Rat Heterogeneous Stock: Can we identify the genetic variants responsible for phenotypic variation?

Rat Genome Sequencing and Mapping Consortium

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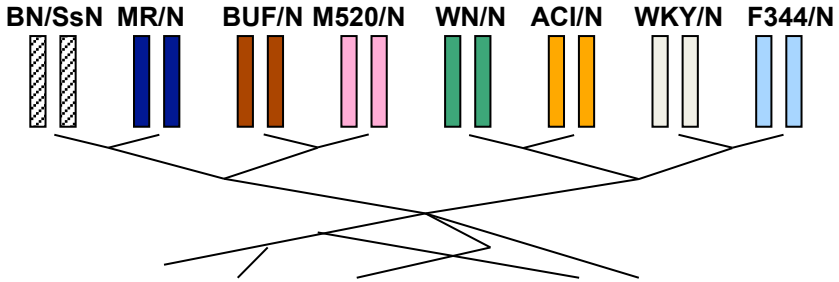
University of Oxford

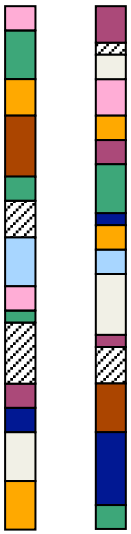
NIH Heterogeneous Stock rats

The rat Heterogeneous Stock



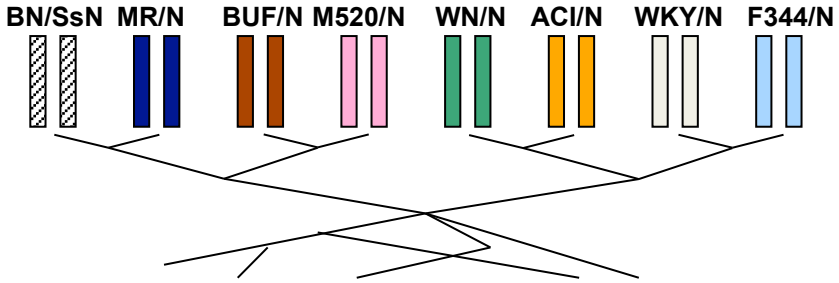
8 inbred founders

Rotational breeding
for 60 generations

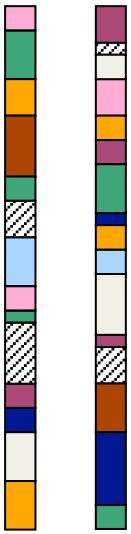


1407 Heterogeneous Stock rats

The rat Heterogeneous Stock



Rotational breeding
for 50 generations



8 inbred founders

- genotyped (850K SNPs)
- sequenced (SOLID)

  Cuppen lab, Hubrecht Inst., Utrecht

1407 Heterogeneous Stock rats

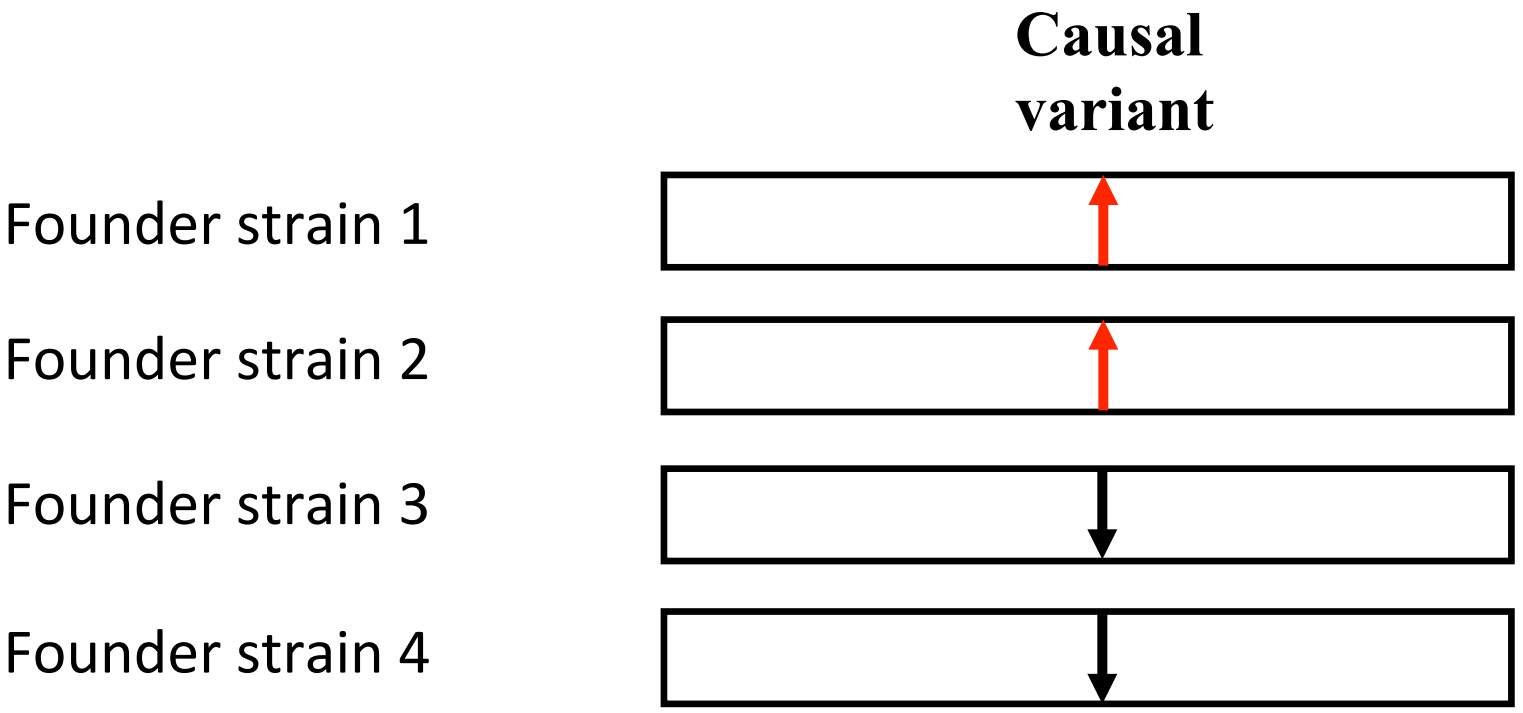
- genotyped (850K SNPs)

  Hübner lab, MDC Berlin, and CNG Evry
- phenotyped (163 measures)

Extensive phenotyping

Phenotype	Number of measures	Week	Responsible laboratory
Healing	1	7 and 17	Oxford (Flint)
Anxiety	15	8 to 10	Barcelona (Fernandez Teruel) and Oxford (Flint)
Glucose tolerance	6	11	Oxford (Gauguier)
Cardiovascular function	2	12	Glasgow (Dominiczak)
Basal hematology	31	13	Oxford (Flint)
Basal immunology	36	13	Stockholm (Holmdahl)
Induced neuroinflammation	12	13 to 17	Stockholm (Olsson)
Bone morphology	40	17	Indiannapolis (Foroud)
Spontaneous vascular lesions	6	17	Berlin (Hübner)
Blood biochemistry	14	17	Oxford (Flint)

Single-point mapping



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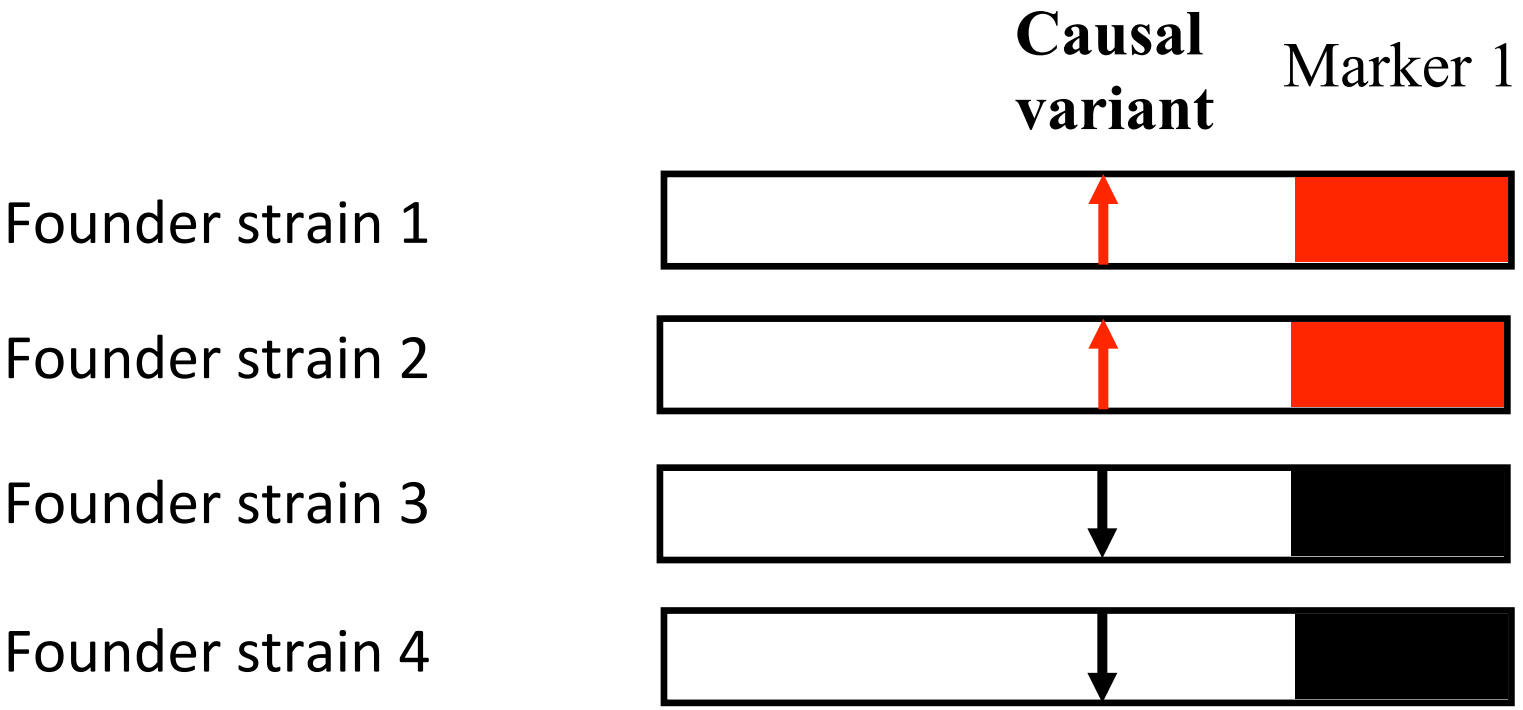

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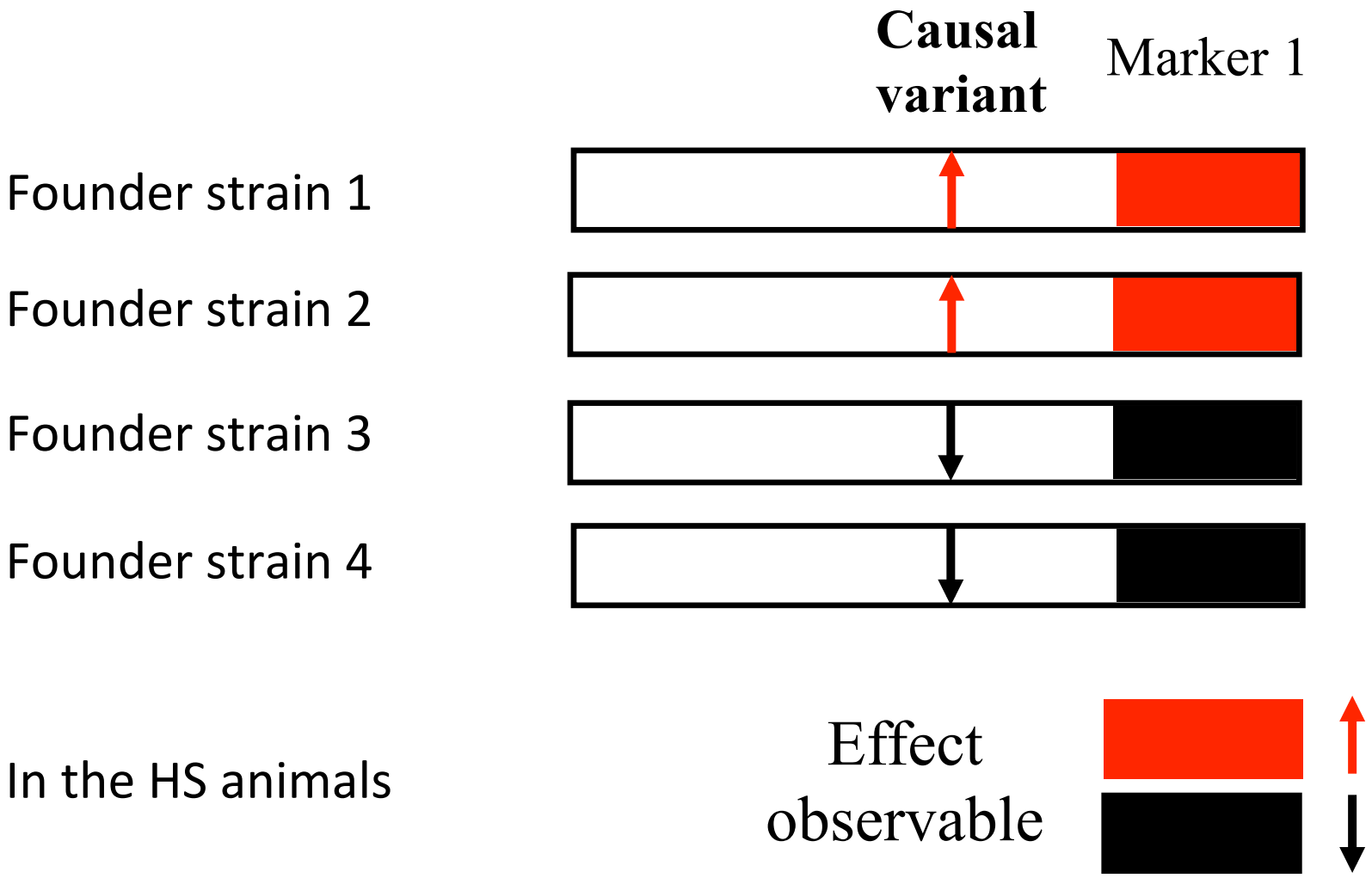

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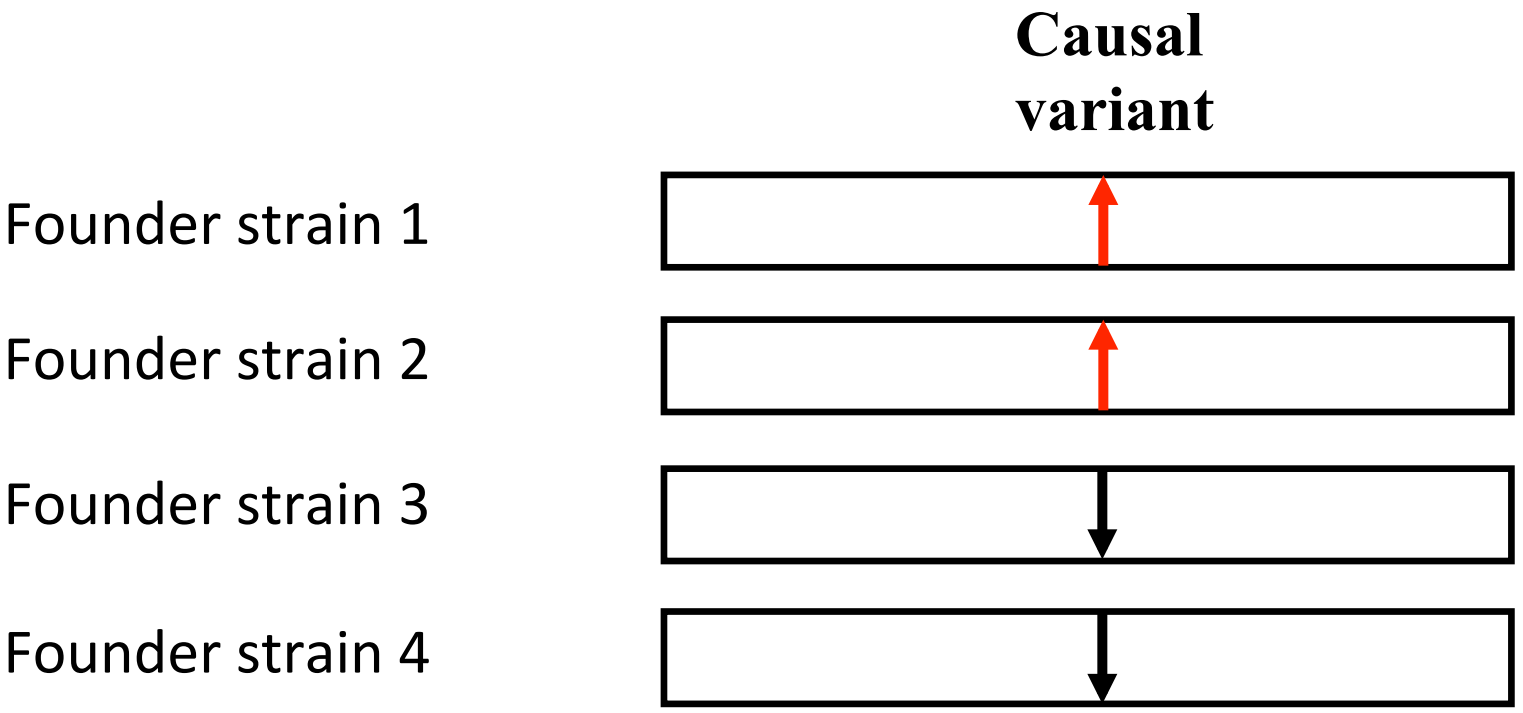

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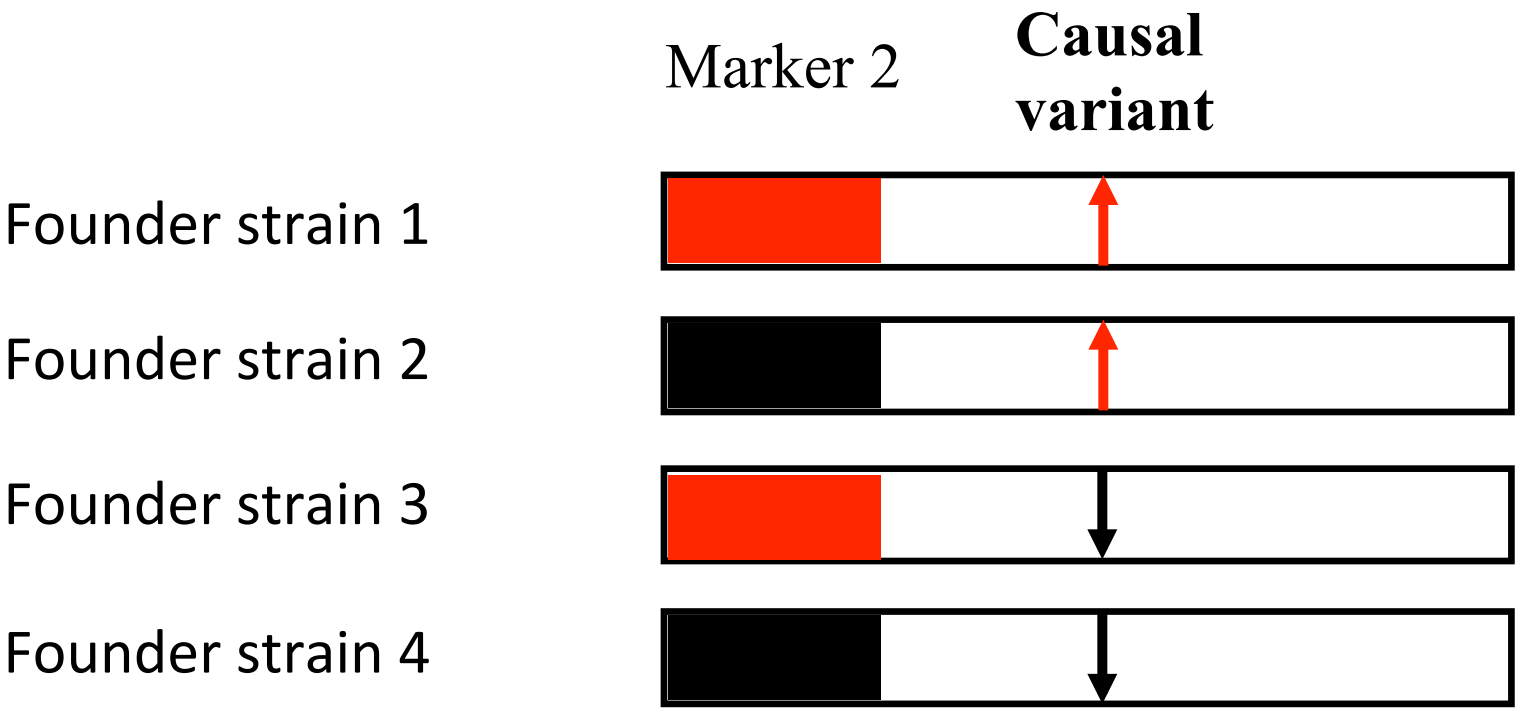

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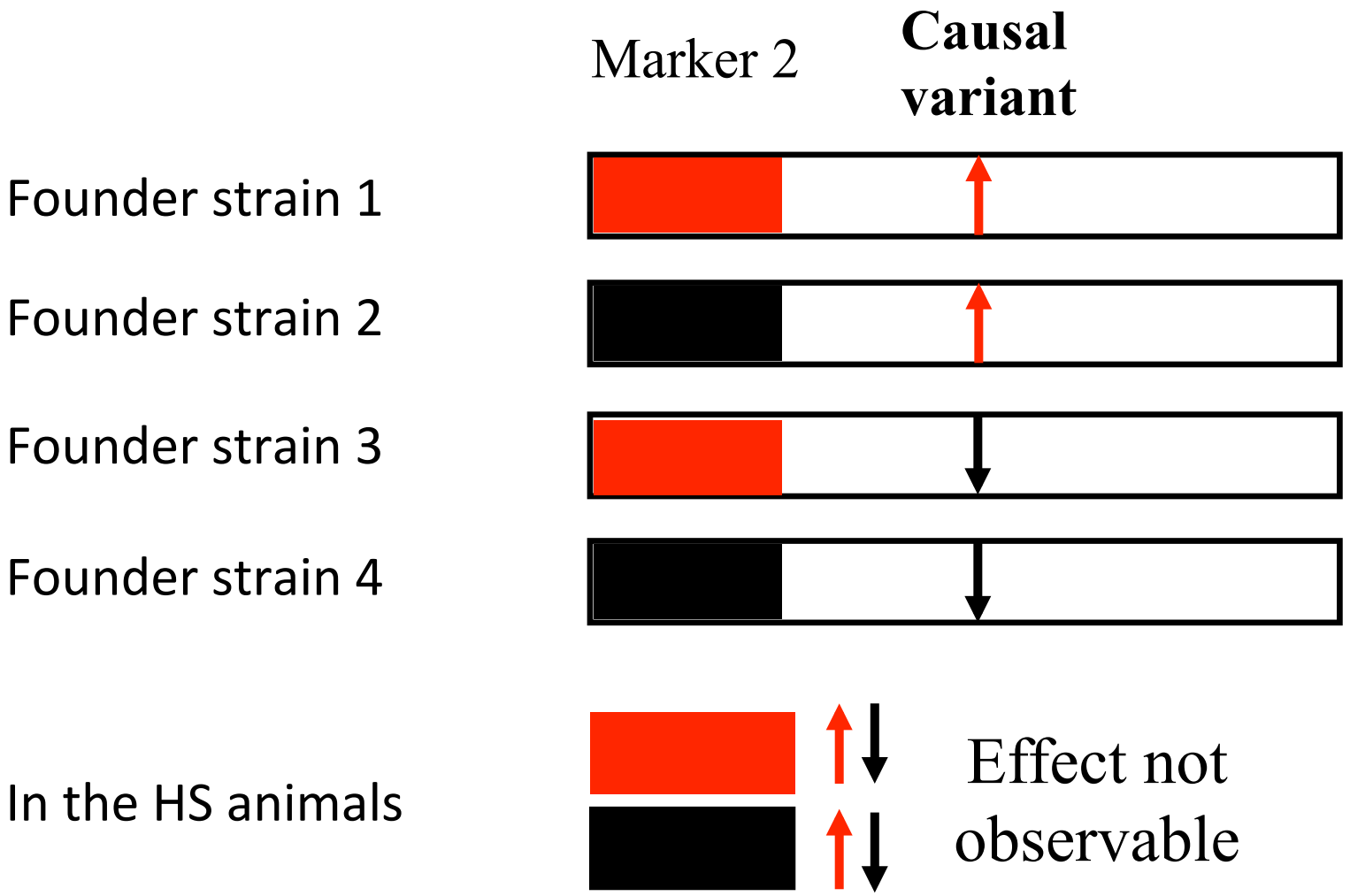
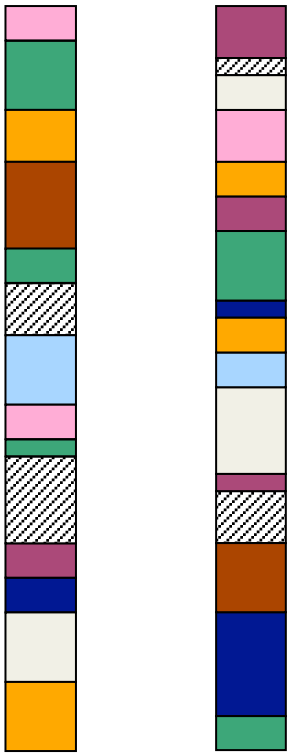


Ancestral haplotype reconstruction

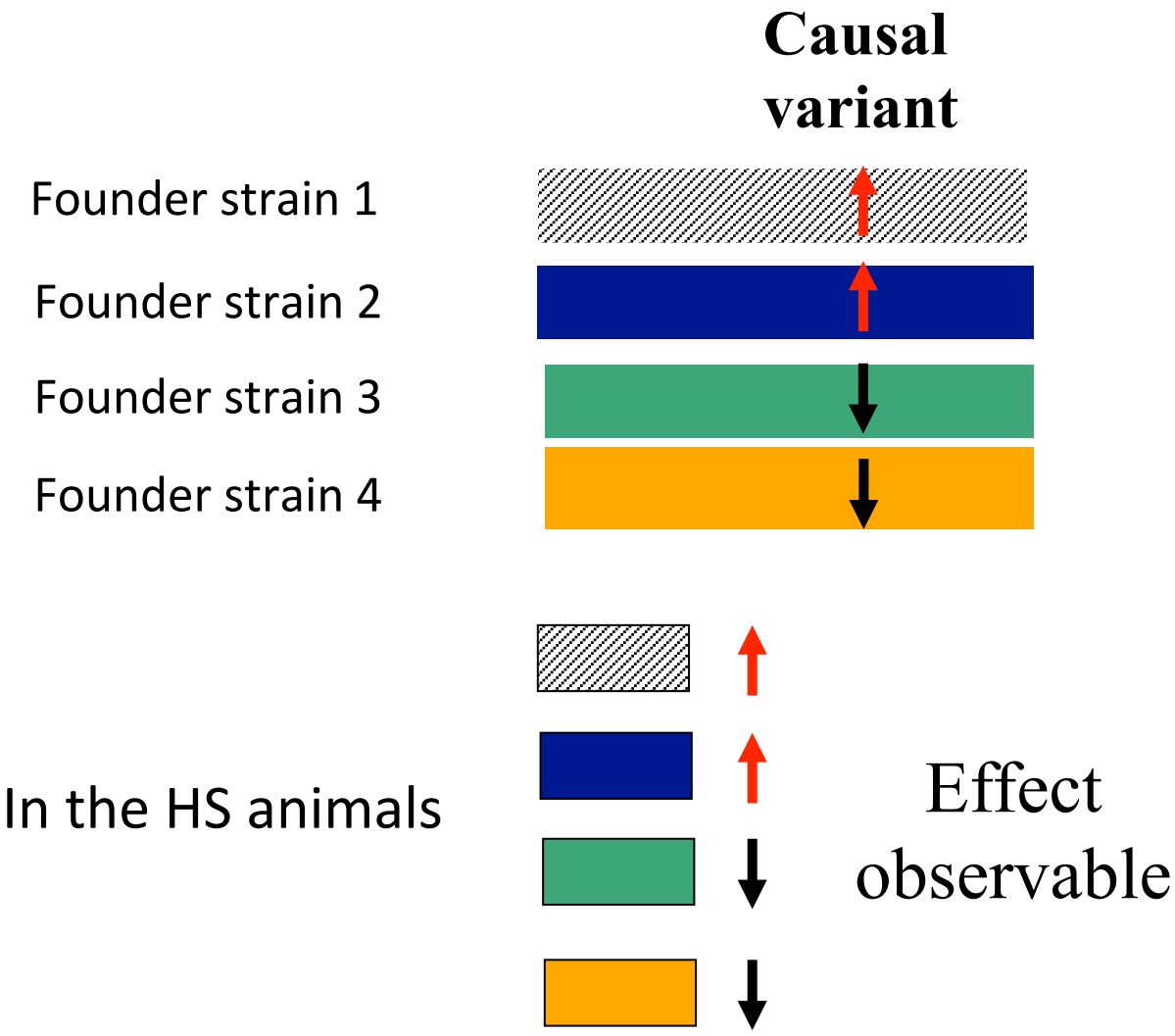
Founder strains:

- BN/SsN
- MR/N
- BUF/N
- M520/N
- WN/N
- ACI/N
- WKY/N
- F344/N

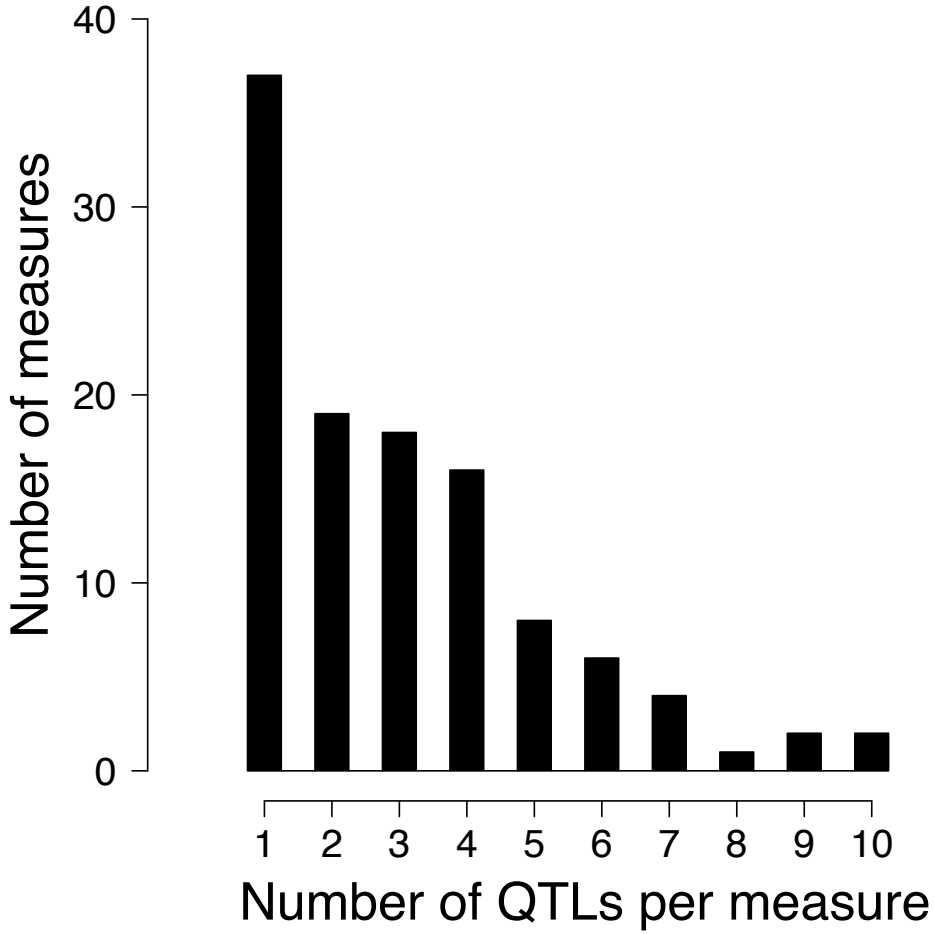


Pair of HS rat chromosomes

Haplotype mapping

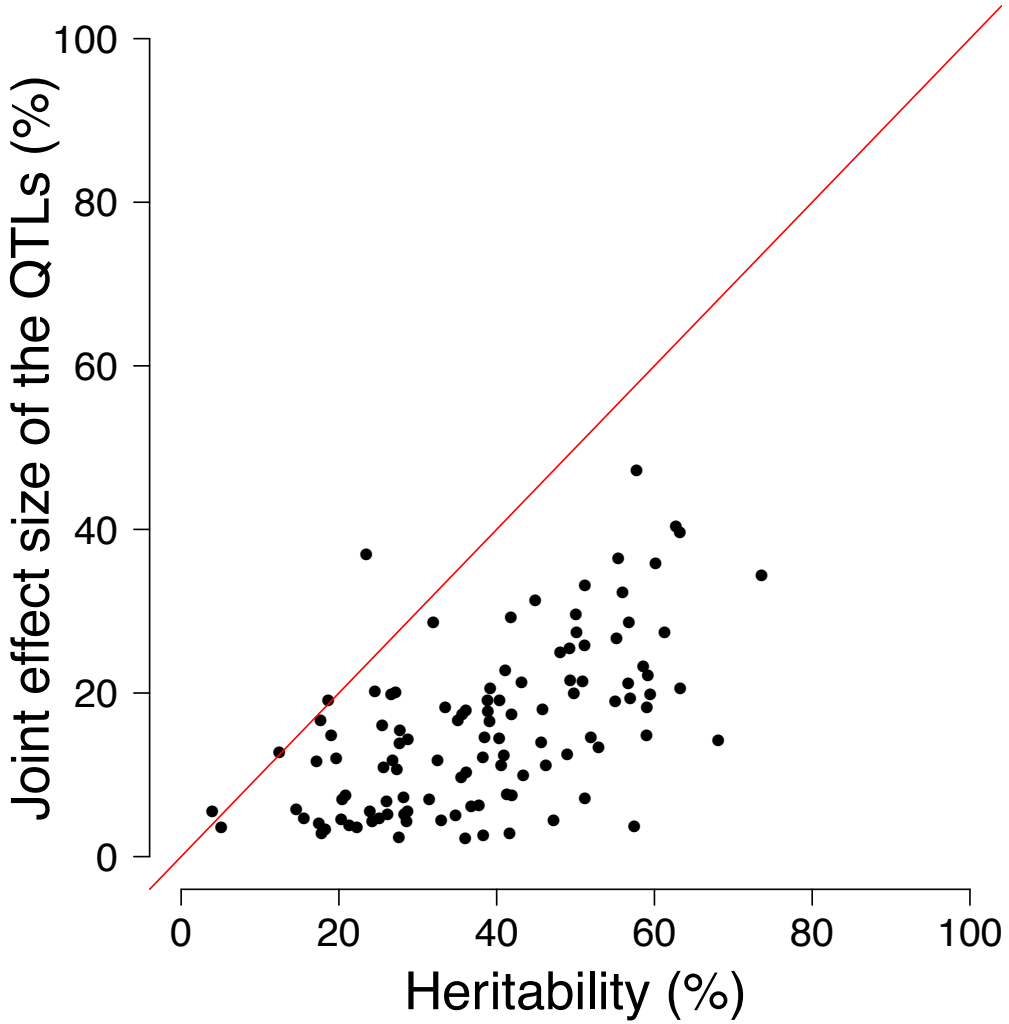


Large number of QTLs detected



352 QTLs detected in total (FDR 10%)

Large proportion of the heritable phenotypic variation explained by the QTLs



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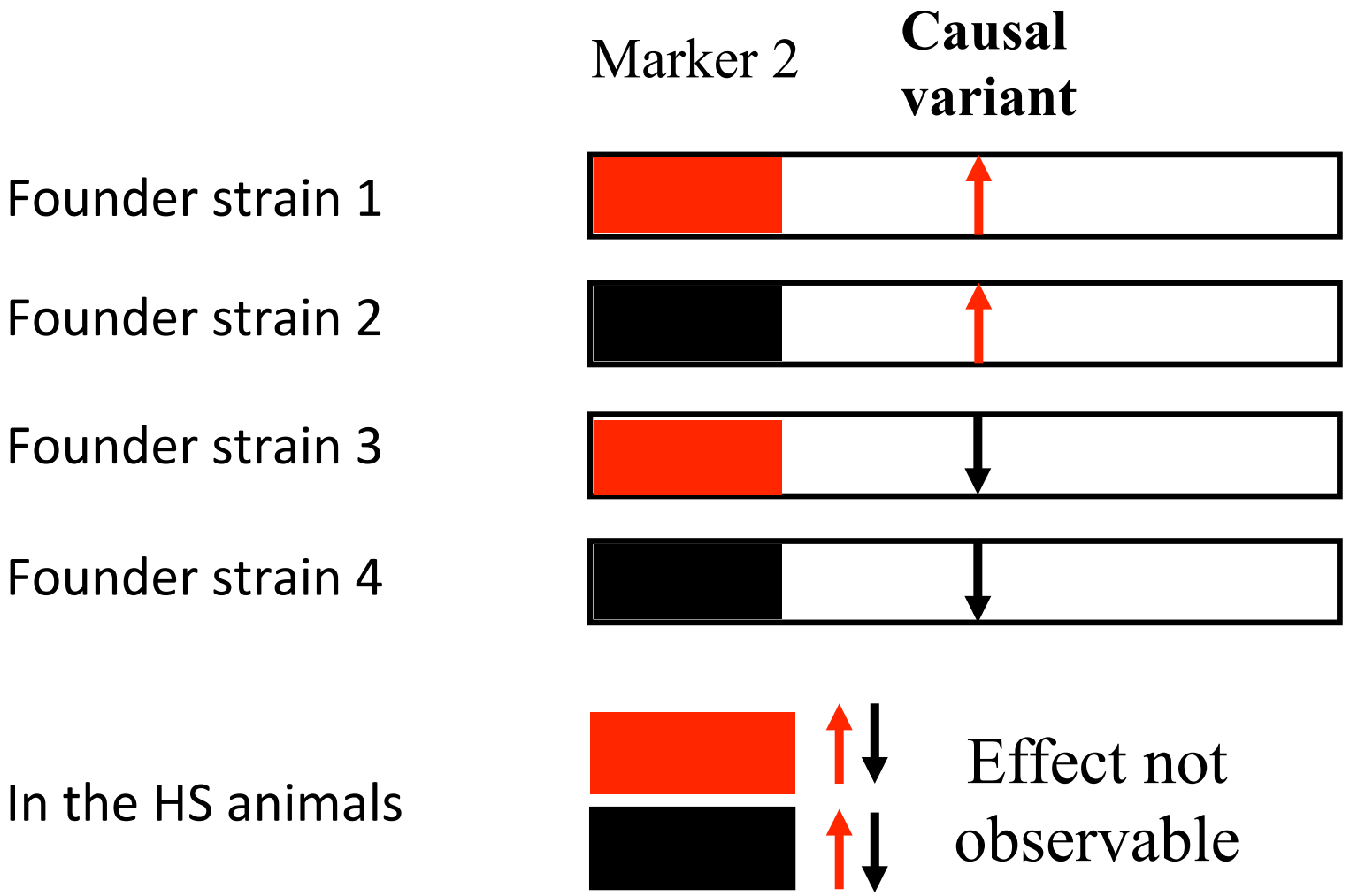

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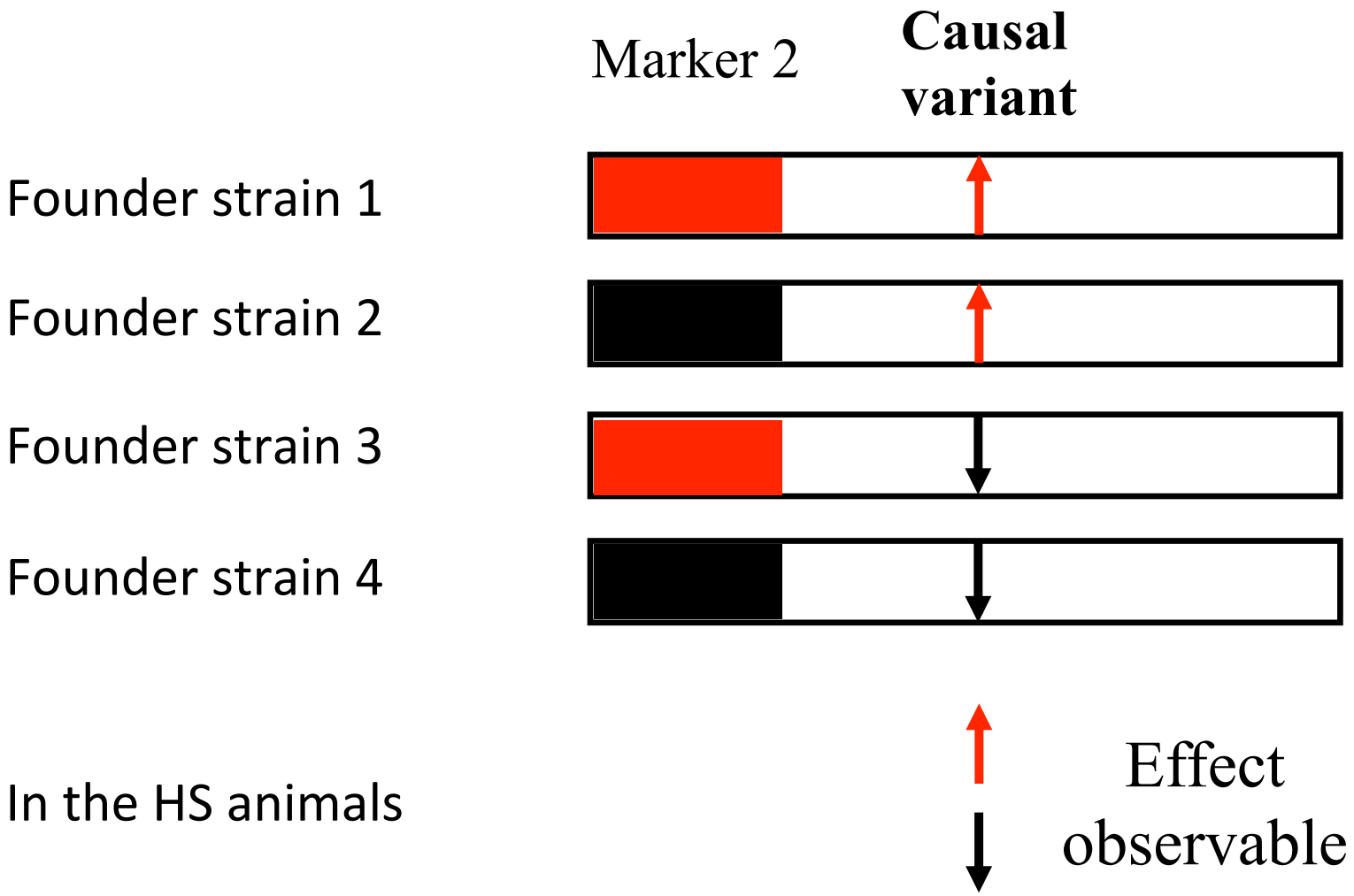
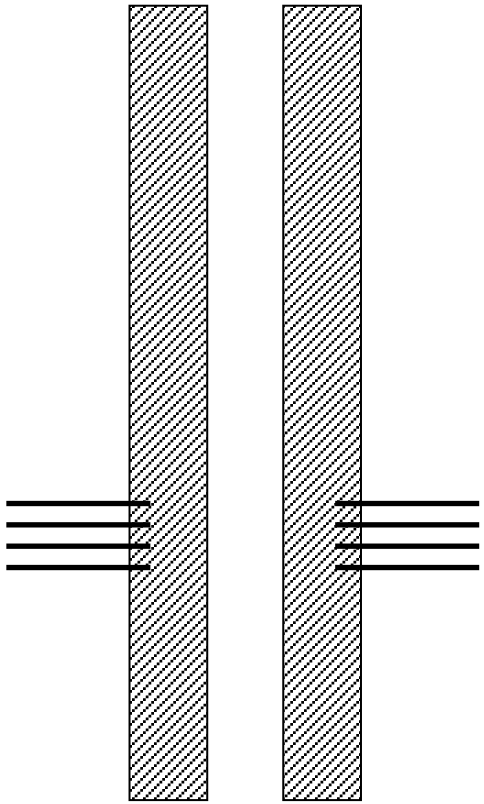
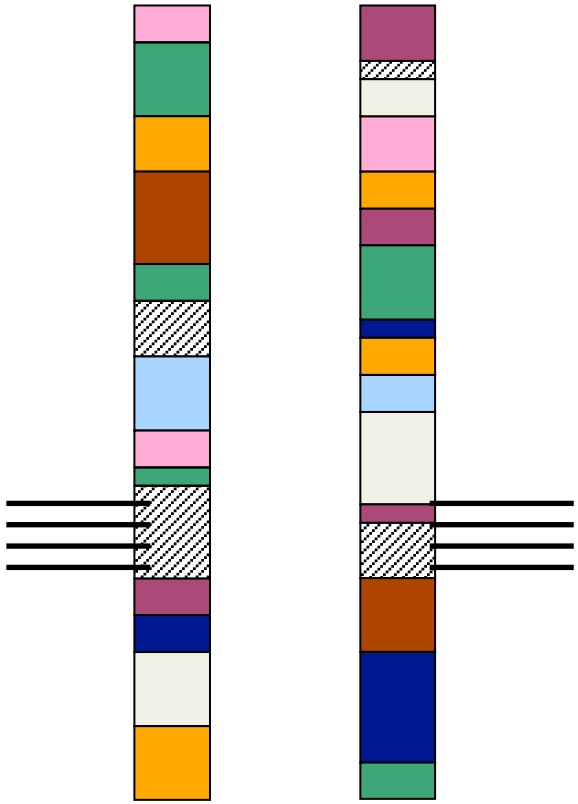


Imputation in the HS

—— genotyped SNP



BN/SsN HS founder



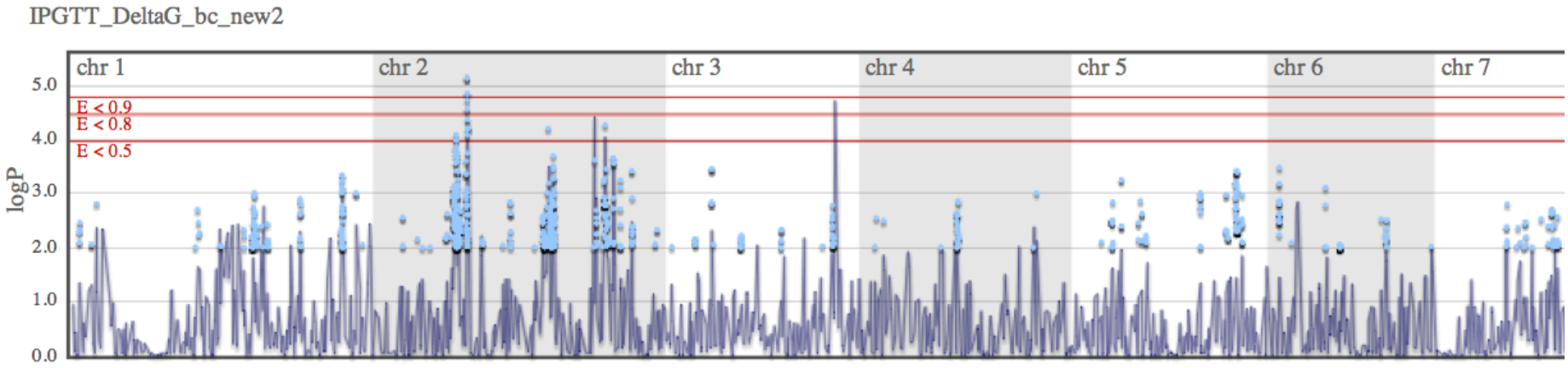
HS rat

Founders sequences

- 8 founder strains sequenced (Cuppen's group, Hubrecht Institute, Utrecht, NL)
- SOLID platform, > 22X coverage
- 7.2M SNPs, 633K indels, and 44K structural variants identified
- Imputed in the HS animals

Genome-wide association mapping

http://mus.well.ox.ac.uk/gscandb/rat/



— Association with ancestral haplotypes

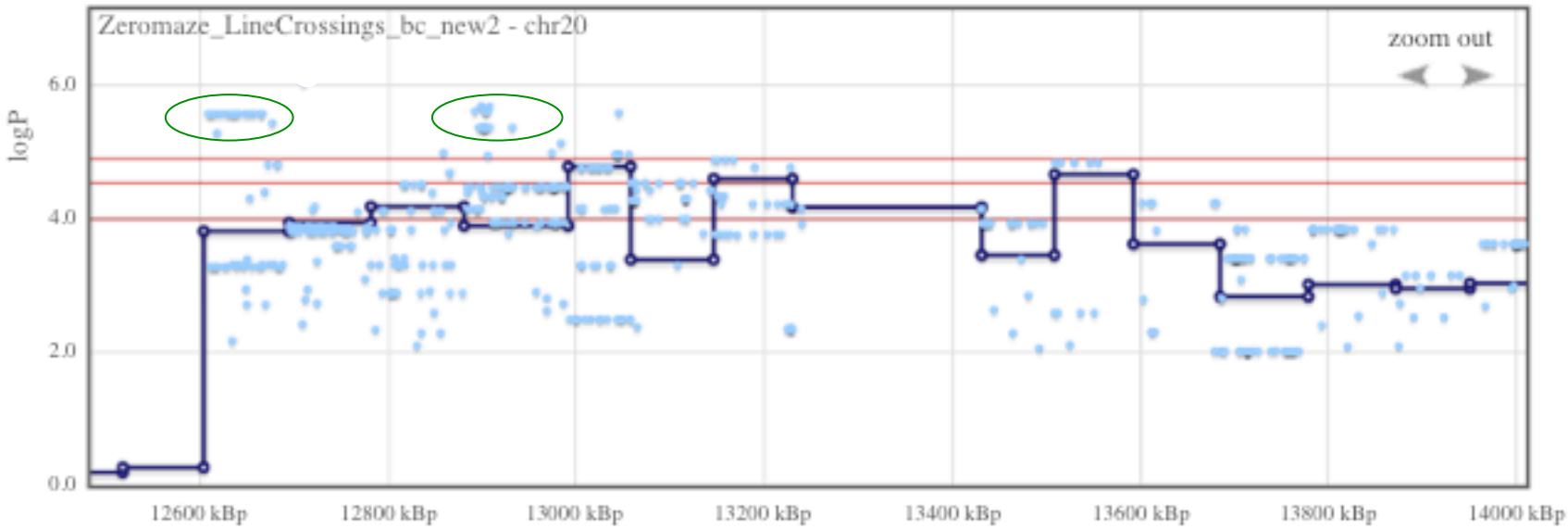
● Association with imputed variant

Do we identify the causative variants?

Do we identify the causative variants?

Can any of the variants at a QTL
explain the genetic signal?

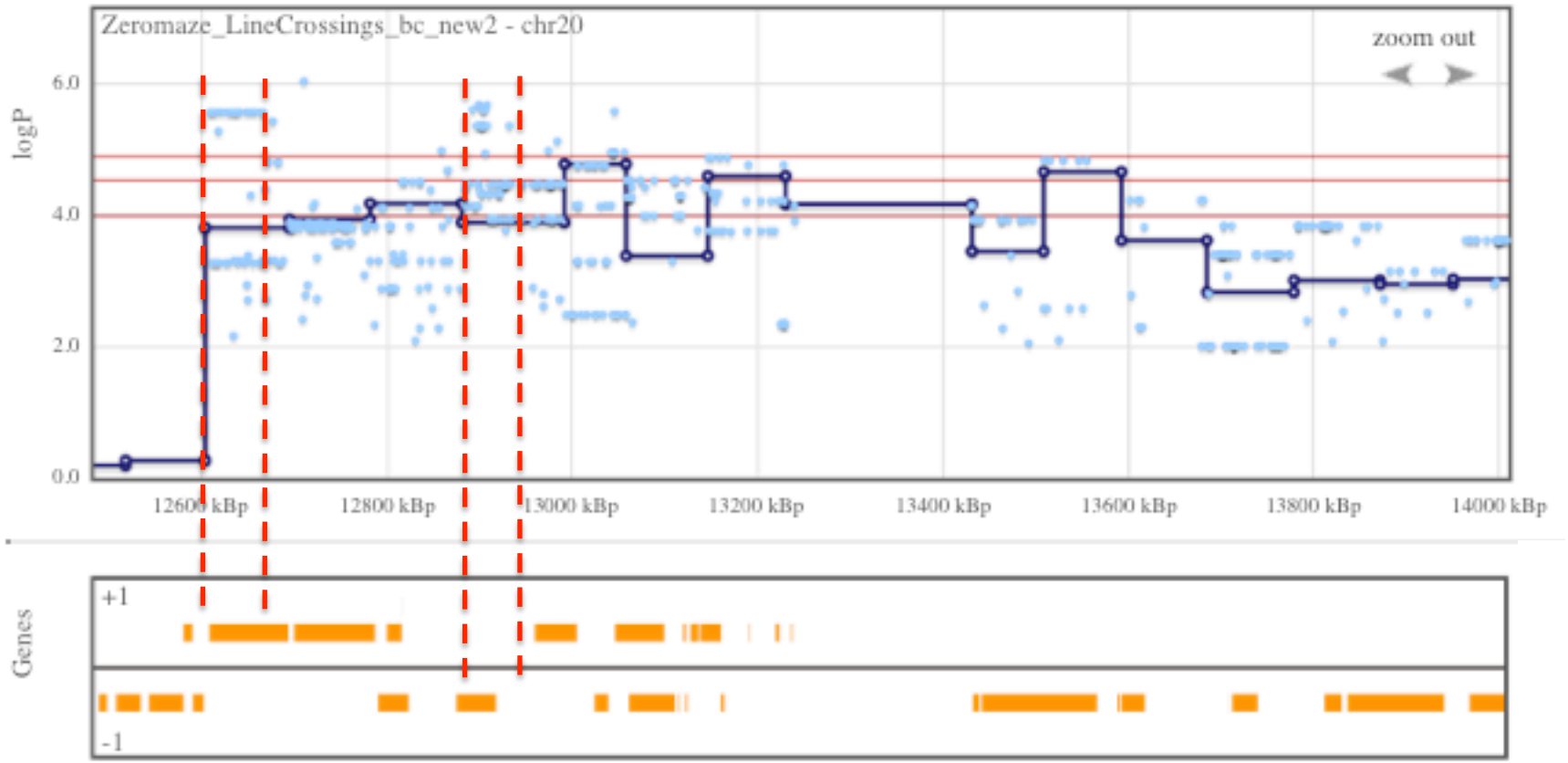
QTL effect captured by a single variant



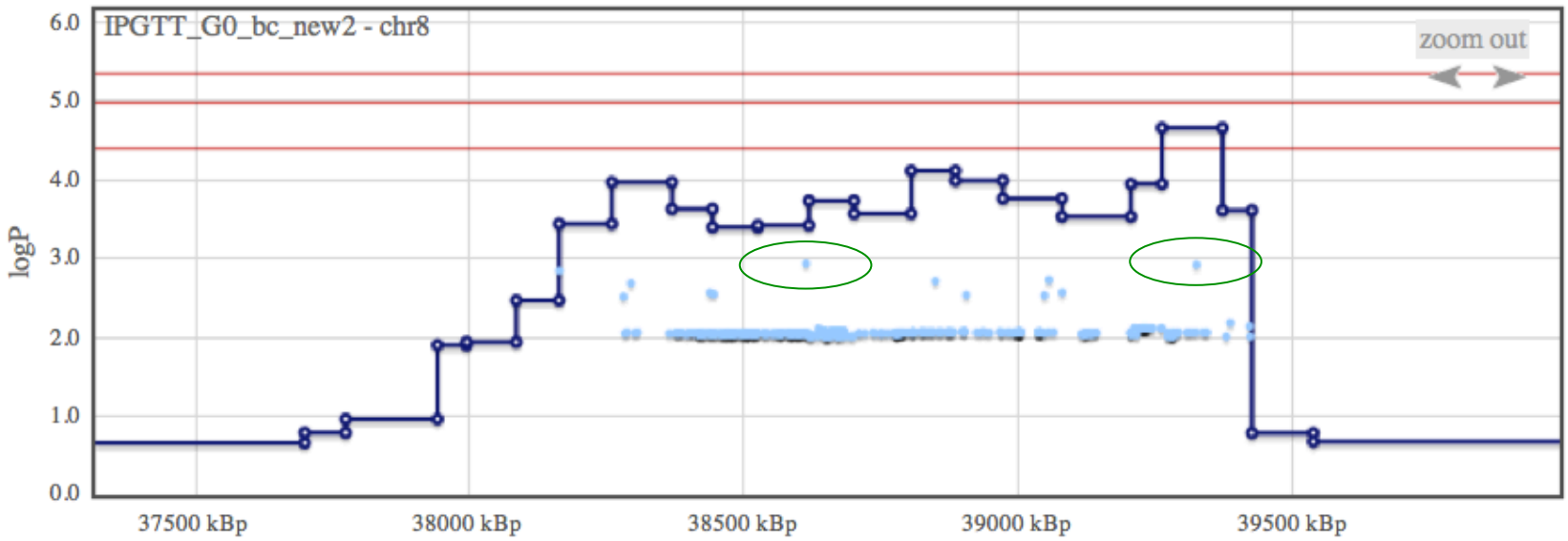
— Association with haplotypes

● Association with sequence variant

Fine mapping



QTL effect not captured by a single variant



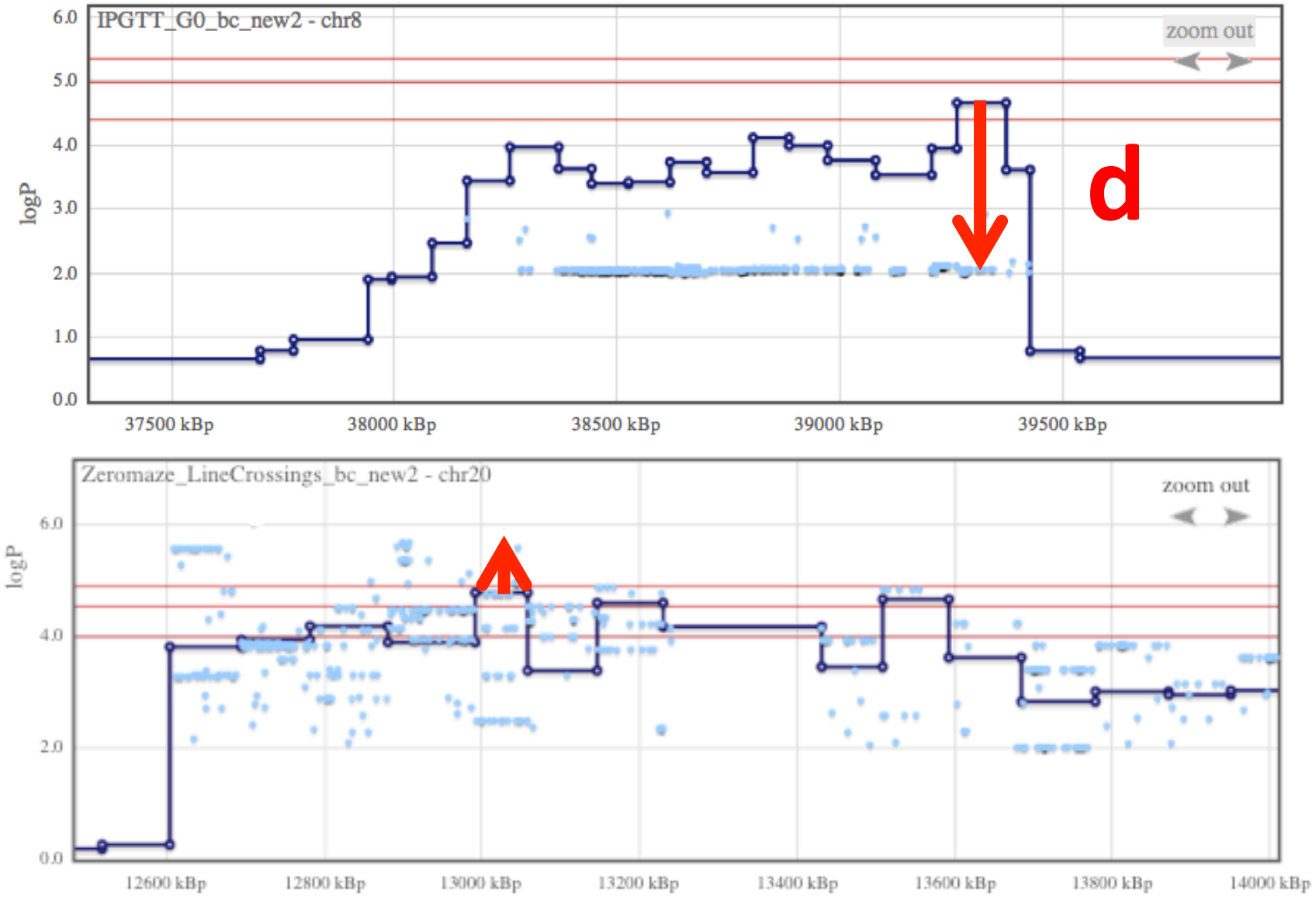
Association with haplotypes

Association with sequence variant

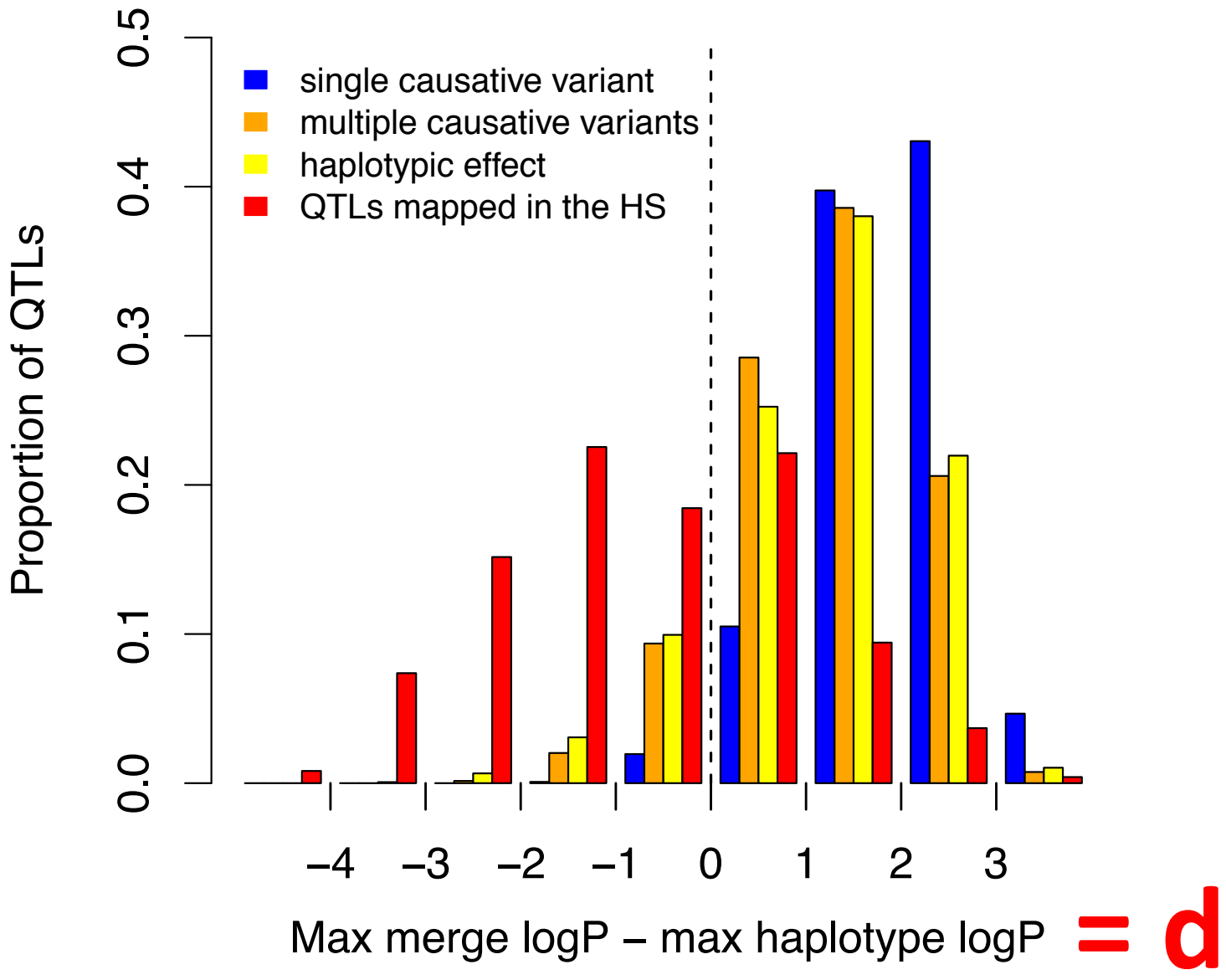
QTL effect not captured by a single variant

	Rat HS QTLs	**Mouse** HS QTLs
QTL effect **not** captured by a single variant	62%	55%

d: capacity of single variants to explain the QTL



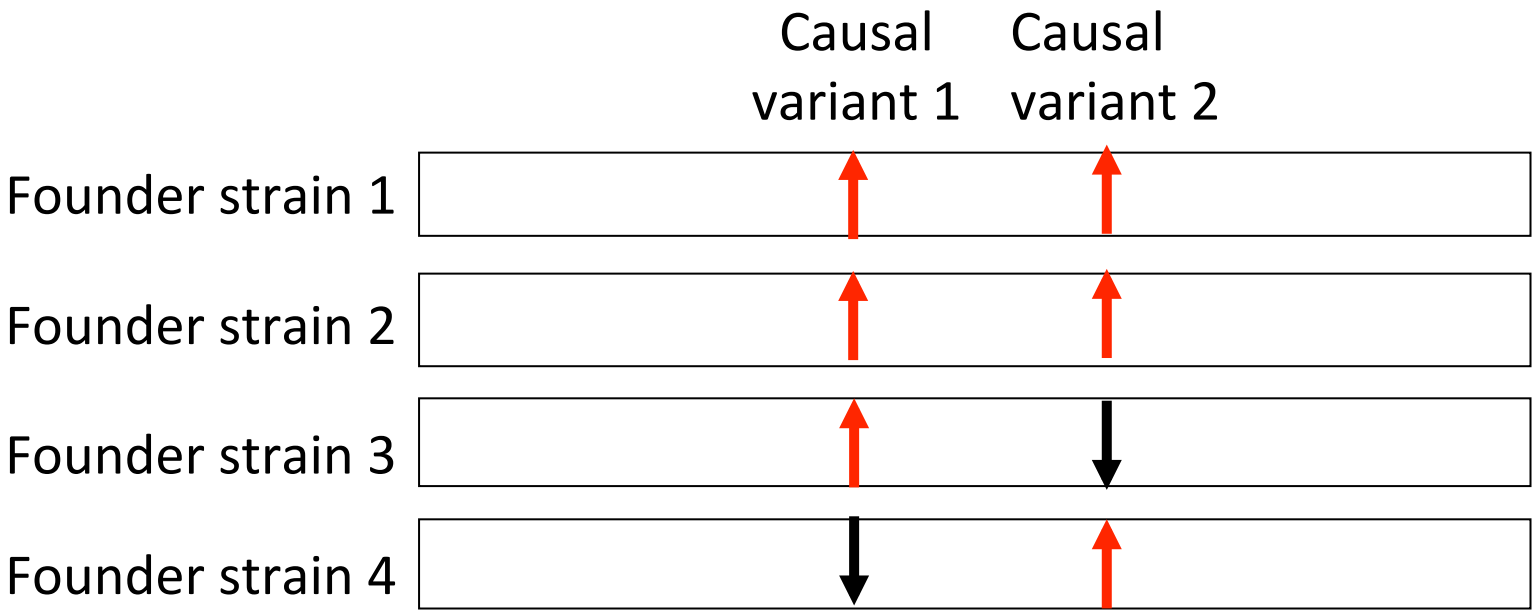
Multiple causal variants at a QTL



Do we identify the causative variants?

Multiple causal variants underly a QTL

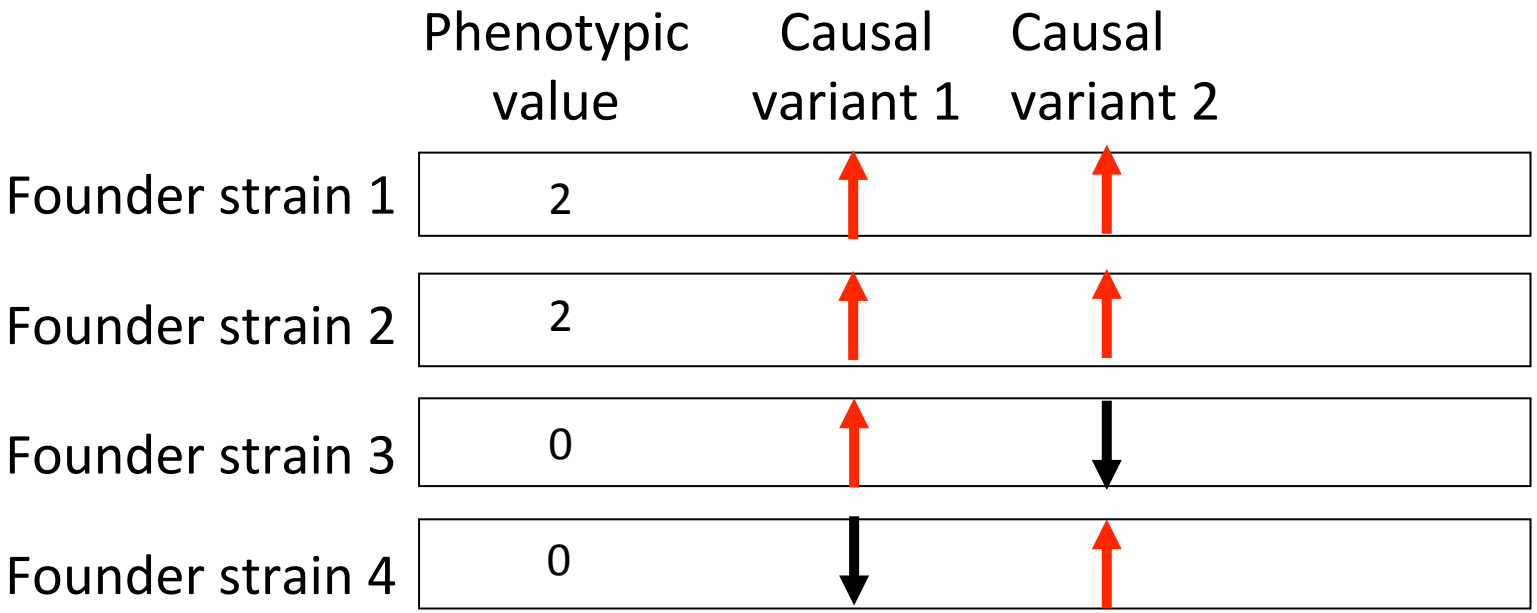
At a QTL due to multiple causative variants:



decrease phenotype by 1 unit

increases phenotype by 1 unit

At a QTL due to multiple causative variants:



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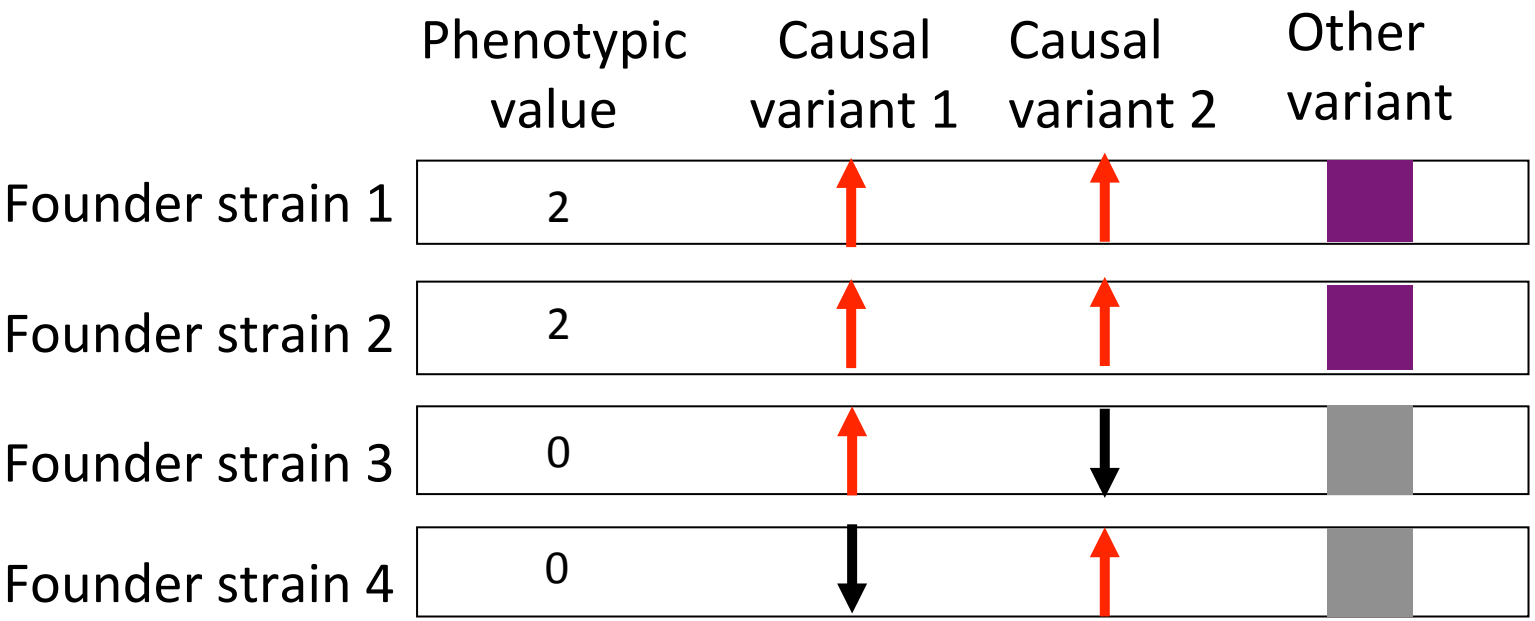
At a QTL due to multiple causative variants:



decrease phenotype by 1 unit

increases phenotype by 1 unit

Conclusions

- 352 QTLs for 122 traits, large proportion of heritable phenotypic variation explained

- **At 2/3 of QTLs, a single causal variant cannot account for the association: multiple causal variants?**

- multiple causal variants underly a QTL -> methods that attempt to attribute the signal to a single variant misleading

nature genetics

Combined sequence-based and genetic mapping analysis of complex traits in outbred rats

Rat Genome Sequencing and Mapping Consortium*

nature genetics

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SEVENTH FRAMEWORK PROGRAMME