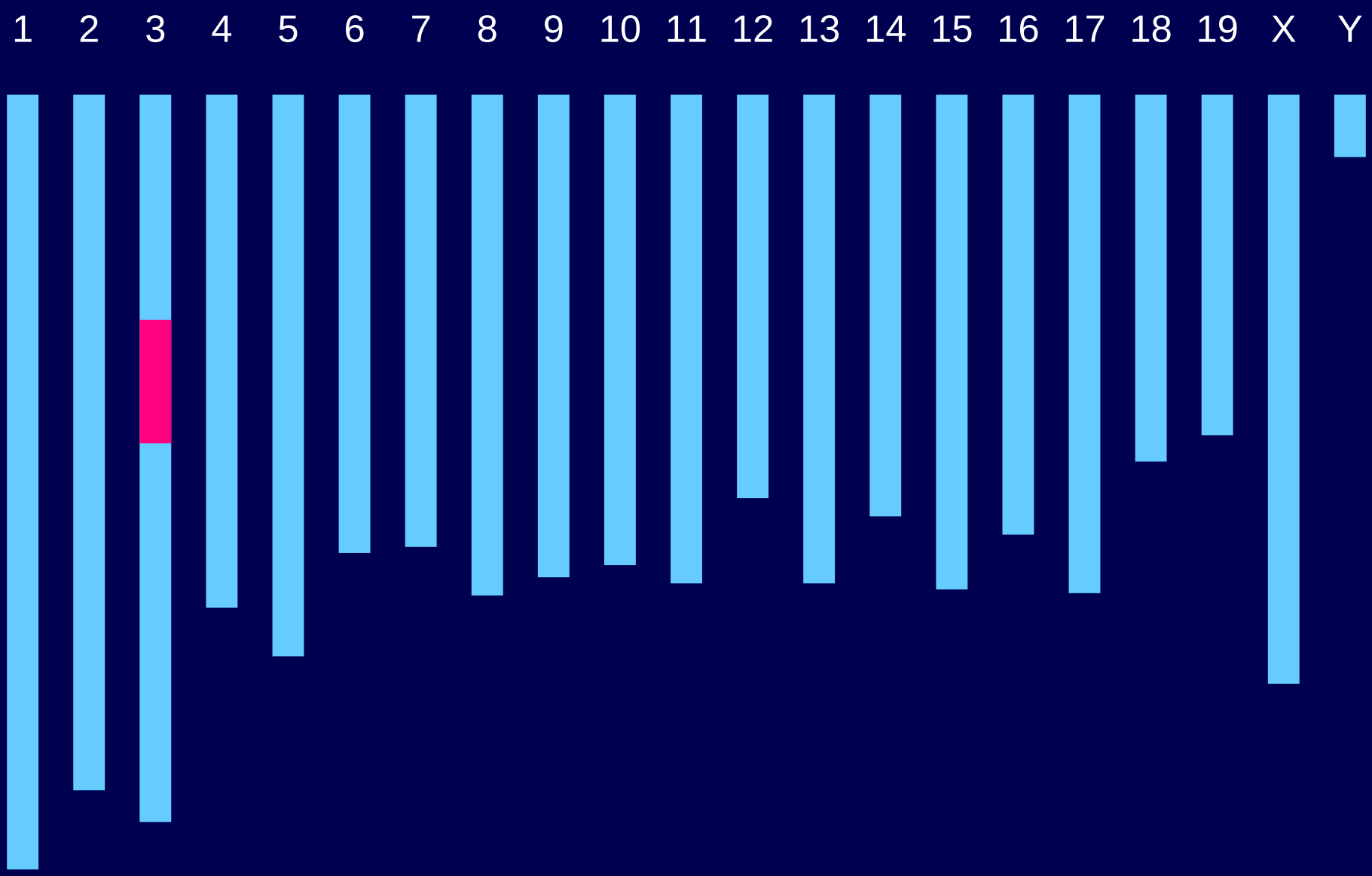
Traditional approach

F_2/BC $\longrightarrow$ QTL $\longrightarrow$ congenic $\longrightarrow$ subcongenics

$\longrightarrow$
- coding/regulatory polymorphism
- expression/function difference
- knock-in / transgenic
- knock-out
- homology to other species

Issues:
- Large QTL regions
- Time consuming and expensive

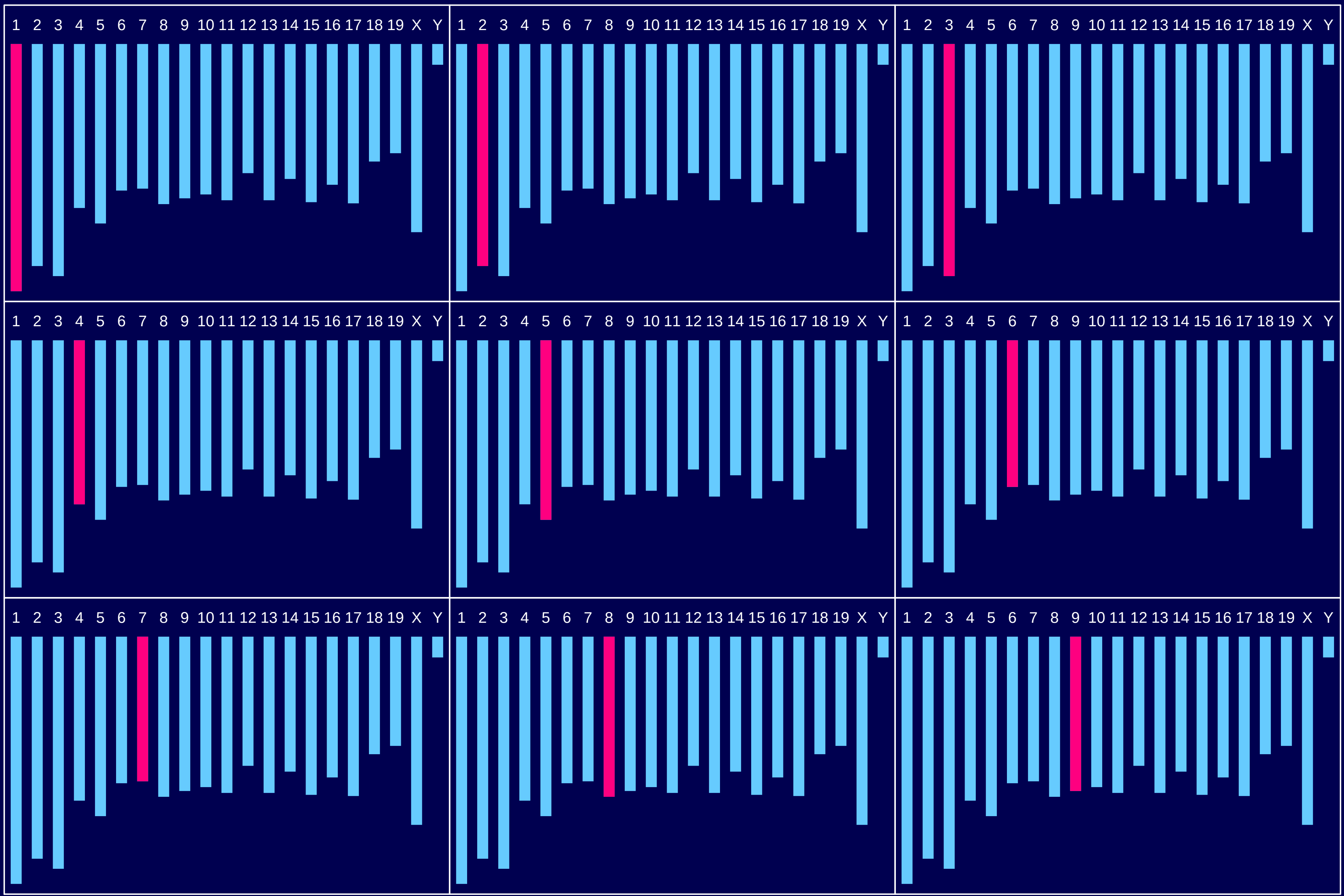
A congenic line



More modern approaches

- Gene expression data
  - and proteins, metabolites, epigenetic marks
  - and eQTL analyses
- Consomics (aka chromosome substitution strains)
- Panels of congenics
- Multiple crosses + haplotype analysis
- Cross-species comparisons
- Advanced intercross lines / Heterogenous Stock
- Recombinant inbred lines / Collaborative Cross
- Association mapping with inbred lines

Consomics



Consomics

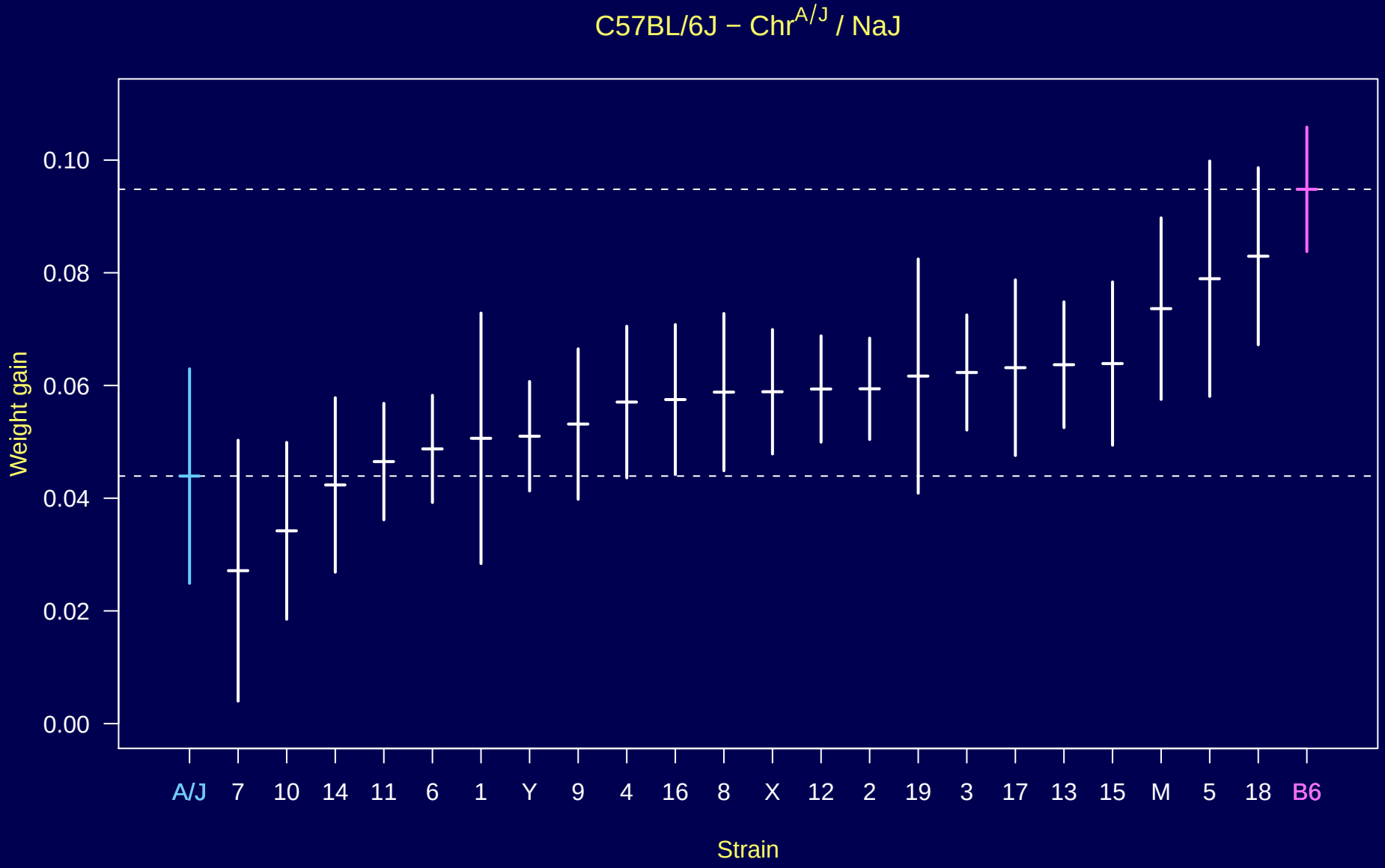
Advantages

+ Just phenotyping can get you to the chromosomes
+ Eliminate the effects of other QTL
+ Easy to create congenics

Disadvantages

– Time-consuming, expensive to create
– Lots of phenotyping required
– Cannot see interactions

B.A on low fat diet



Shao et al., PNAS, 105:19910–19914, 2008

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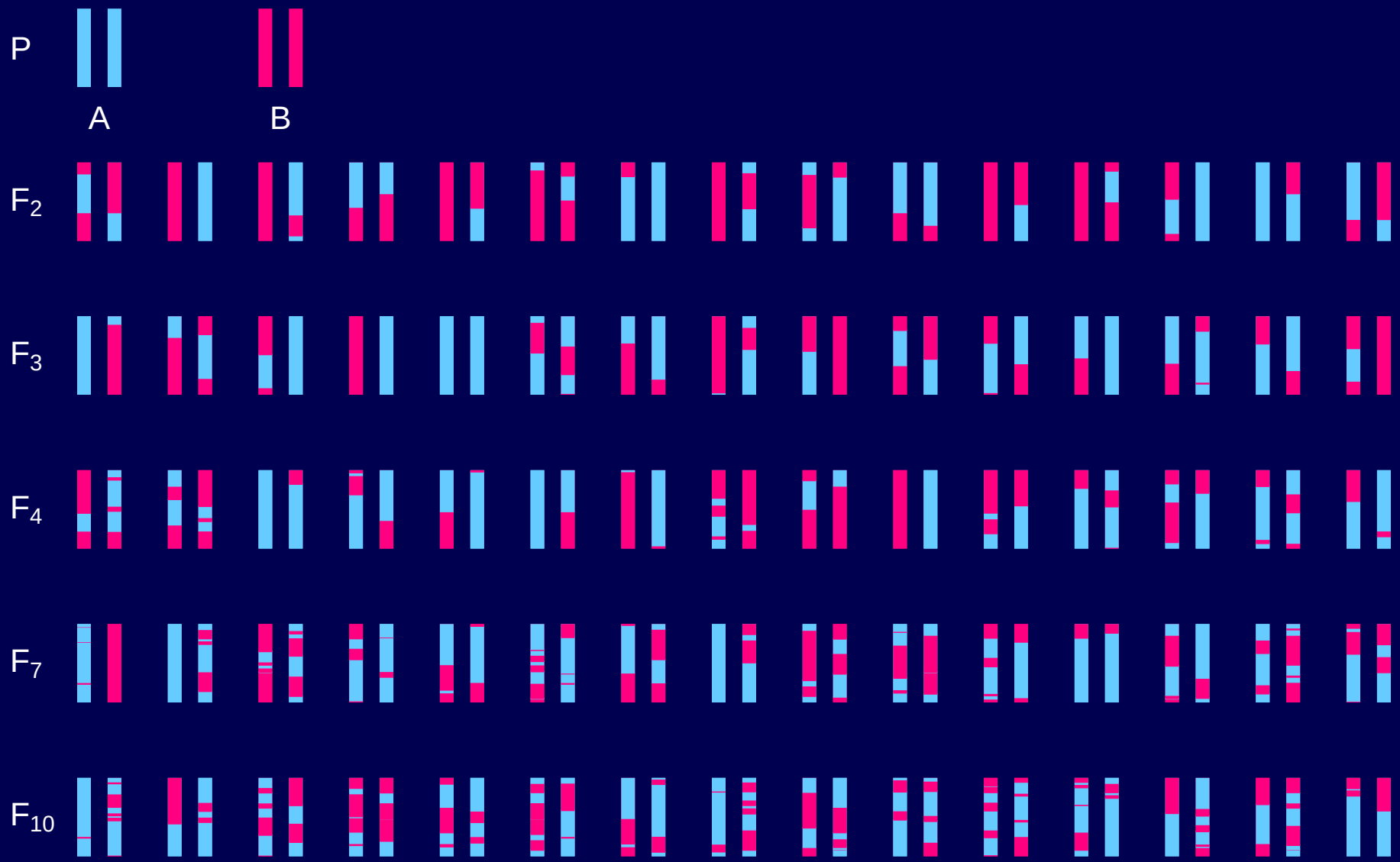
Advanced intercross lines



AIL

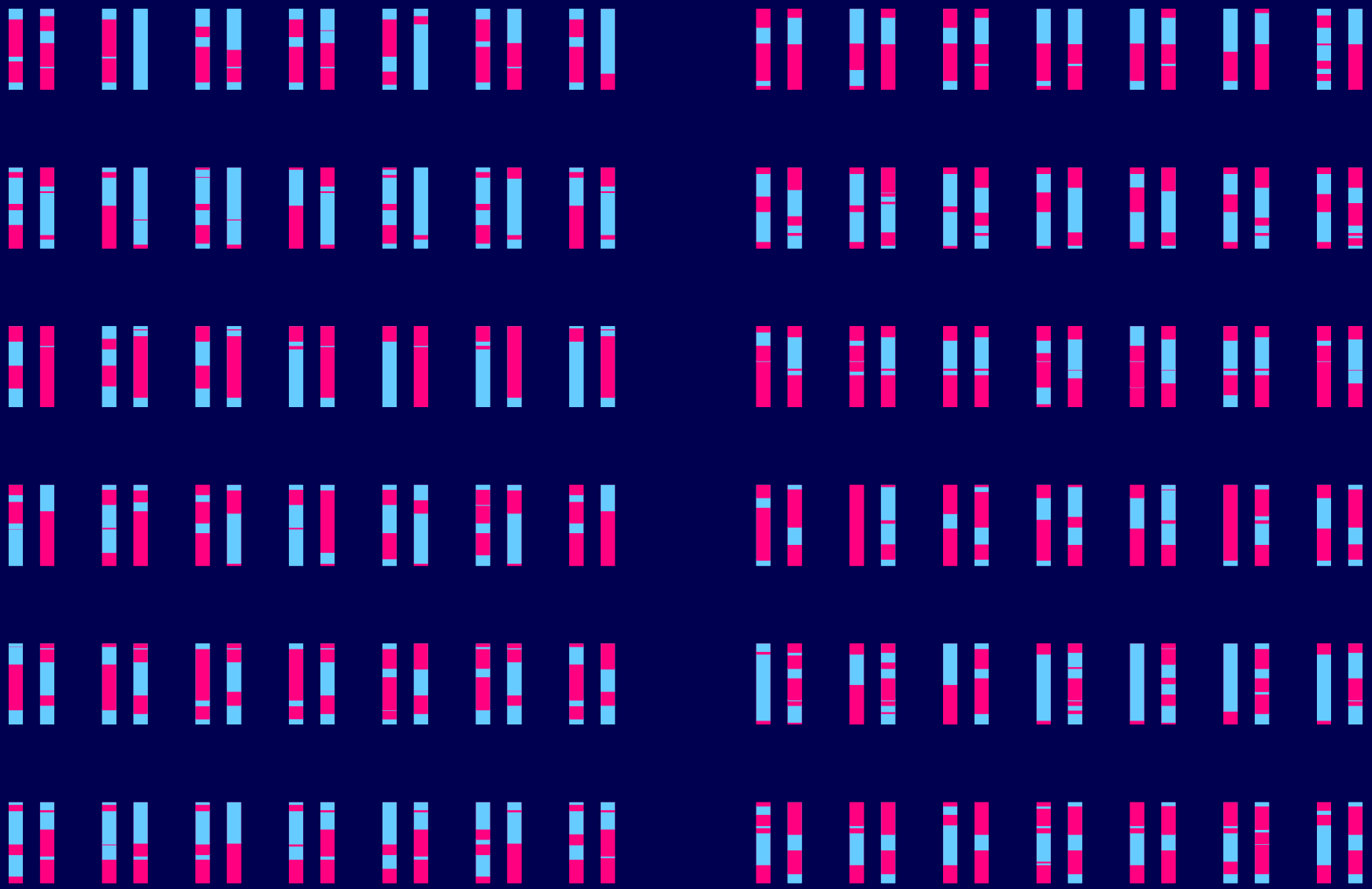
Advantages

+ Many more breakpoints $\Longrightarrow$ more precise mapping
+ Straightforward to create

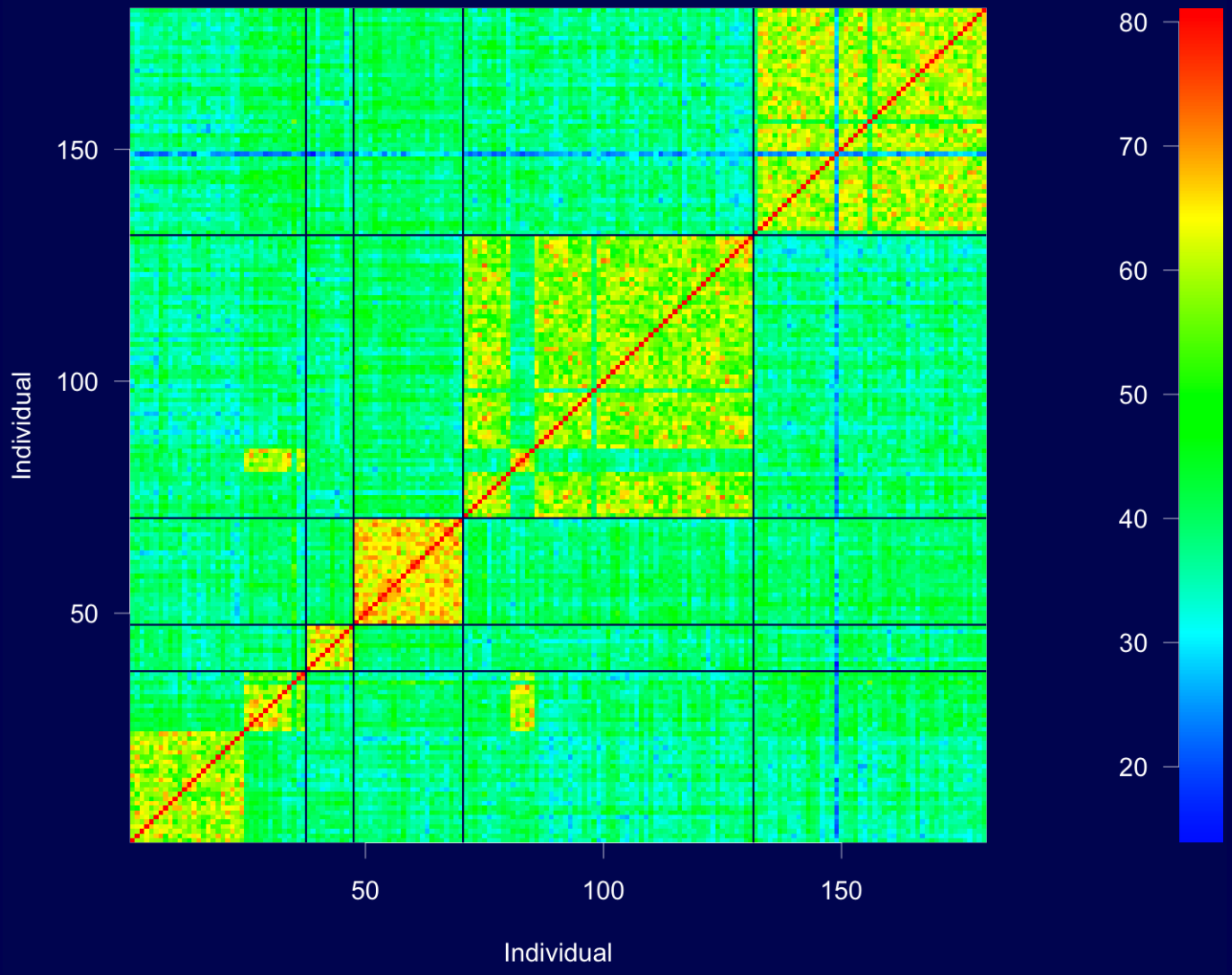
Disadvantages

– Time and cost
– Each individual genetically distinct
– Useful largely for fine-mapping known loci
– Relationships among individuals in final generation

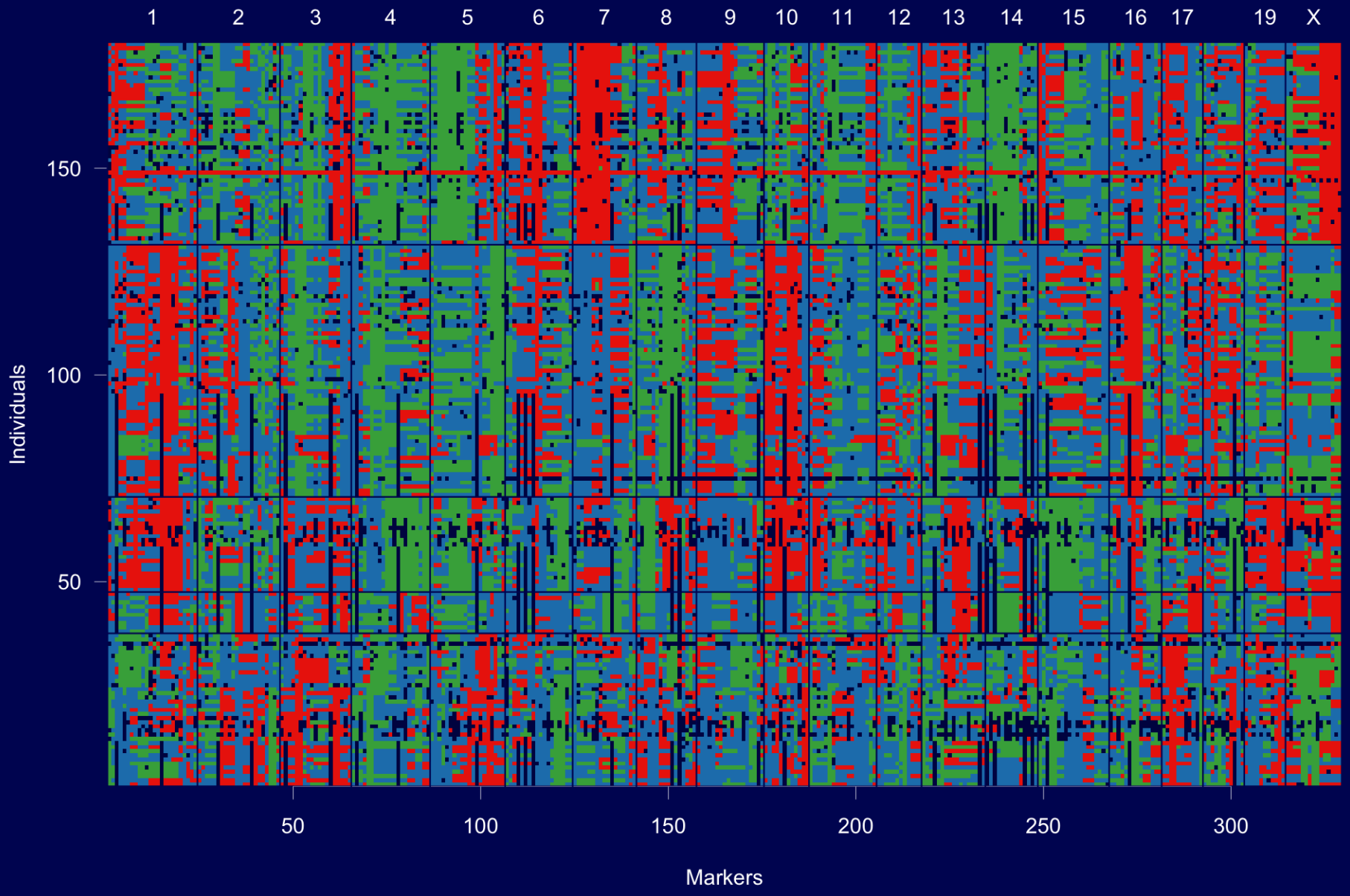
Sibships at F_8



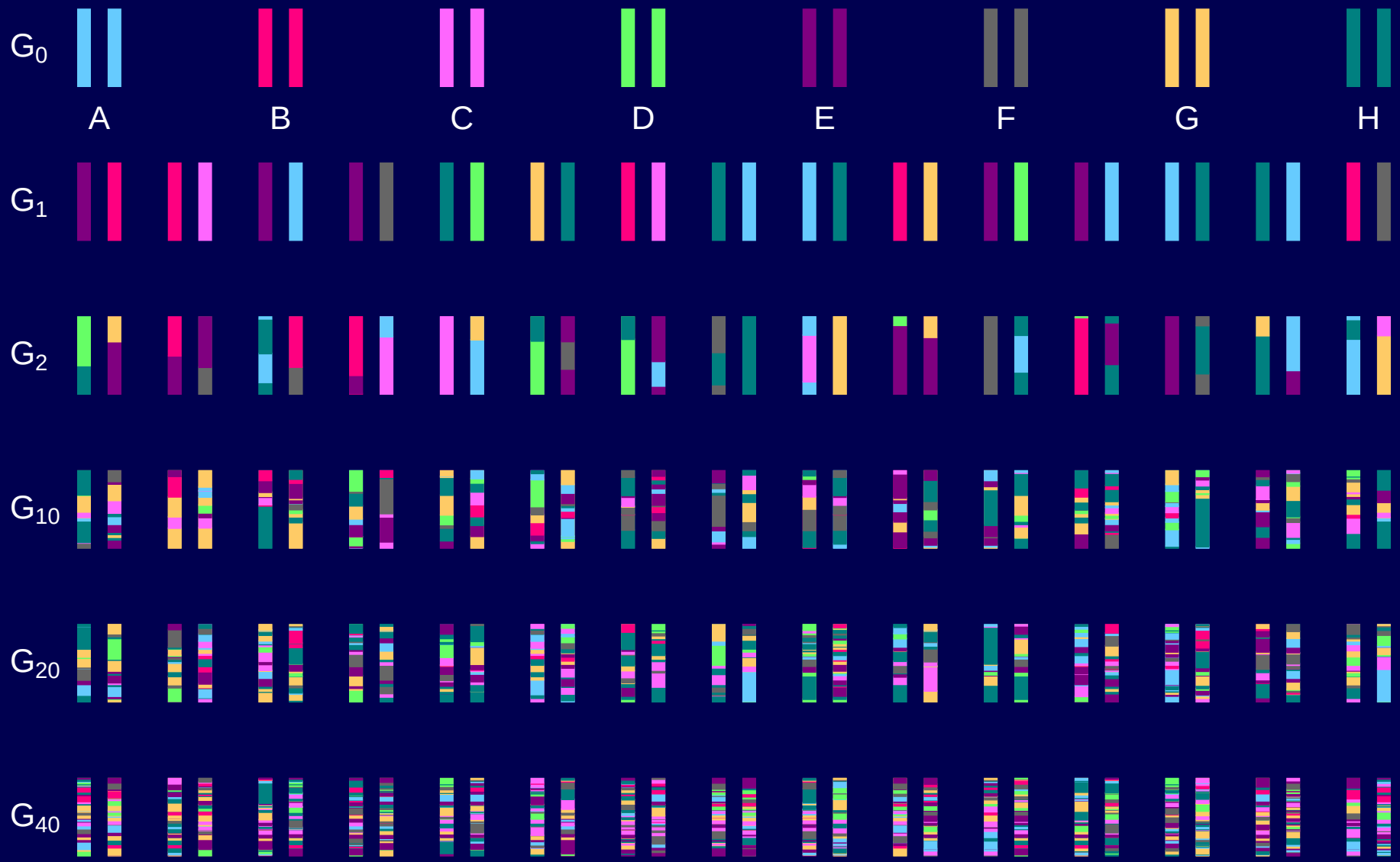
AIL: percent matching genotypes



AIL: genotype data



Heterogeneous stock



HS

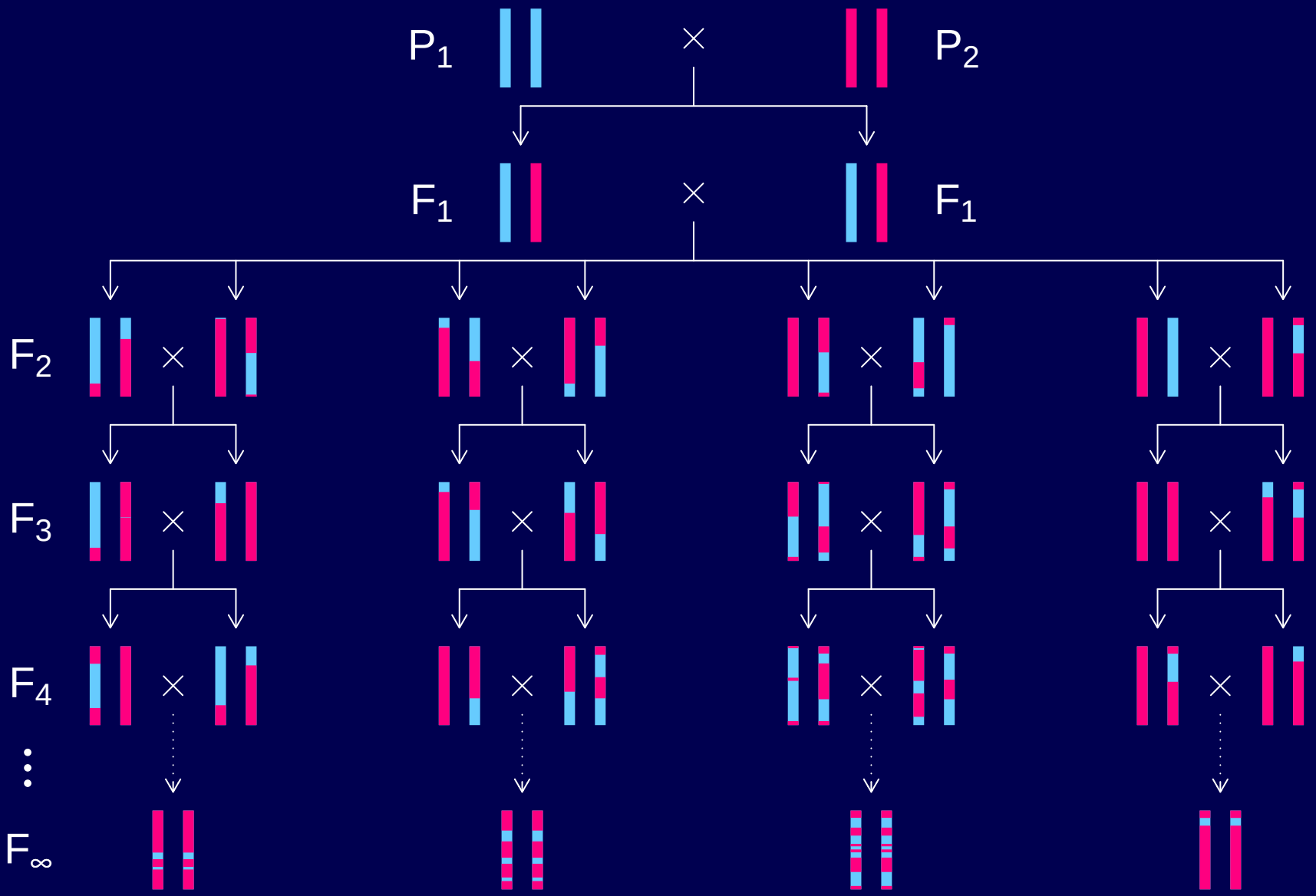
Advantages

+ Super-dense breakpoints
+ Many alleles
+ Heterozygous

Disadvantages

– Must be satisfied with what is available
– Inbreeding: loss of alleles
– Each individual unique
– Like AIL, maybe best for fine-mapping known loci
– Like AIL, relationships at last generations

Recombinant inbred lines



RIL

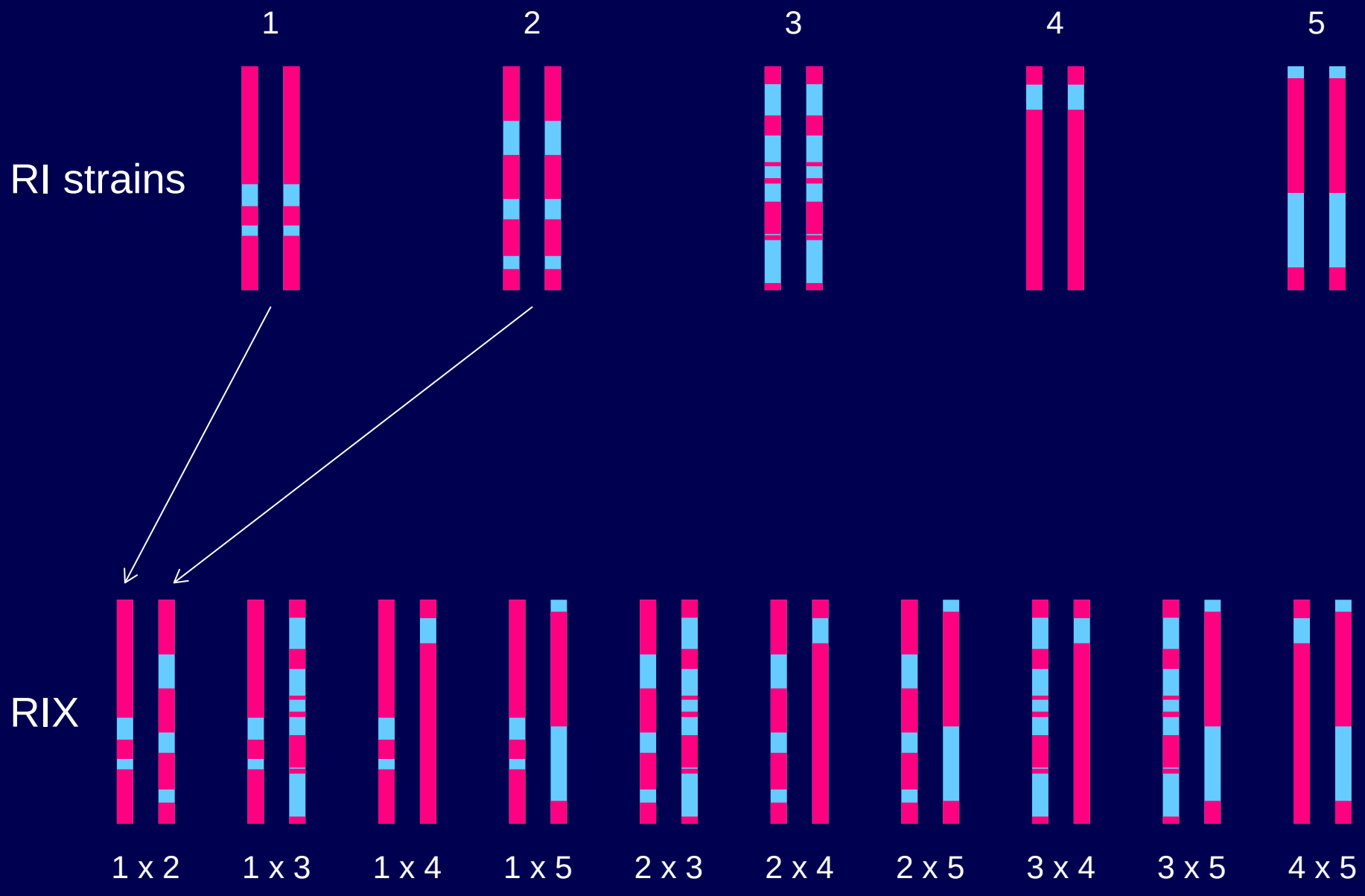
Advantages

+ High density of breakpoints
+ Just genotype once
+ Phenotype multiple individuals to reduce environmental/individual variation
+ Multiple phenotypes on the same genomes
+ Longitudinal phenotypes
+ Genotype $\times$ environment interactions

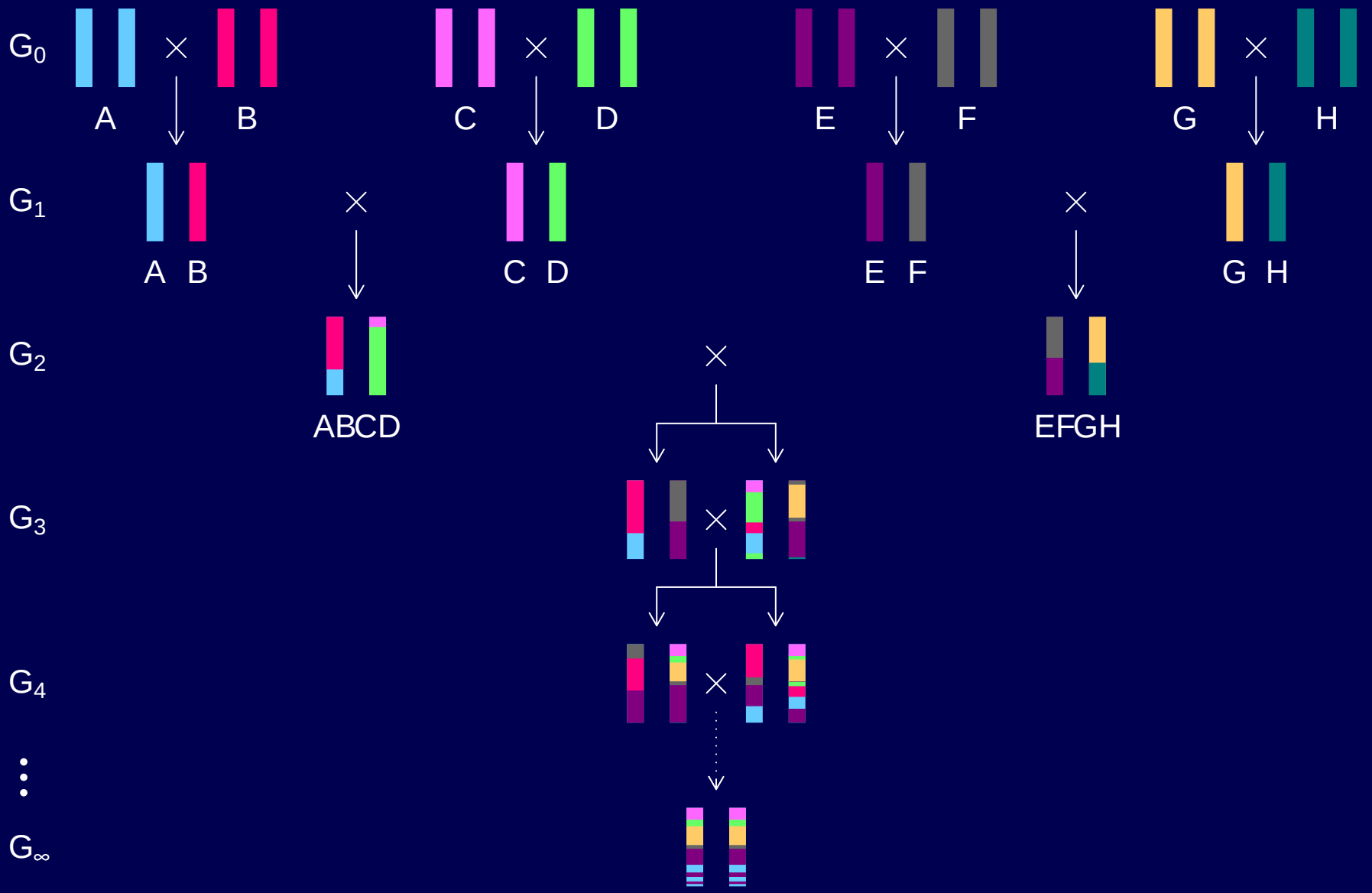
Disadvantages

– Time-consuming, expensive to create
– Available panels generally too small
– Only homozygotes

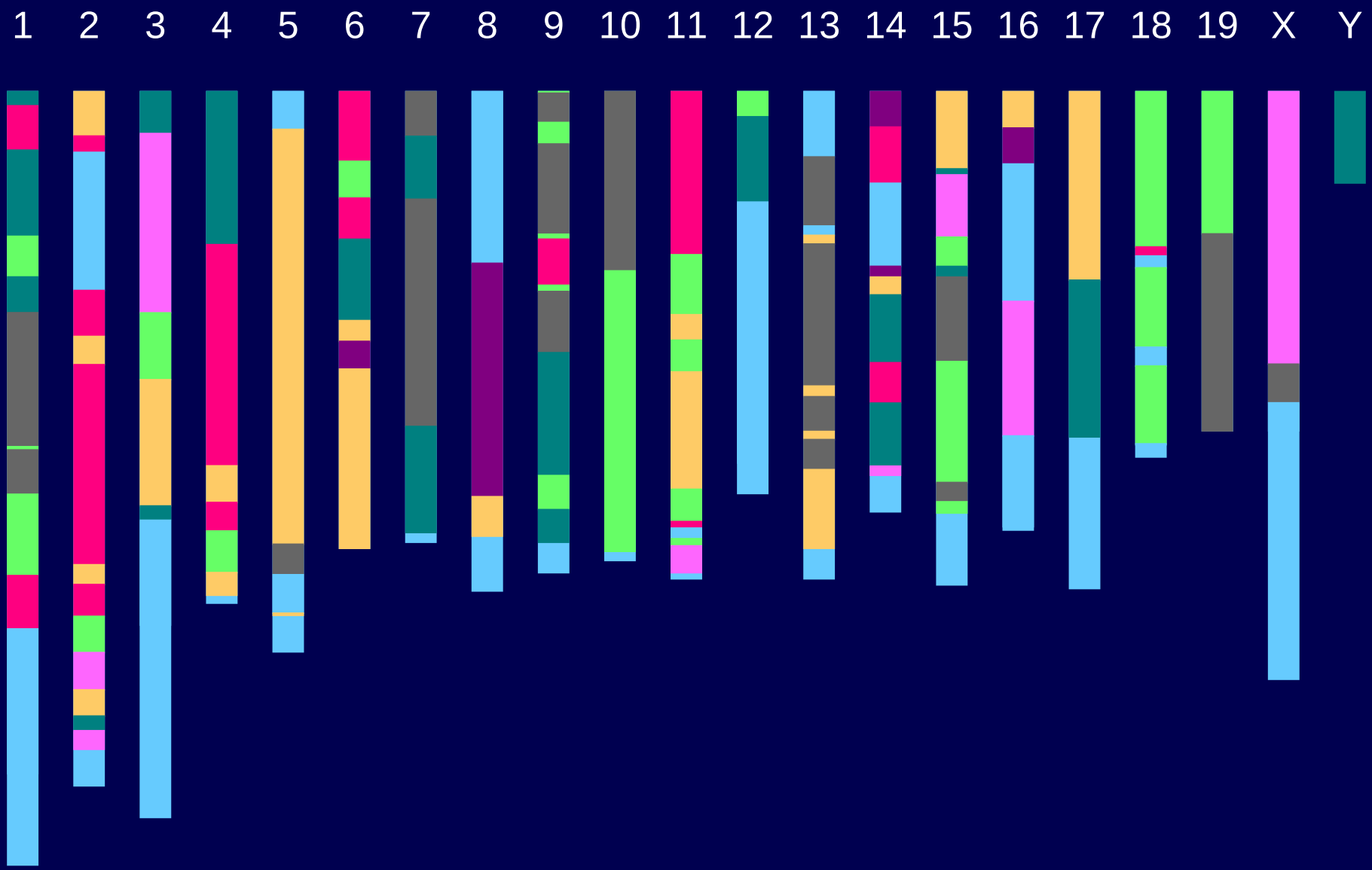
RIX



Collaborative Cross



A CC genome



Association mapping

- Phenotype available inbred strains
- Make use of available SNP data

- Need to account for the correlations among strains
- Likely want to work with haplotypes rather than just individual SNPs
- Be careful about wild-derived strains

Association mapping

Advantages

+ Once you've done a strain survey, no further data needed
+ Potentially very high resolution

Disadvantages

– All the usual problems with association mapping
– Power is unpredictable
– How to account for relationships among strains?

CC vs HS vs association mapping

These approaches have many similarites.

Key differences:

- CC, HS: pattern of association along chromosomes by design
- HS: each individual unique

Summary

- QTL mapping in mice is fun and useful
- But we need to be able to get to gene
- There are lots of new strategies to speed things along
- Numerous interesting statistical problems remain
- Need to consider human GWAS