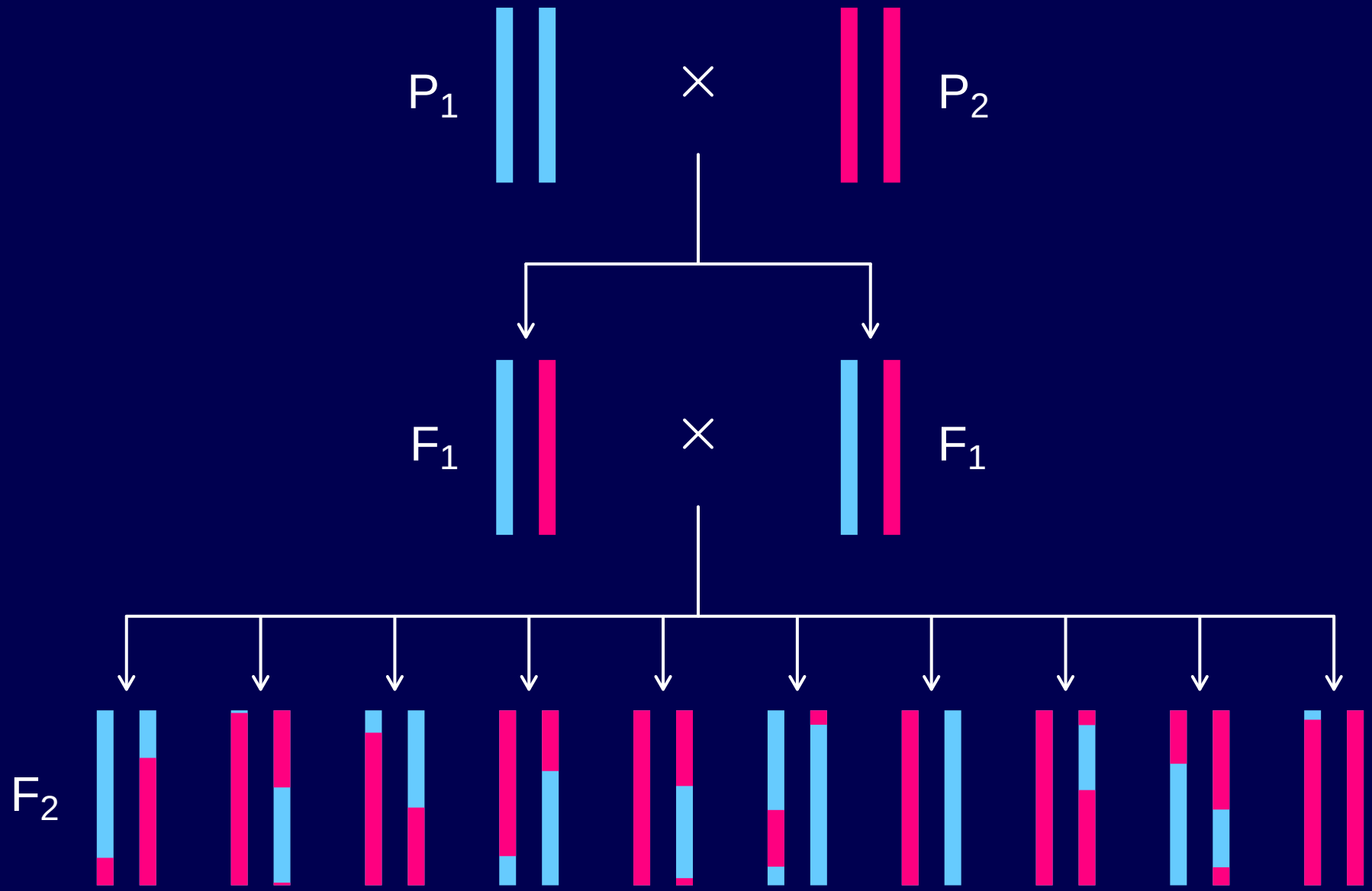
Identifying and correcting sample mix-ups in high-dimensional data

Karl W Broman

Department of Biostatistics & Medical Informatics
University of Wisconsin – Madison

www.biostat.wisc.edu/~kbroman

Intercross



Alan Attie project

$\sim$500 B6 $\times$ BTBR intercross mice, all ob/ob

Genotypes at 2057 SNPs (Affymetrix arrays)

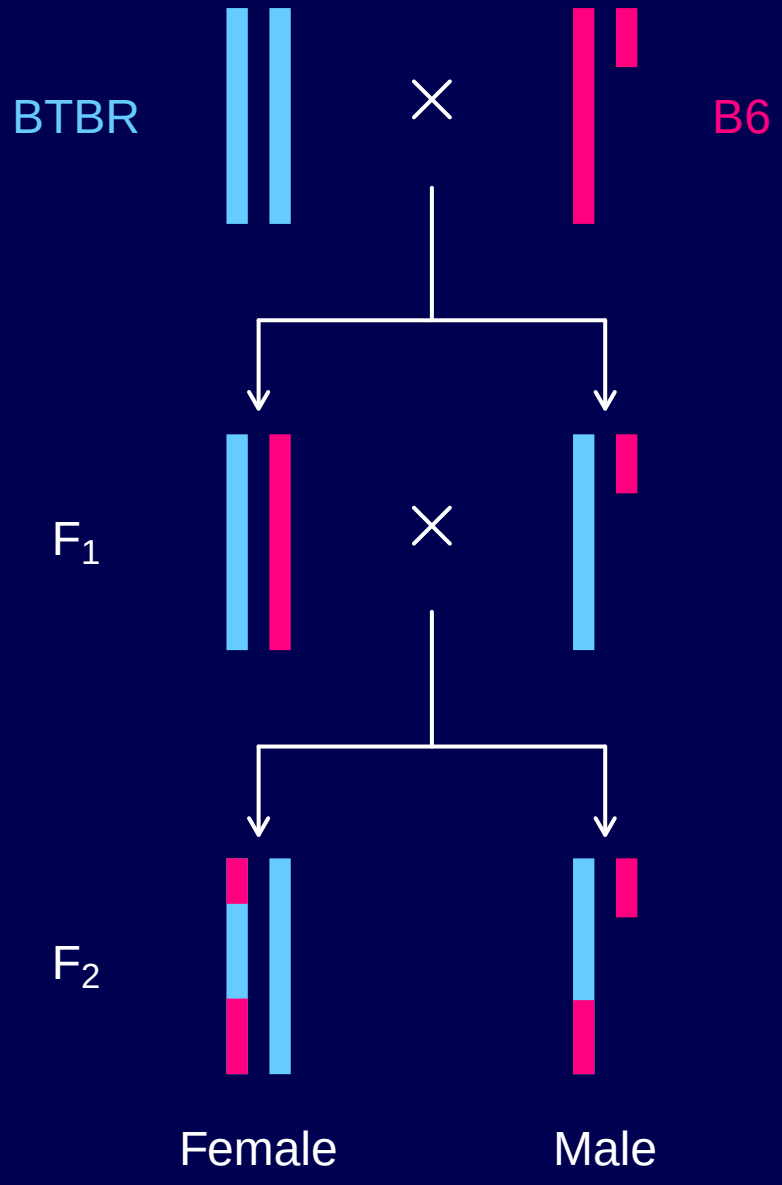
Gene expression in six tissues (Agilent arrays)

- adipose
- gastrocnemius muscle
- hypothalamus
- pancreatic islets
- kidney
- liver

Numerous clinical phenotypes

(e.g., body weight, insulin and glucose levels)

Sex and the X chr

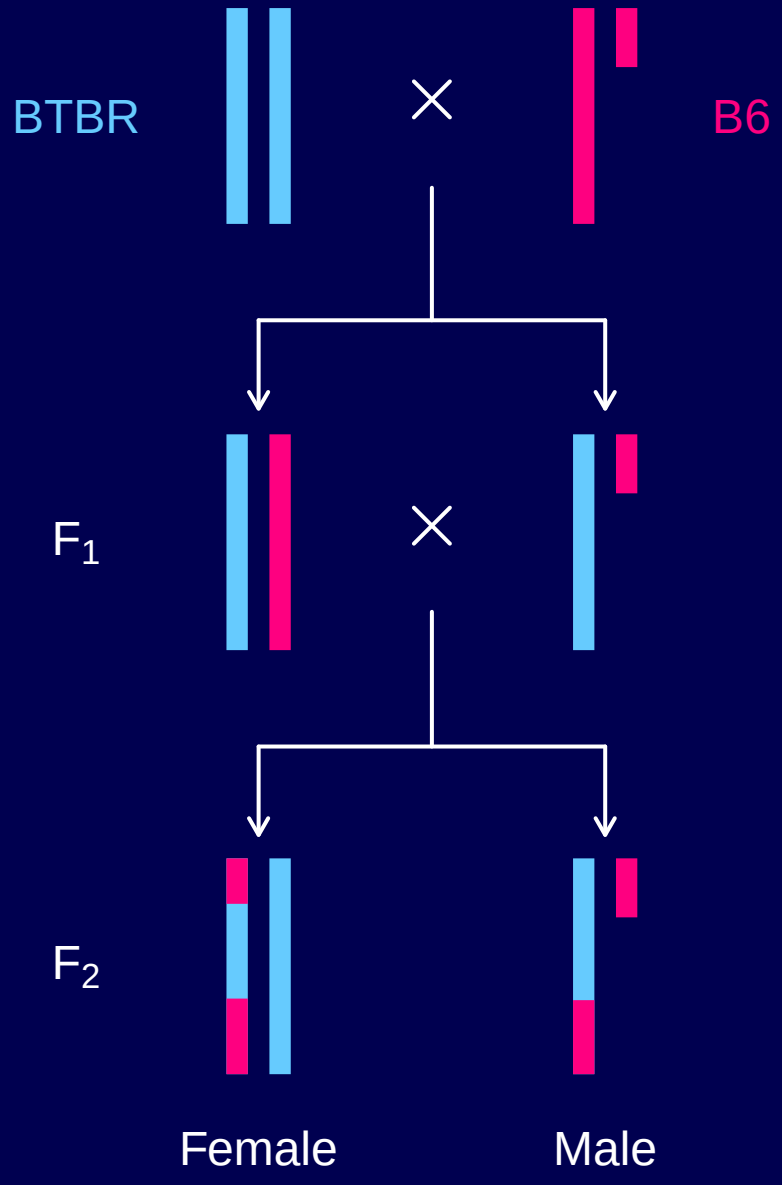


F_2 females: R/R or B/R

F_2 males: hemizygous B or R

Genotype mix-ups

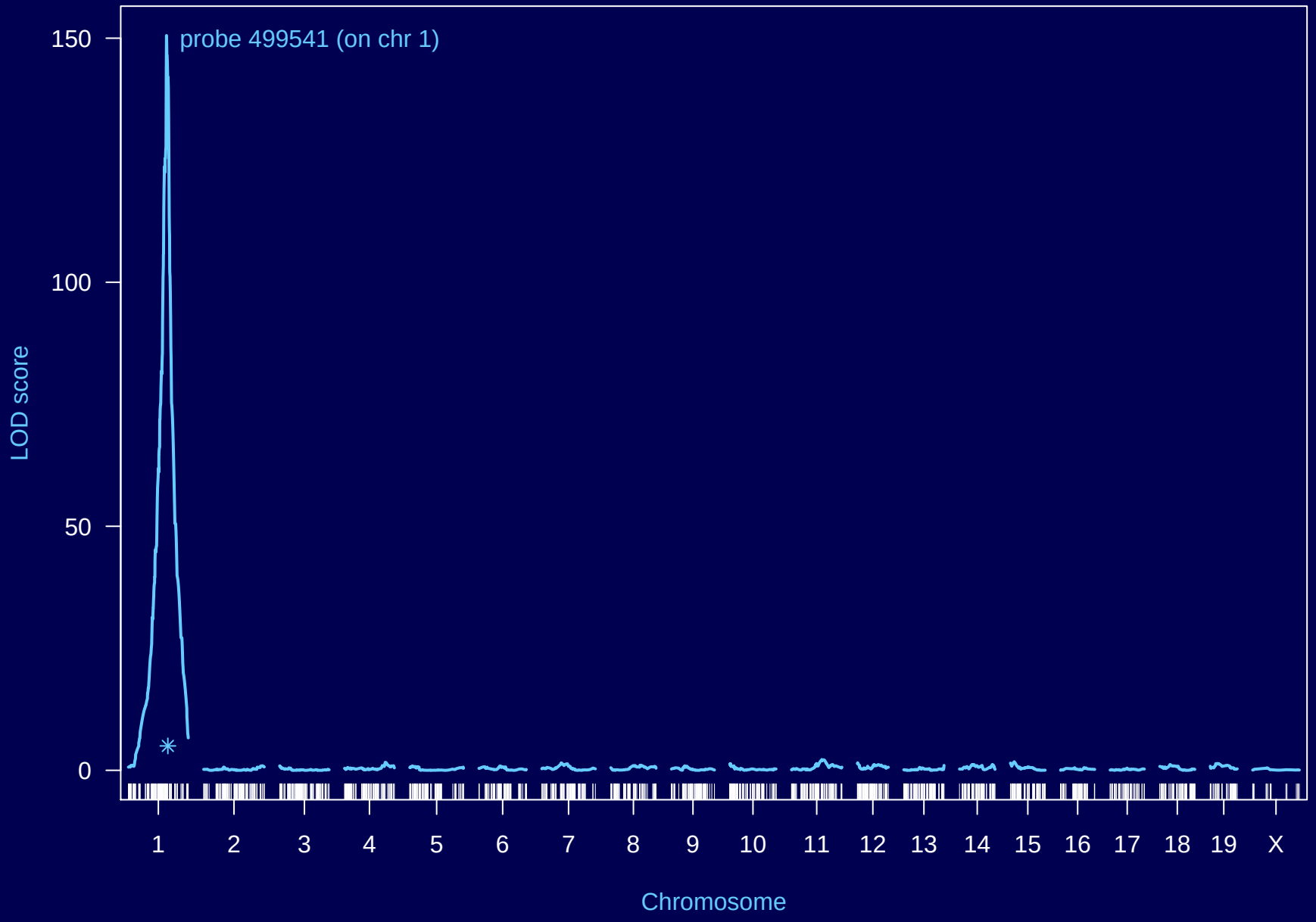
Sex and the X chr



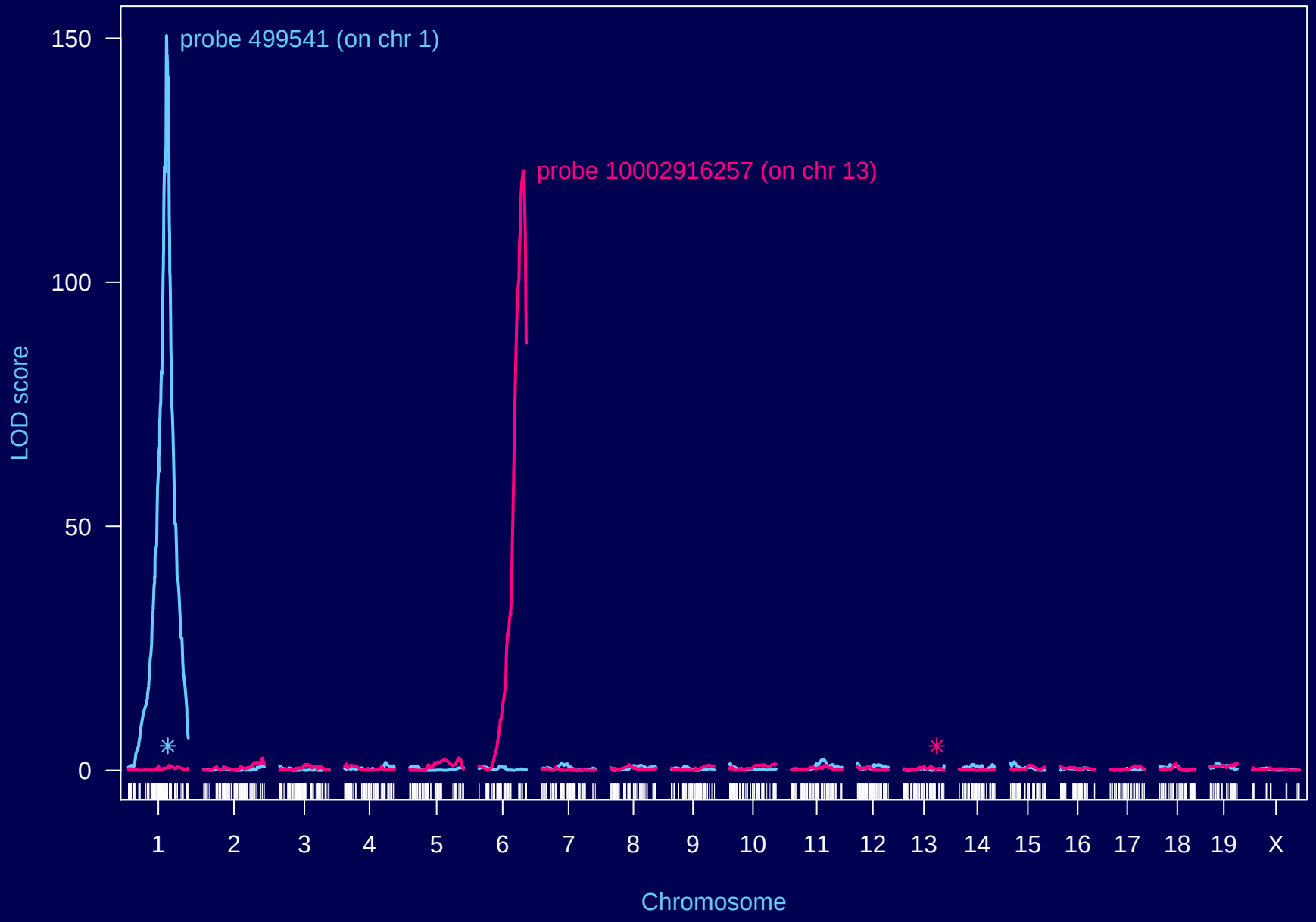
F_2 females: R/R or B/R

F_2 males: hemizygous B or R

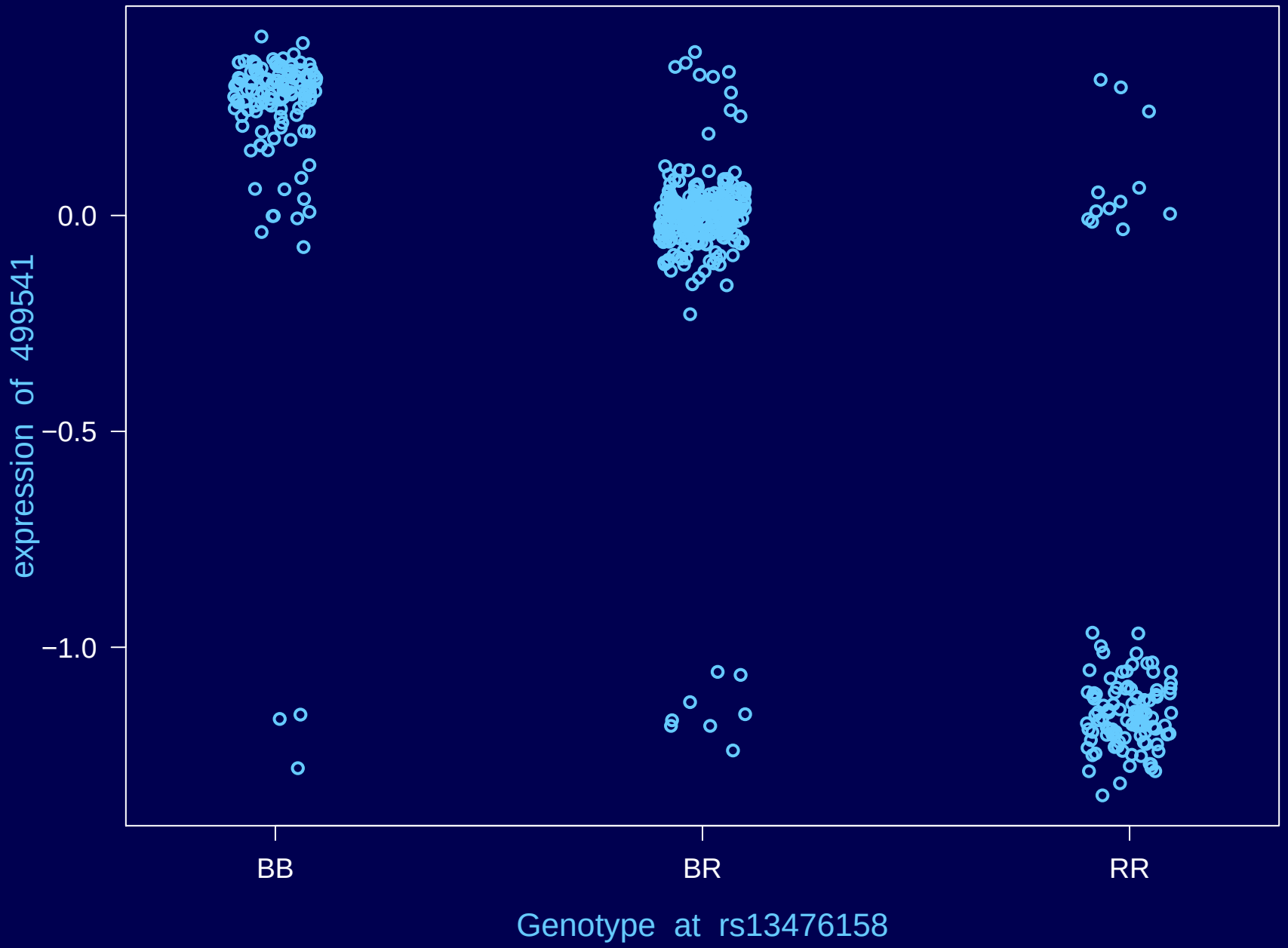
Strong eQTL


probe 499541 (on chr 1)
150
100
50
0
LOD score
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

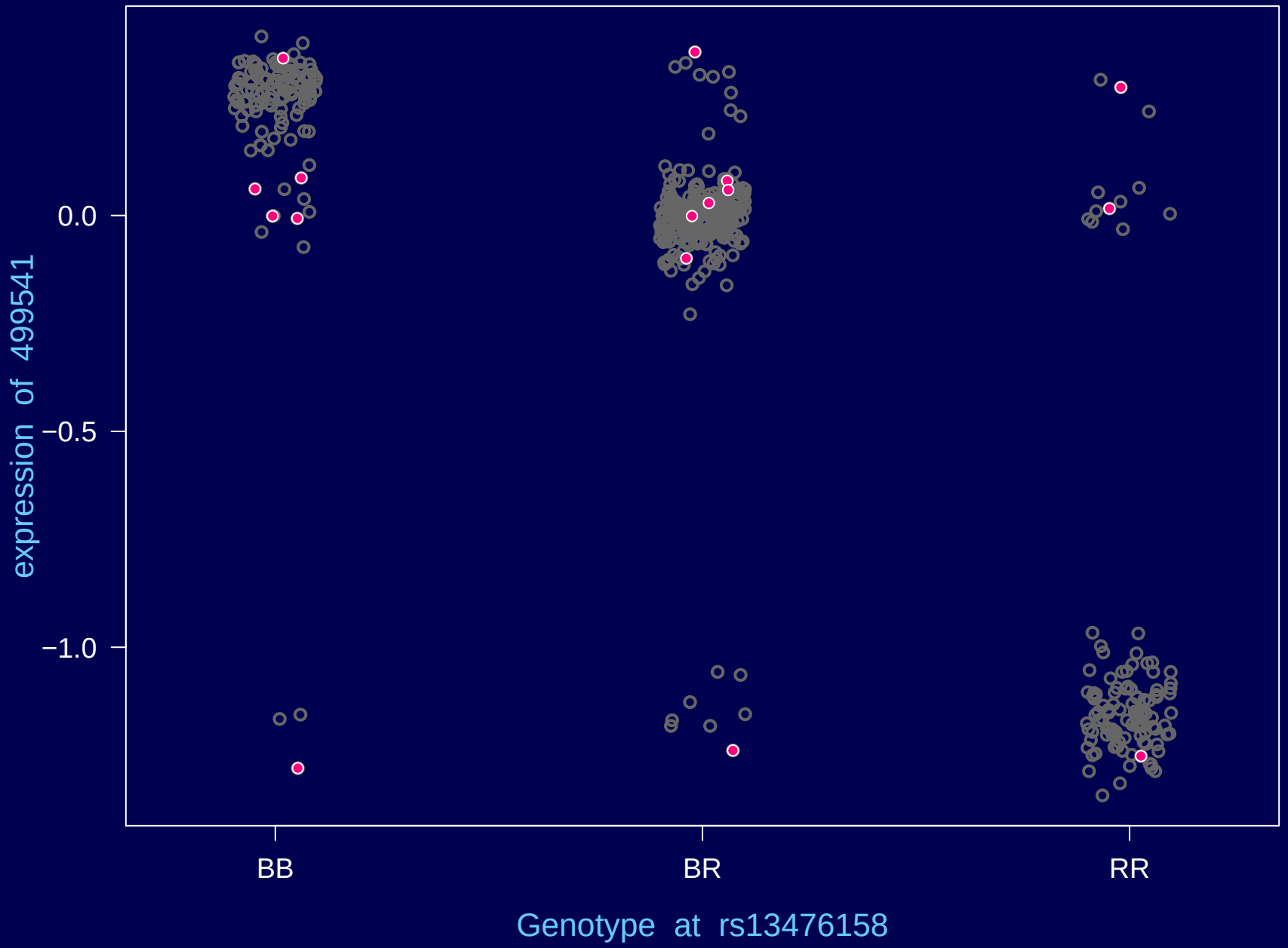
Strong eQTL


probe 499541 (on chr 1)
probe 10002916257 (on chr 13)
150
100
50
0
LOD score
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

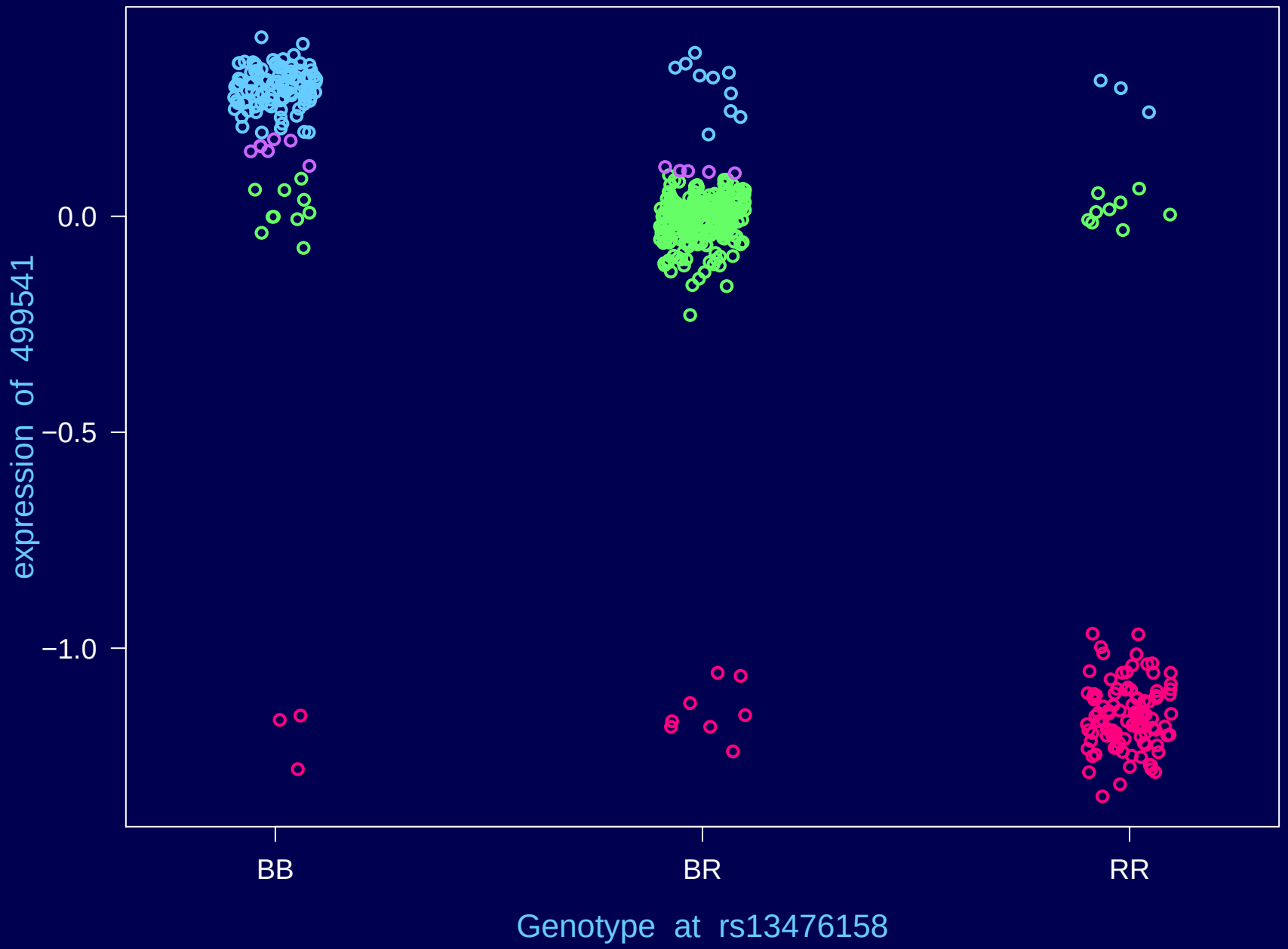
E vs G


0.0
−0.5
−1.0
expression of 499541
BB
BR
RR
Genotype at rs13476158

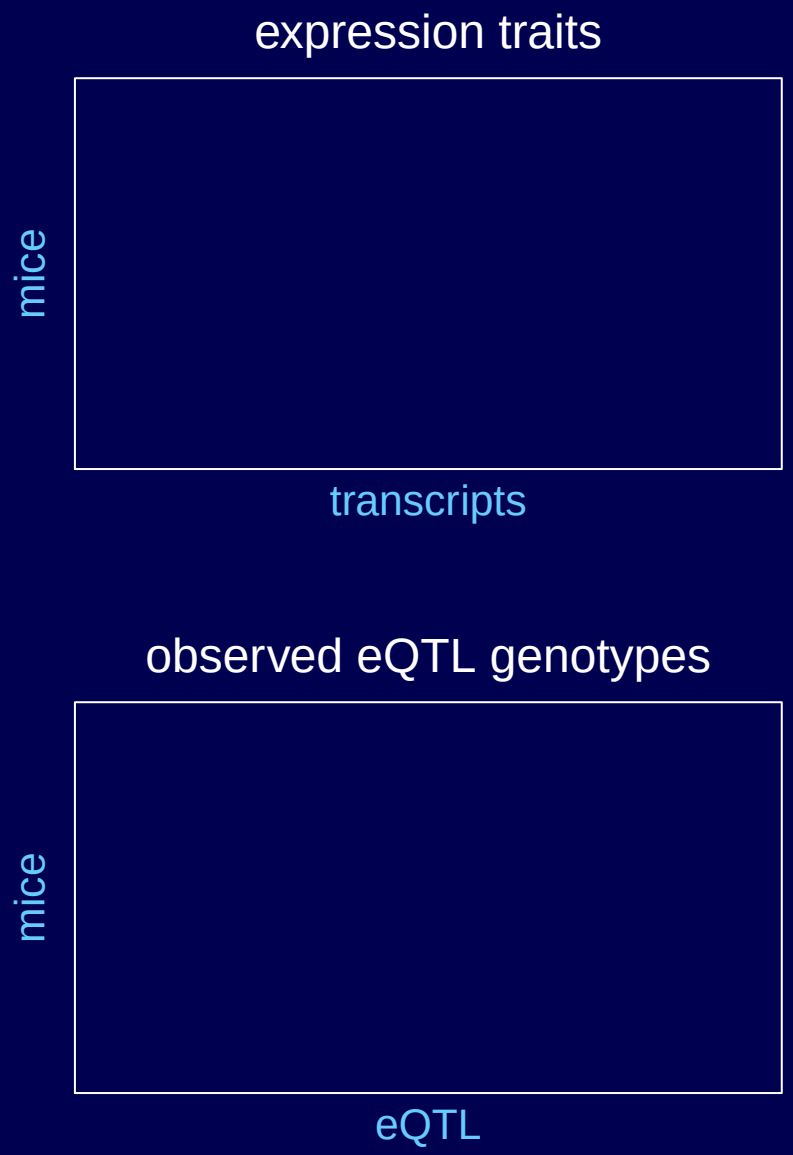
E vs G


0.0
−0.5
−1.0
expression of 499541
BB
BR
RR
Genotype at rs13476158

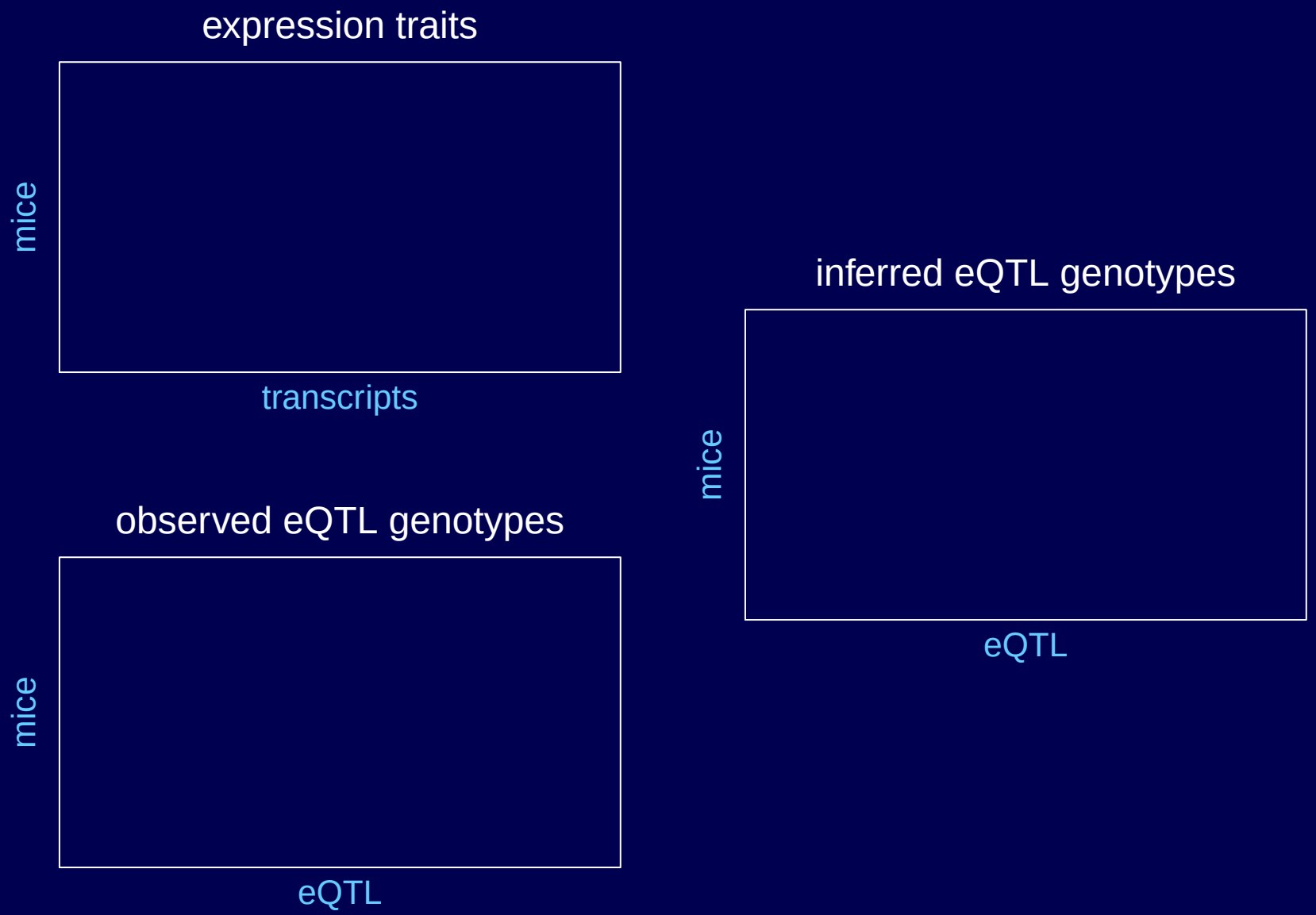
kNN classifier



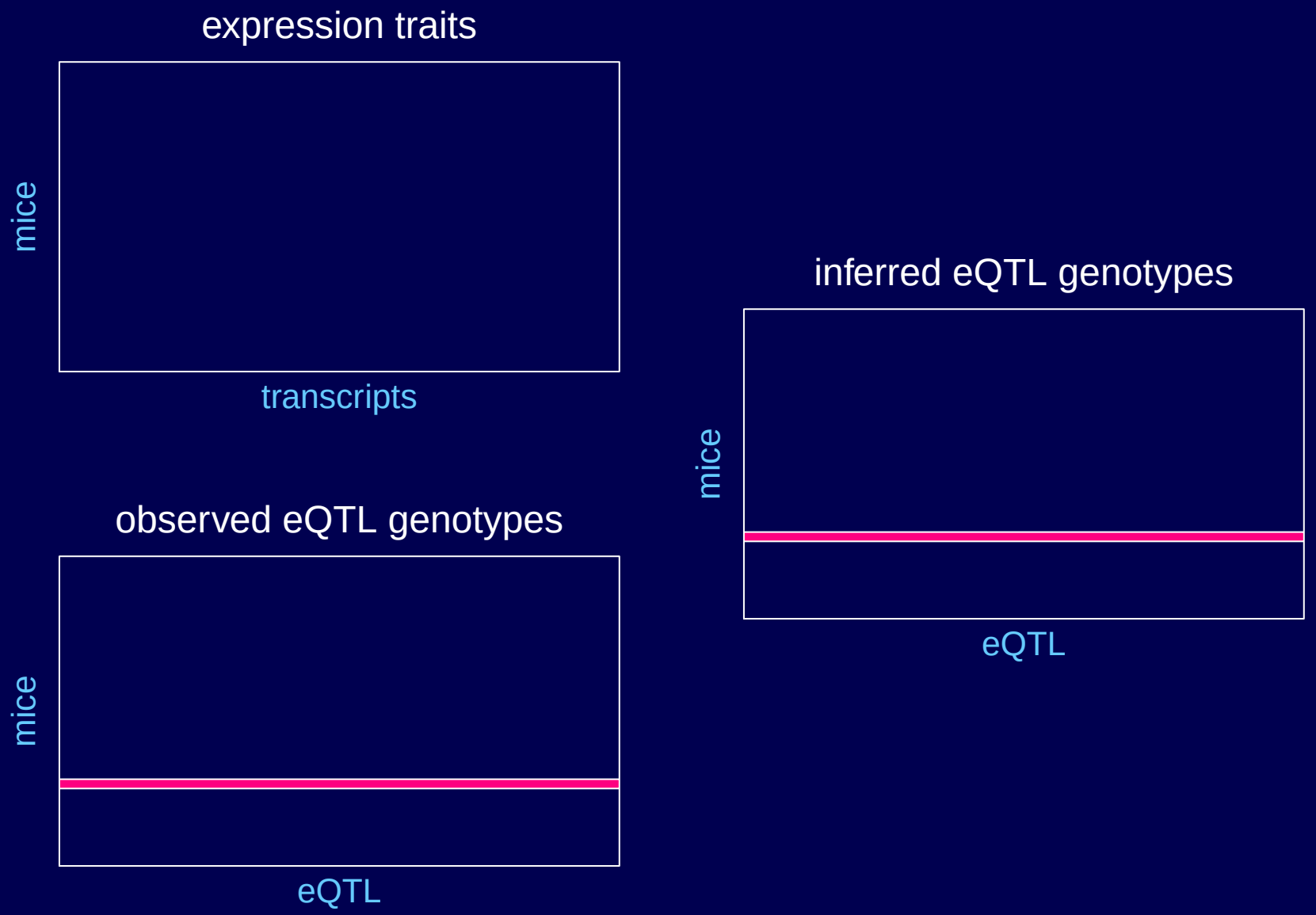
Basic scheme



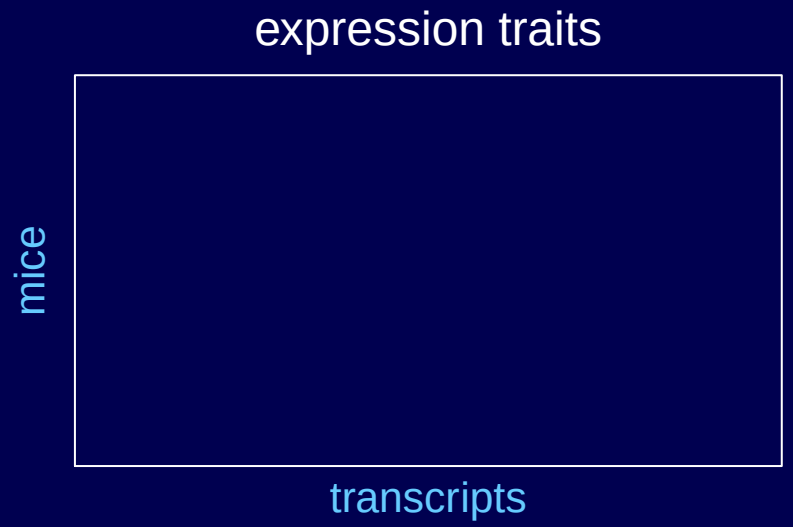
Basic scheme

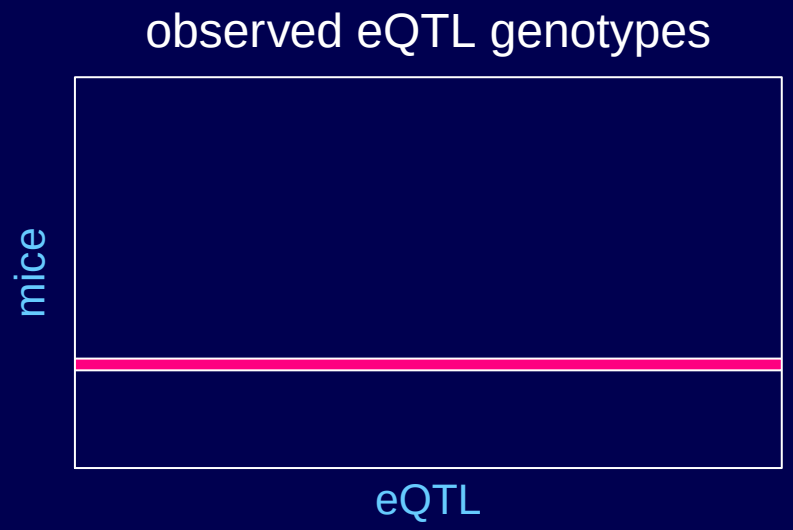


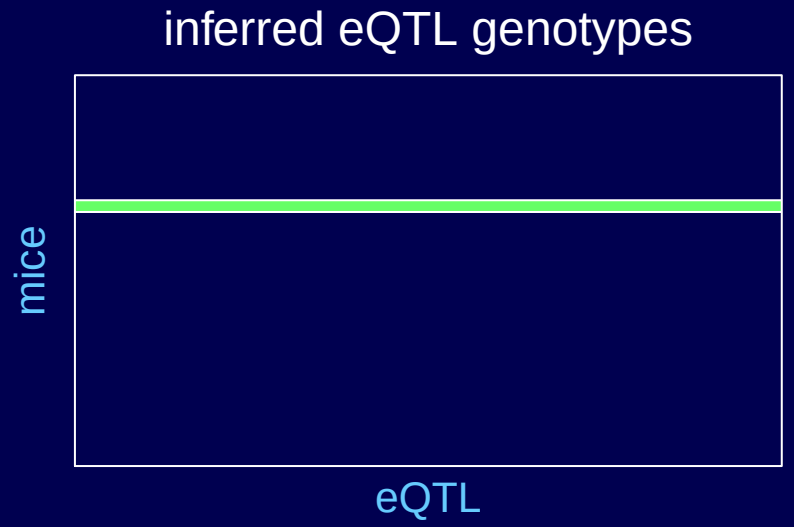
Basic scheme



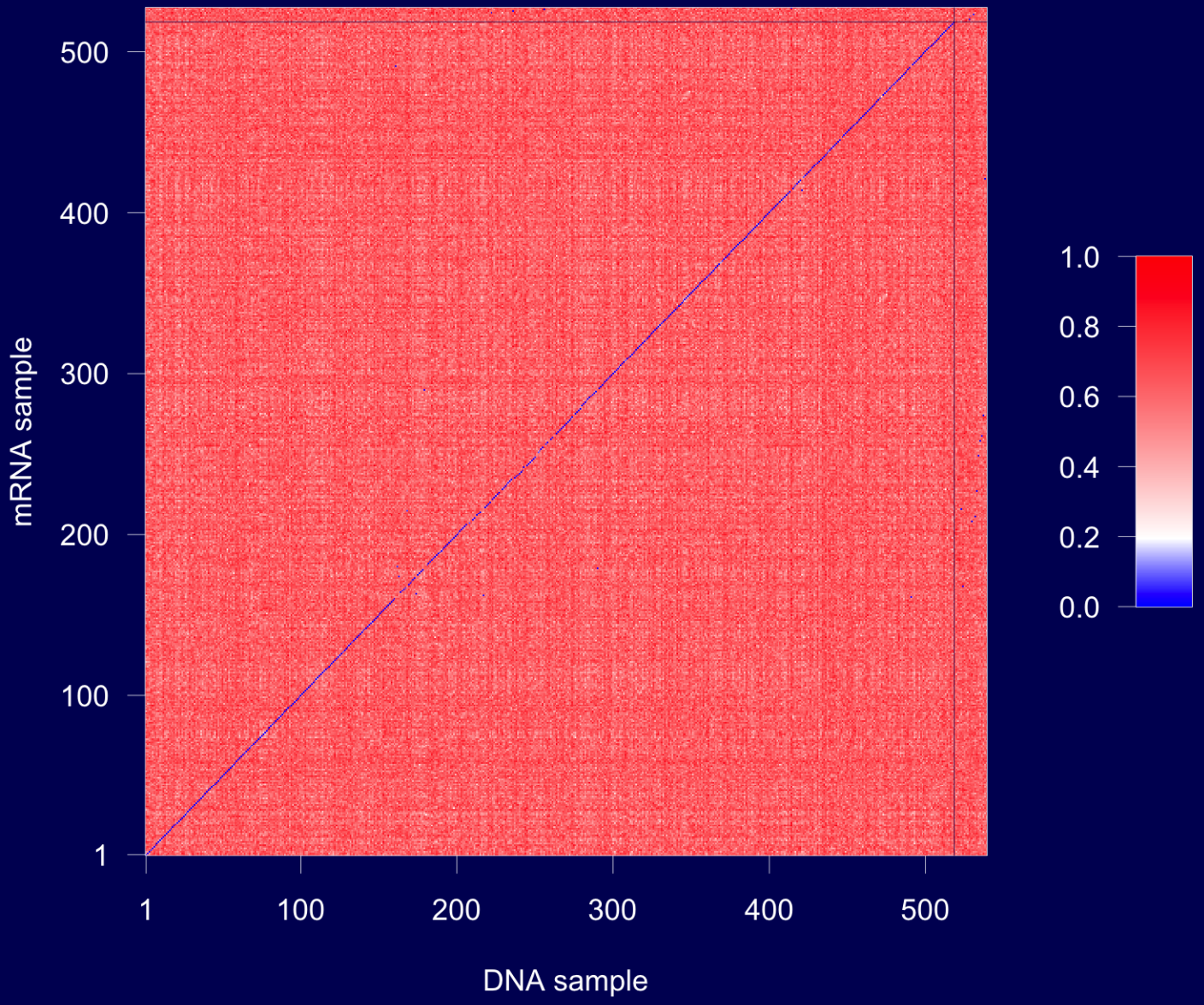
Basic scheme



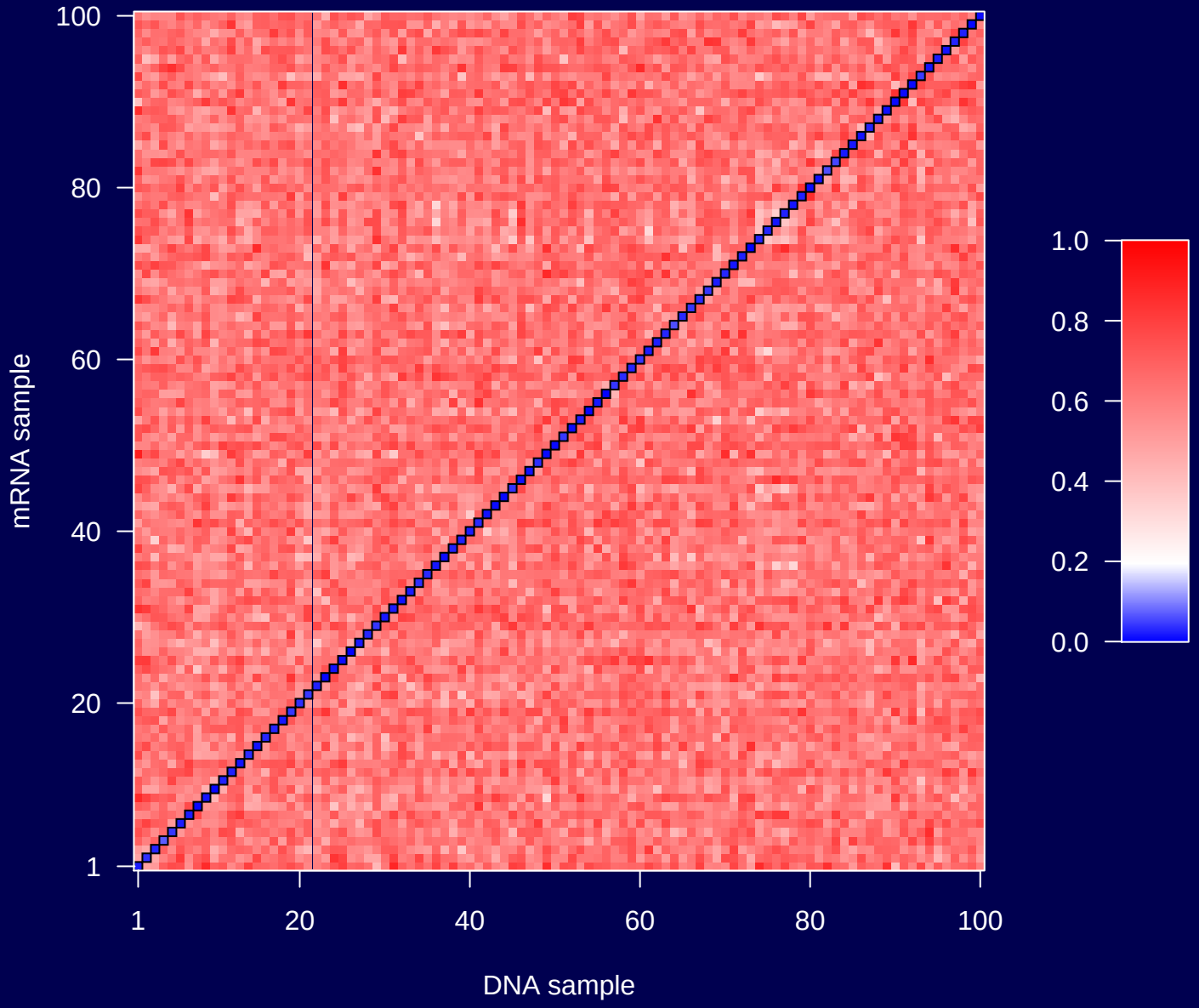




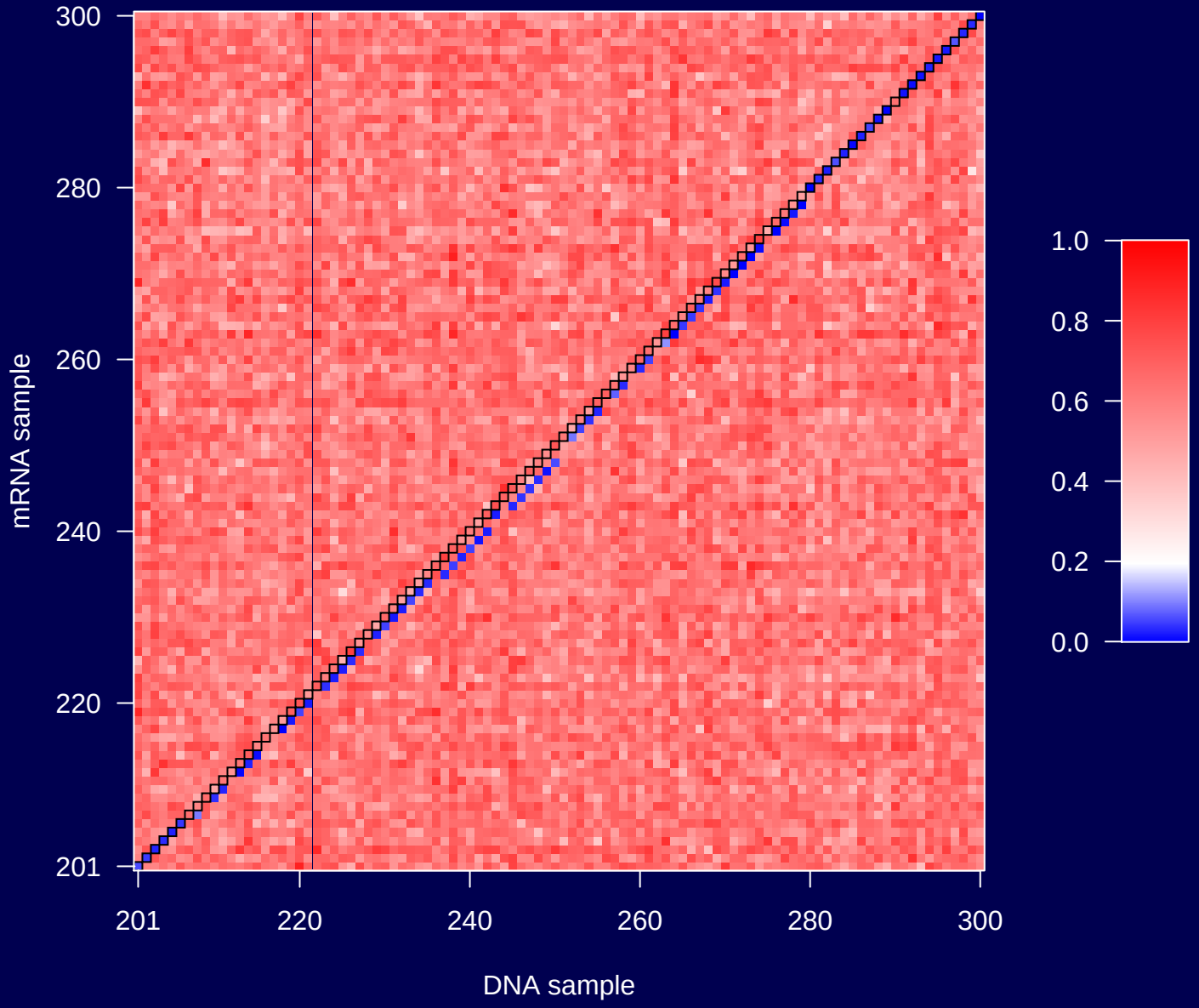
Prop'n mismatches



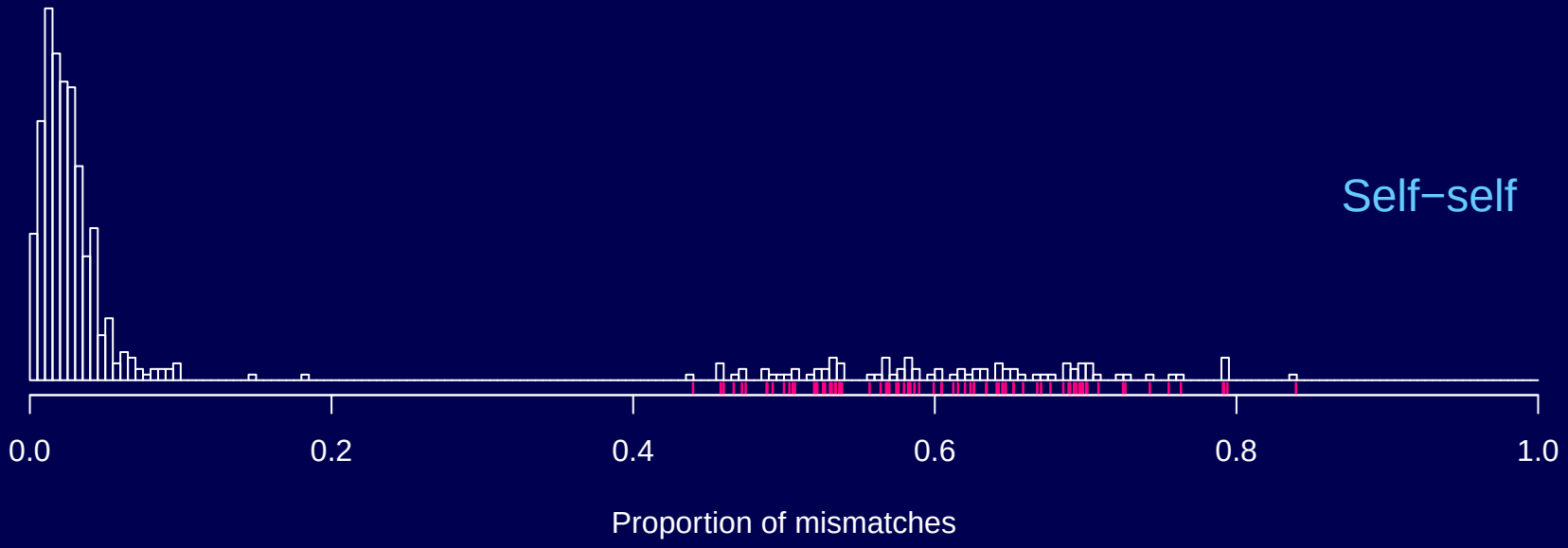
Prop'n mismatches

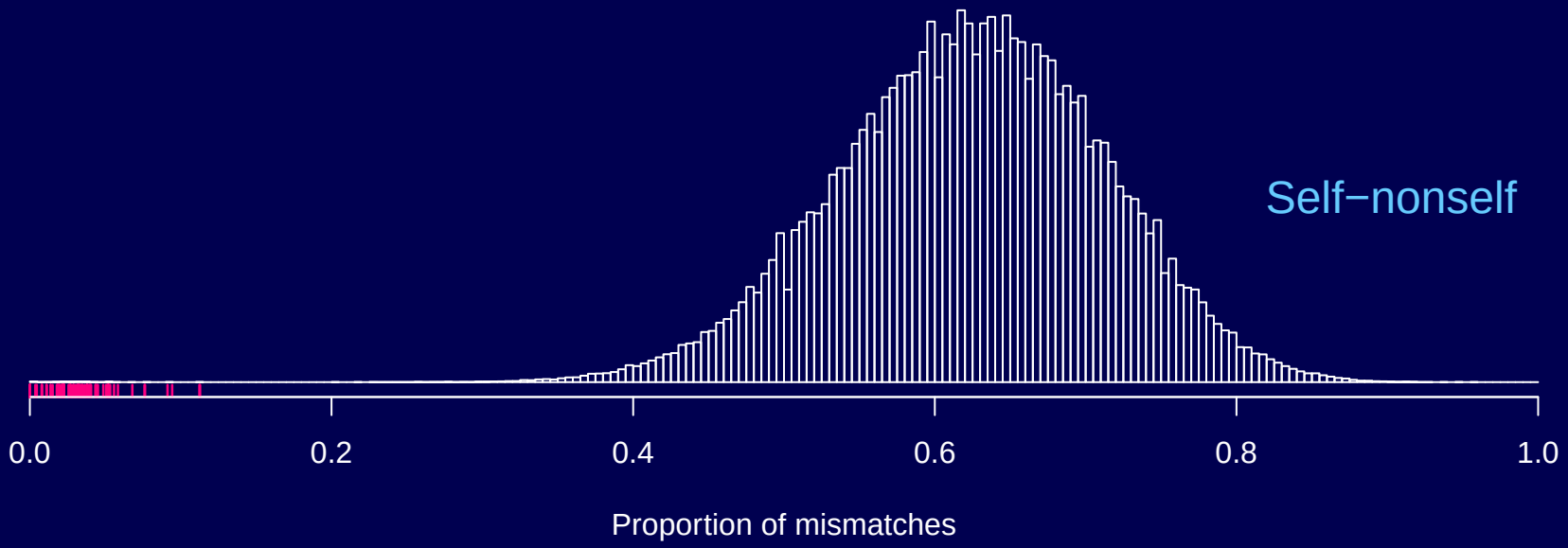


Prop'n mismatches

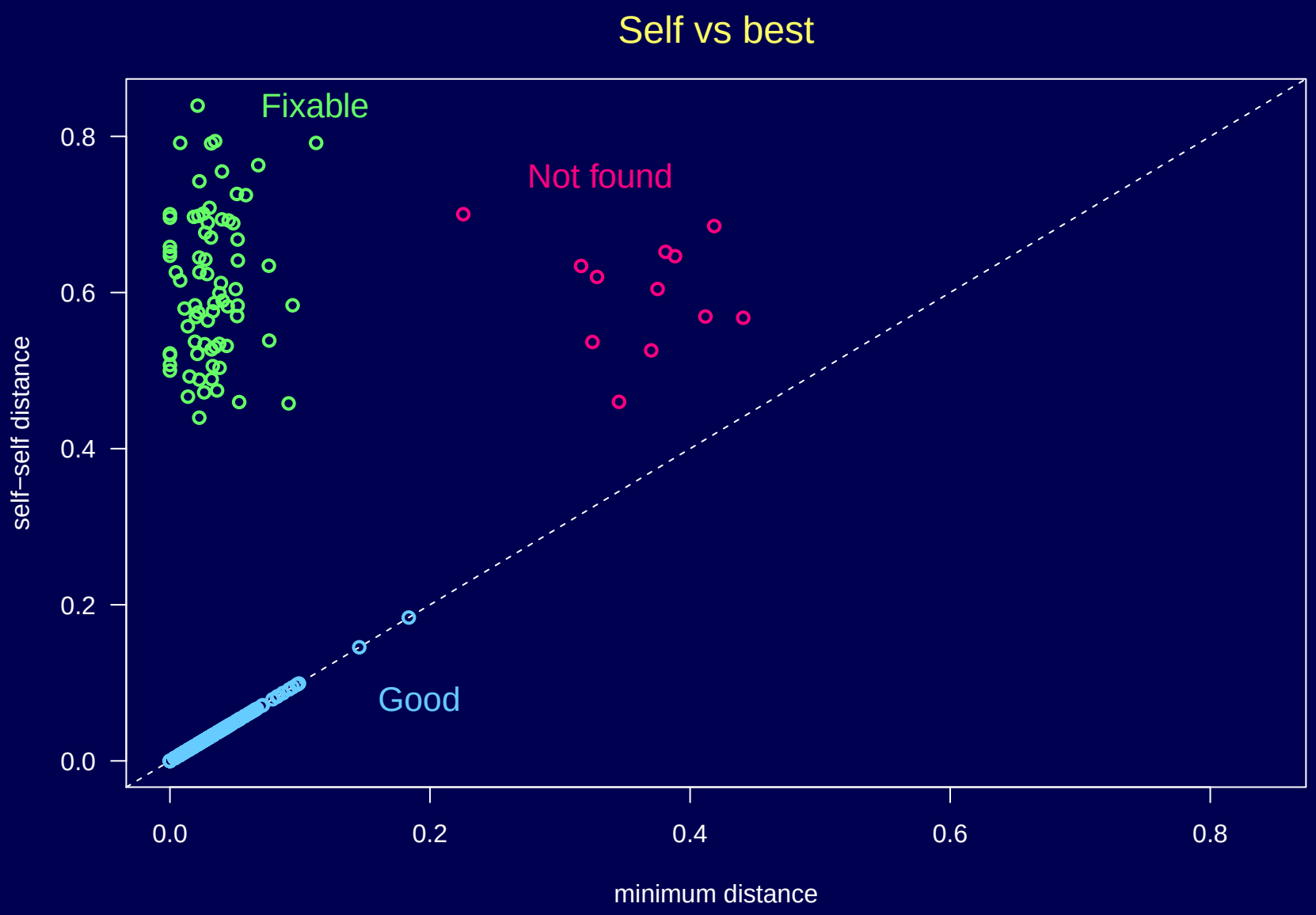


Prop’n mismatches





Decisions


Self vs best
Fixable
Not found
Good
self−self distance
minimum distance
0.0
0.2
0.4
0.6
0.8

Genotype mix-ups

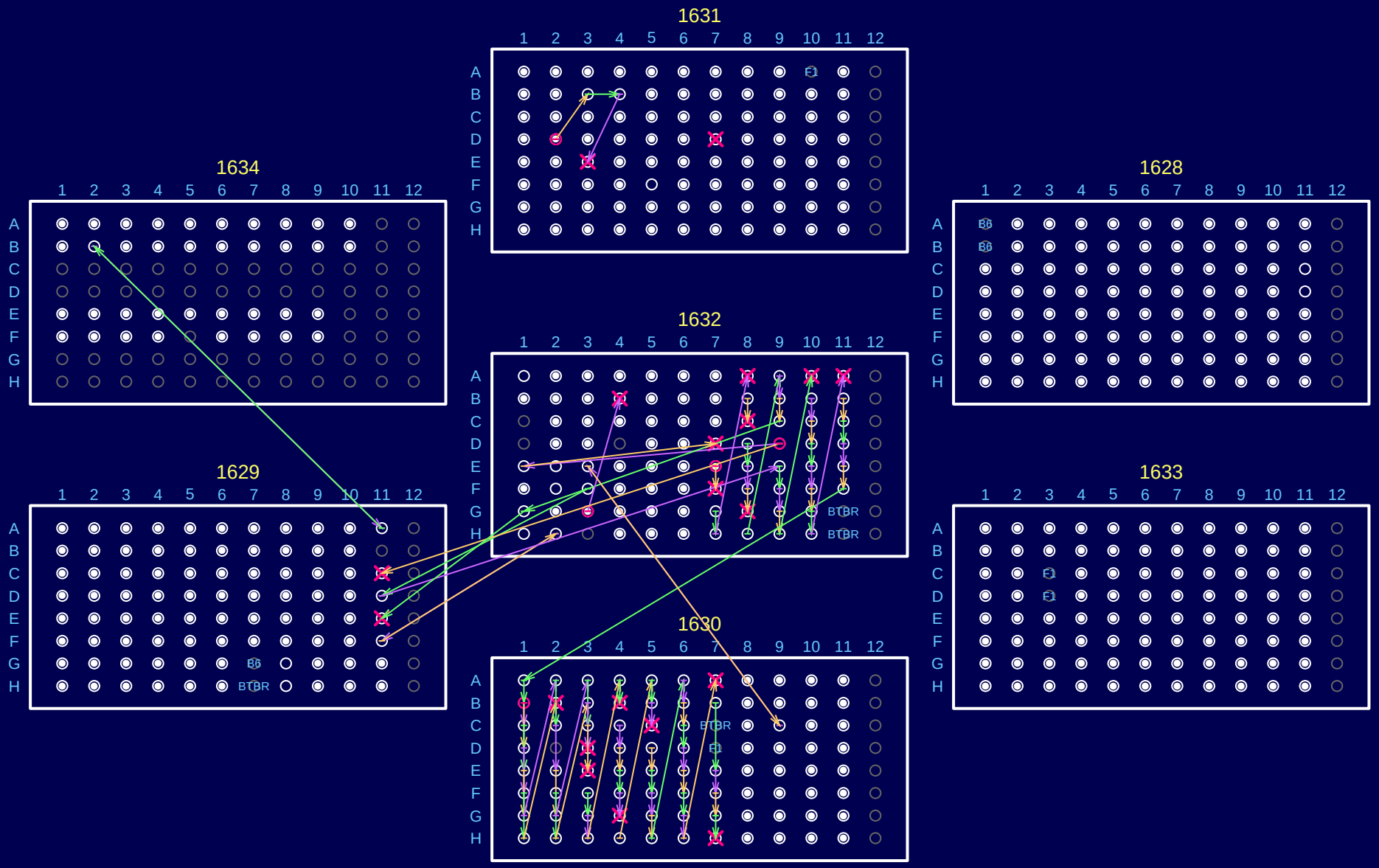
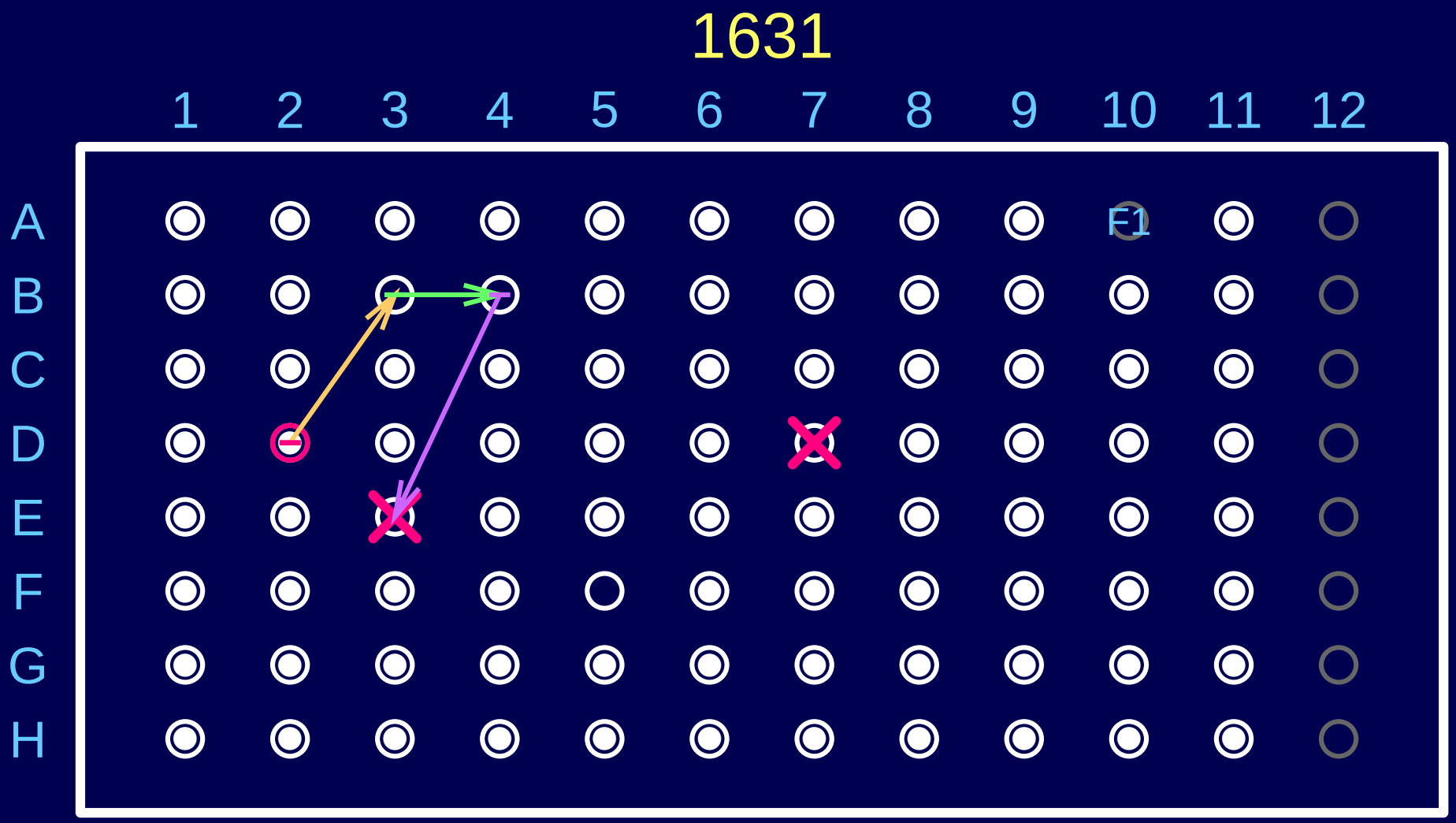


Plate 1631



Plates 1632 and 1630

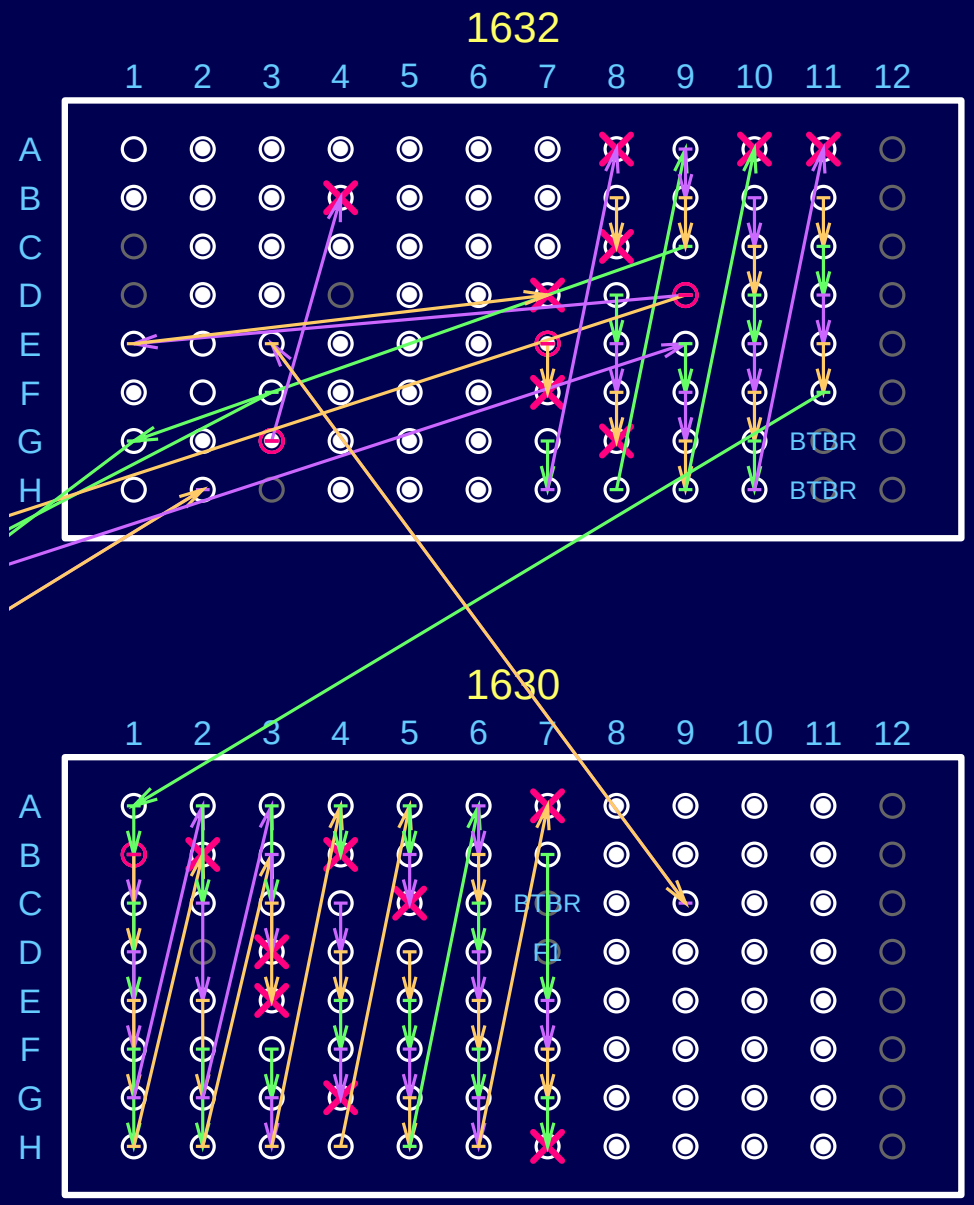
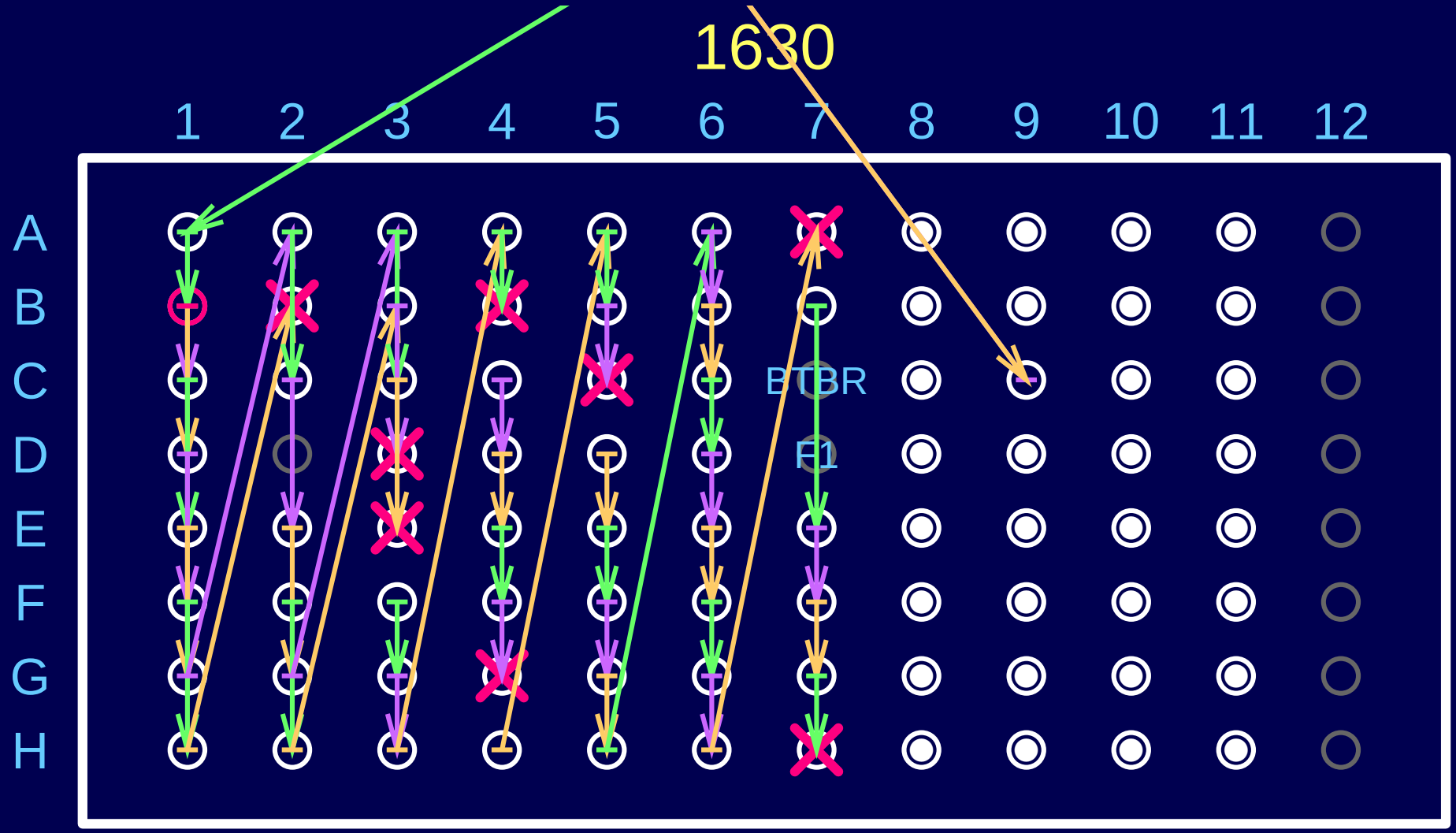


Plate 1630



E vs E


expression in islet
mice
transcripts

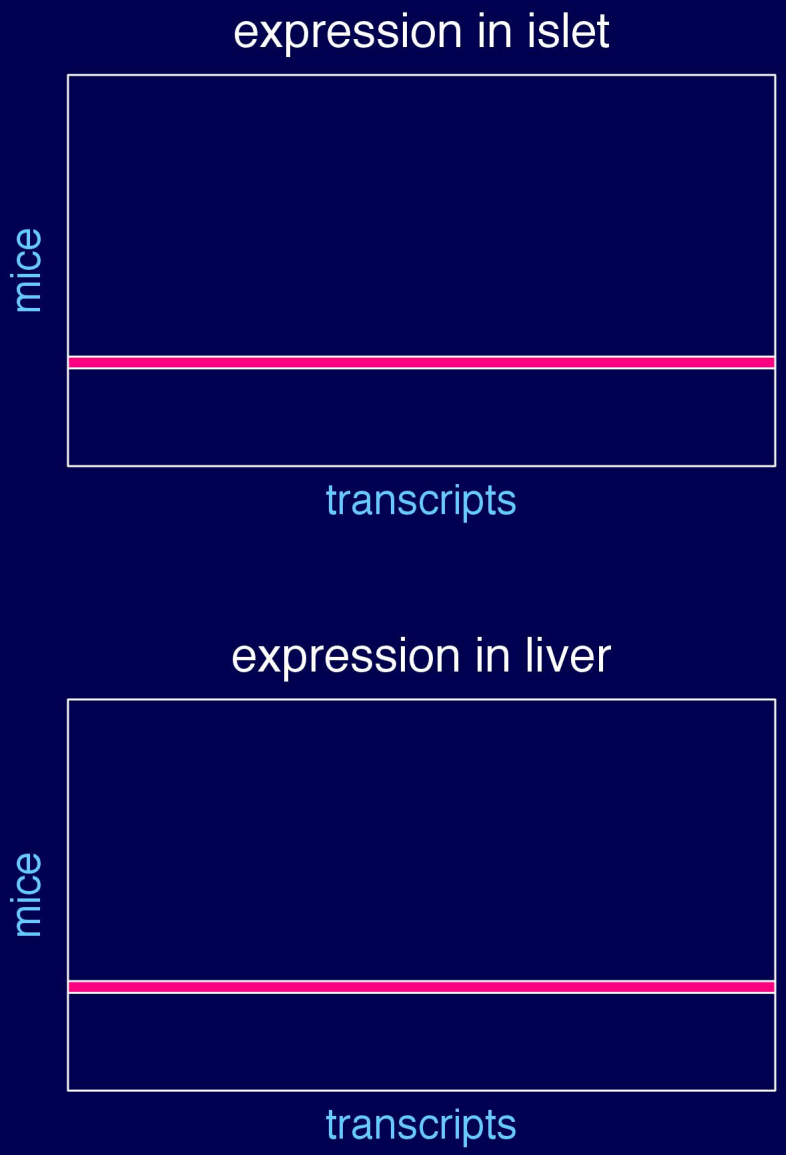

expression in liver
mice
transcripts

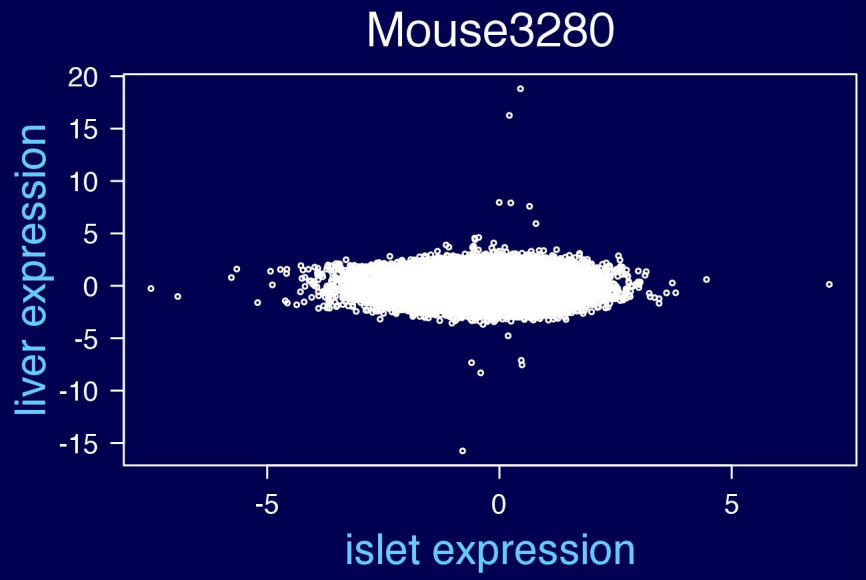
E vs E


expression in islet
mice
transcripts

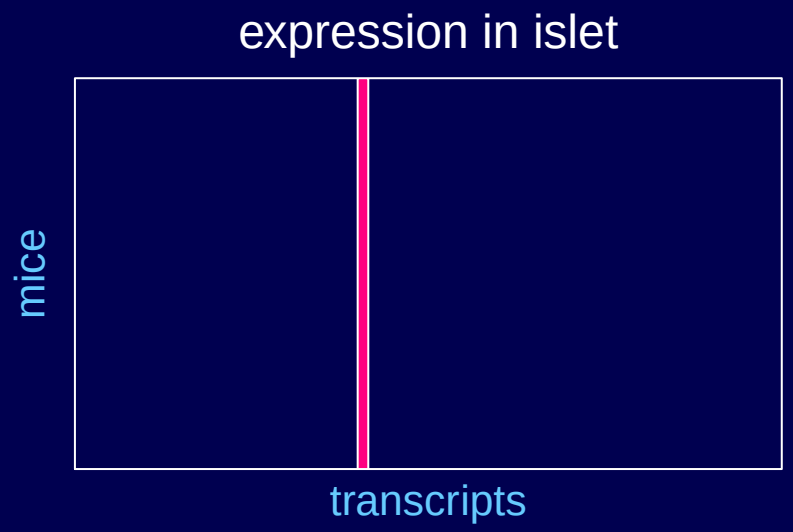

expression in liver
mice
transcripts

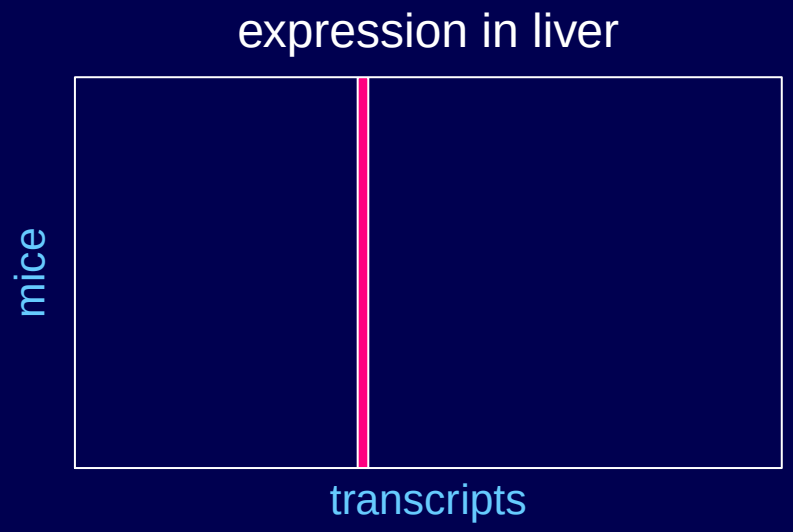
E vs E

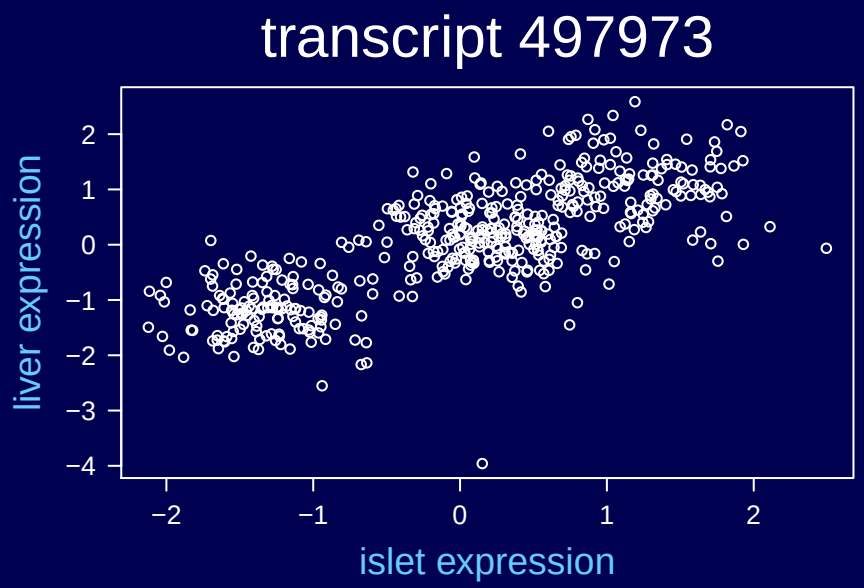

expression in islet
mice
transcripts
expression in liver
mice
transcripts


Mouse3280
liver expression
20
15
10
5
0
-5
-10
-15
-5
0
5
islet expression

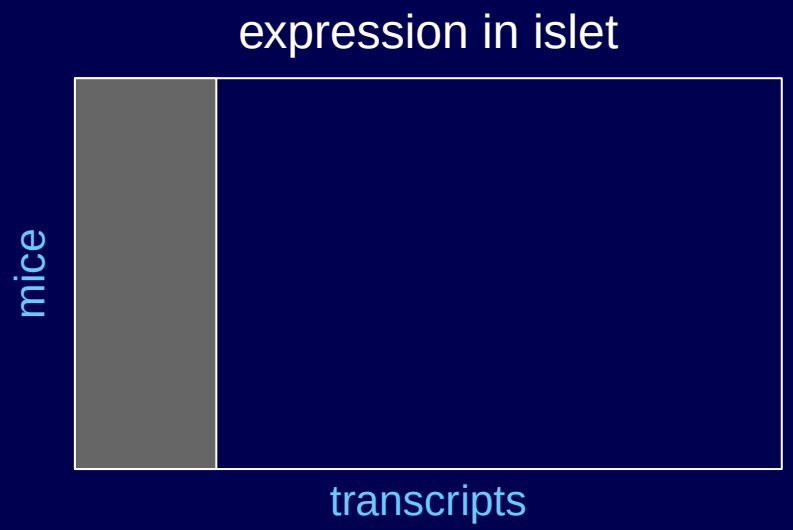
E vs E

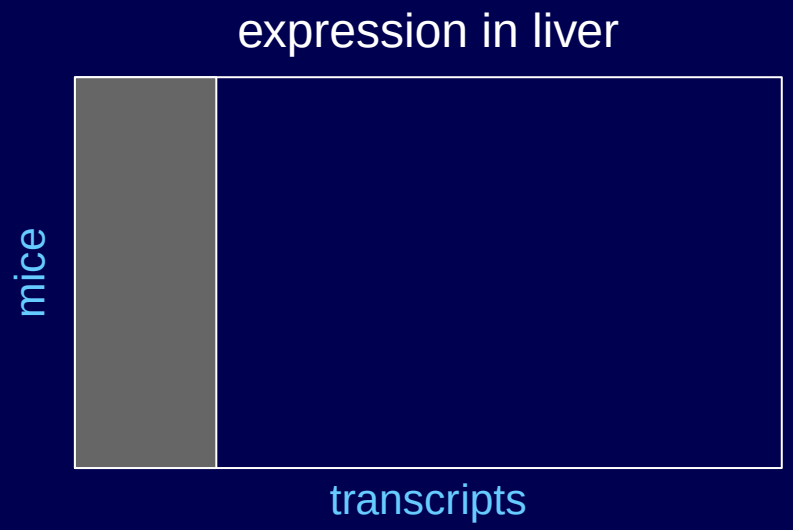

expression in islet
mice
transcripts


expression in liver
mice
transcripts

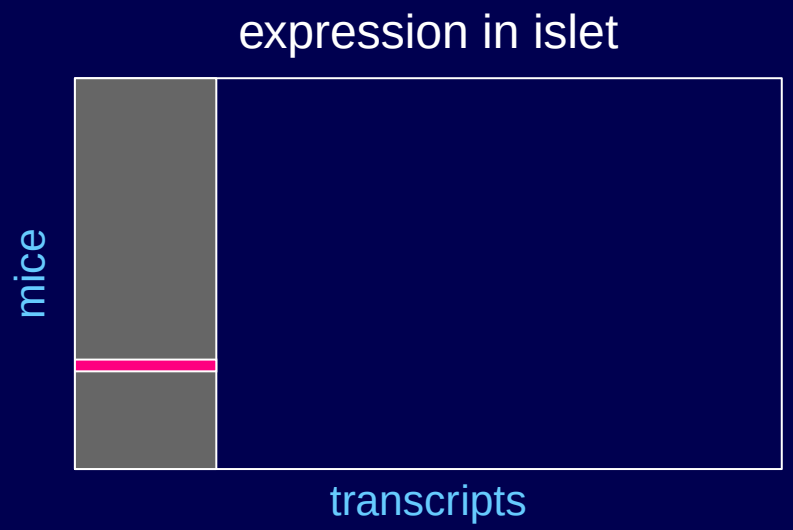

transcript 497973
liver expression
islet expression
2
1
0
−1
−2
−3
−4
−2
−1
0
1
2

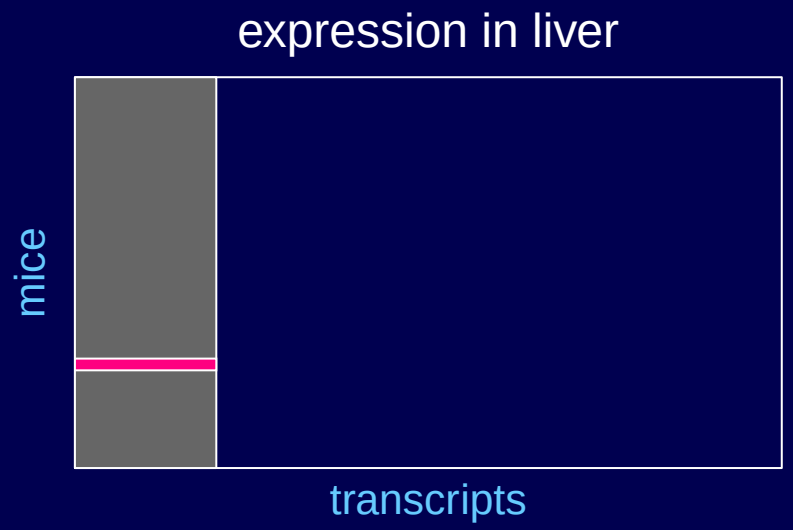
E vs E

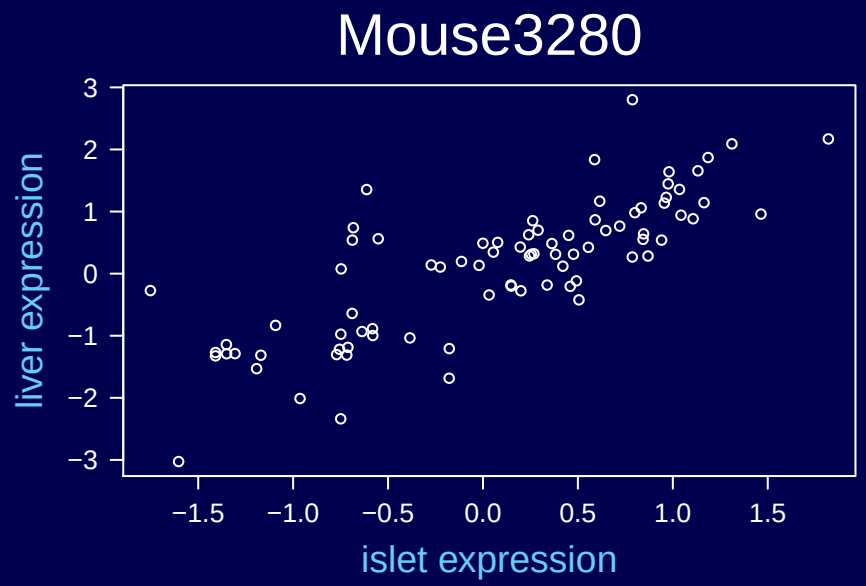

expression in islet
mice
transcripts


expression in liver
mice
transcripts

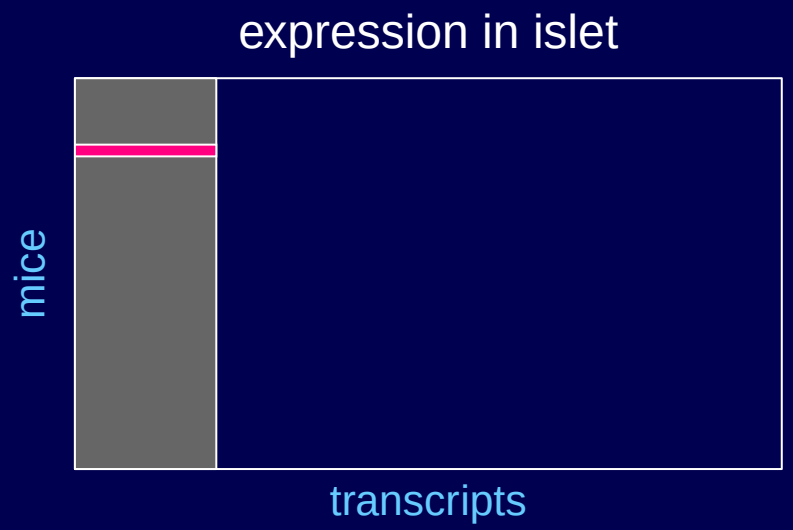
E vs E

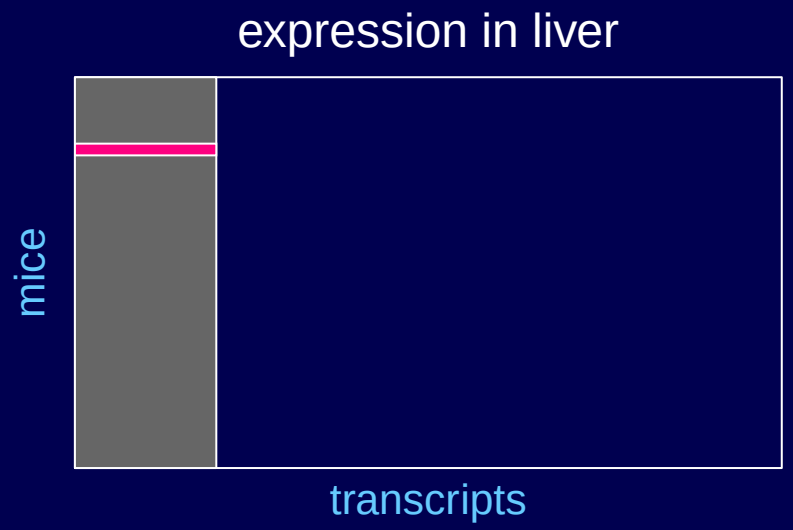

expression in islet
mice
transcripts

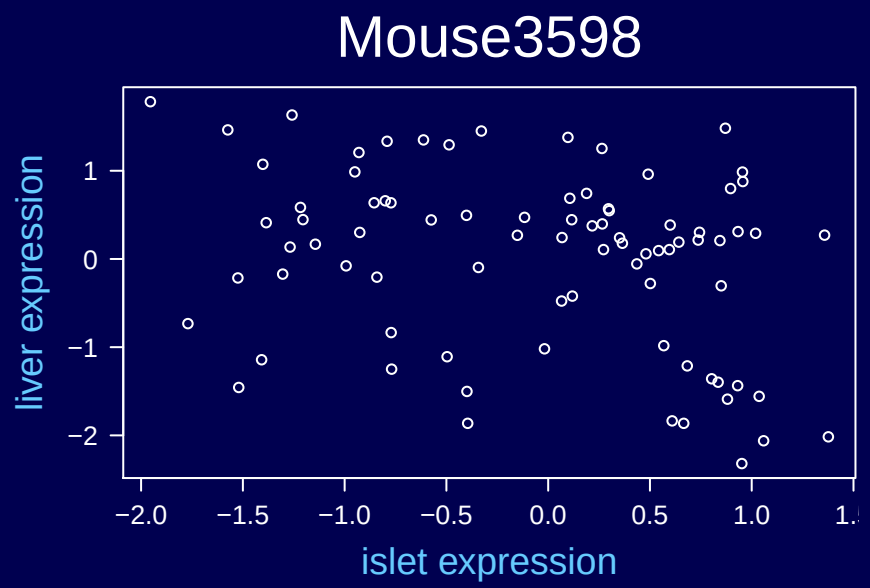

expression in liver
mice
transcripts


Mouse3280
liver expression
islet expression
3
2
1
0
−1
−2
−3
−1.5
−1.0
−0.5
0.0
0.5
1.0
1.5

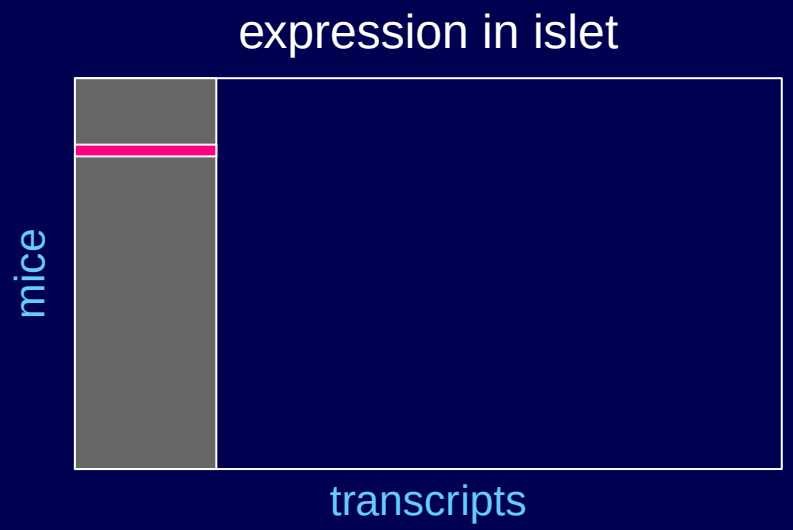
E vs E

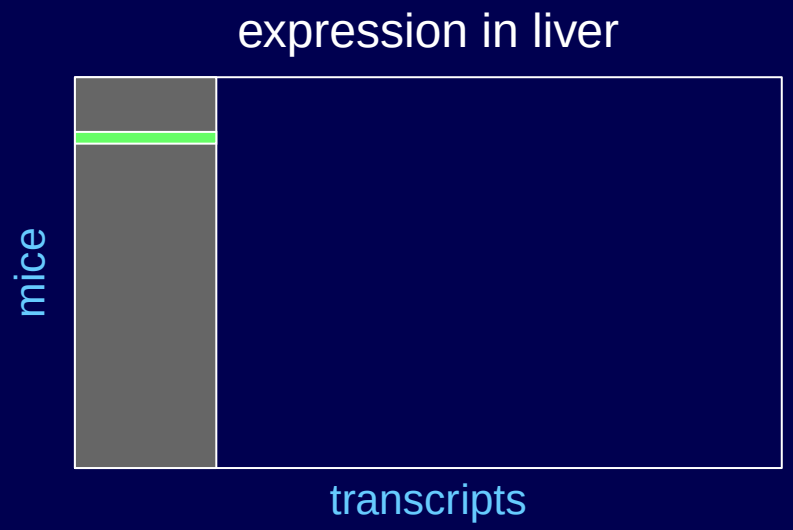

expression in islet
mice
transcripts

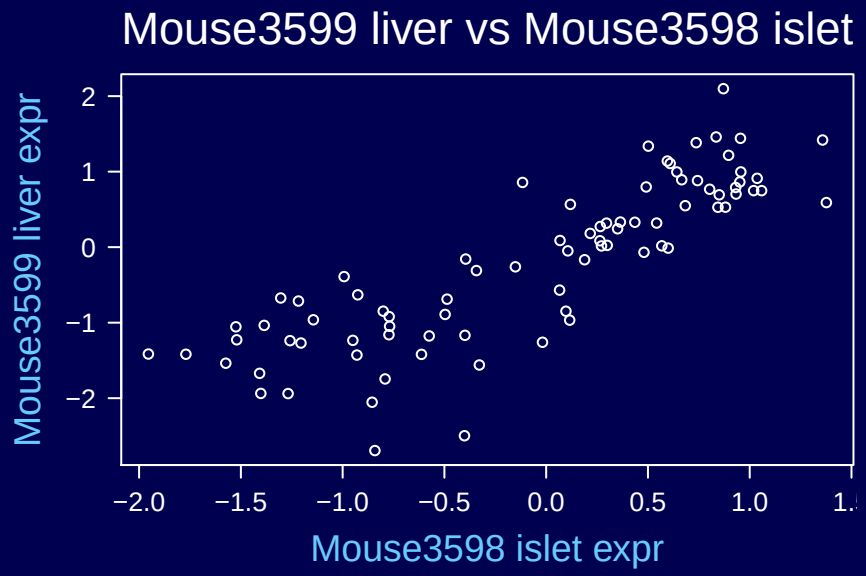

expression in liver
mice
transcripts


Mouse3598
liver expression
1
0
−1
−2
−2.0
−1.5
−1.0
−0.5
0.0
0.5
1.0
islet expression

E vs E

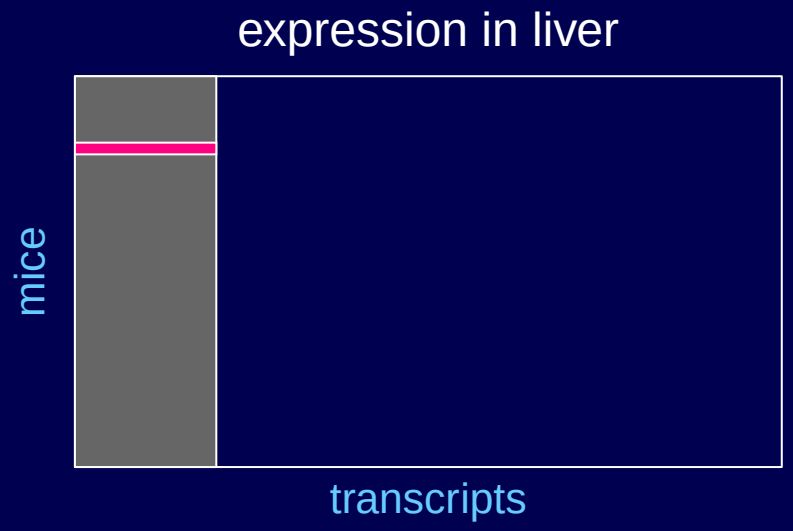

expression in islet
mice
transcripts

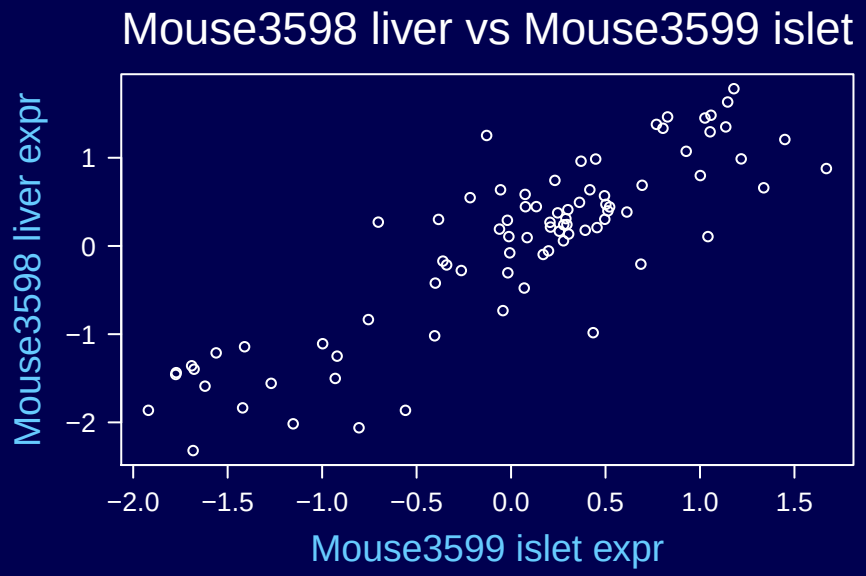

expression in liver
mice
transcripts


Mouse3599 liver vs Mouse3598 islet
Mouse3599 liver expr
2
1
0
−1
−2
−2.0
−1.5
−1.0
−0.5
0.0
0.5
1.0
Mouse3598 islet expr

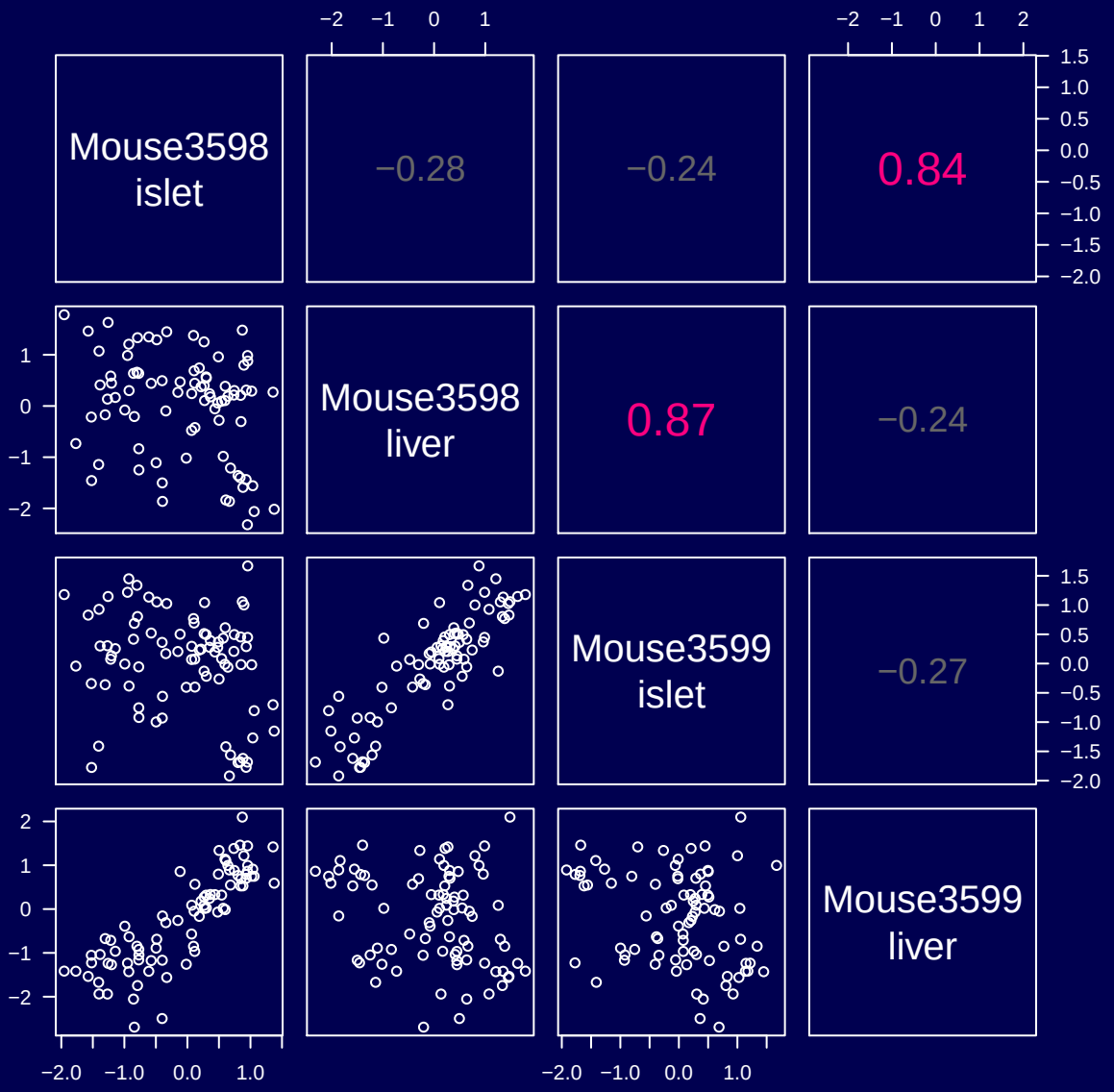
E vs E


expression in islet
mice
transcripts

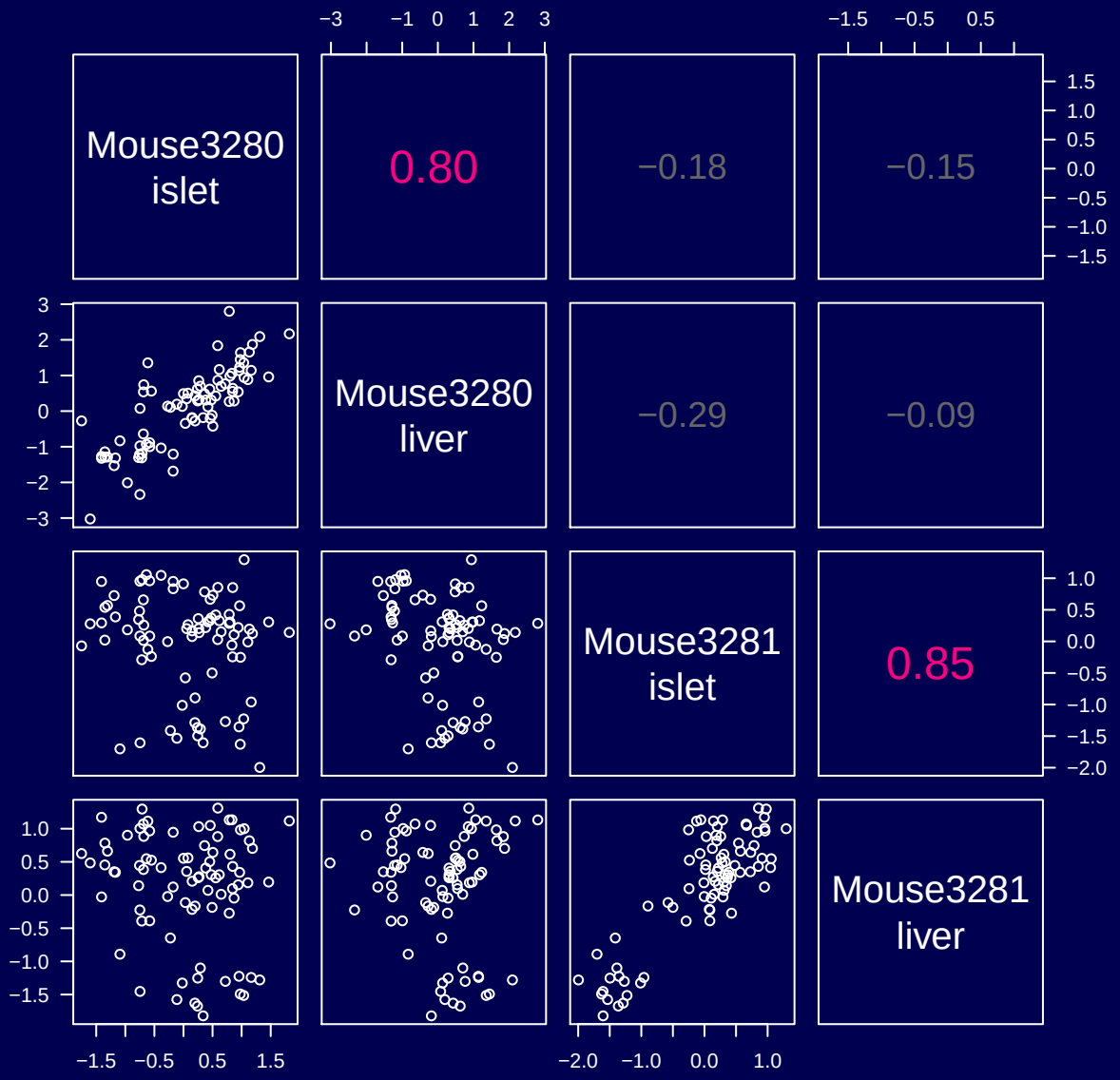

expression in liver
mice
transcripts


Mouse3598 liver vs Mouse3599 islet
Mouse3598 liver expr
Mouse3599 islet expr
1
0
−1
−2
−2.0
−1.5
−1.0
−0.5
0.0
0.5
1.0
1.5

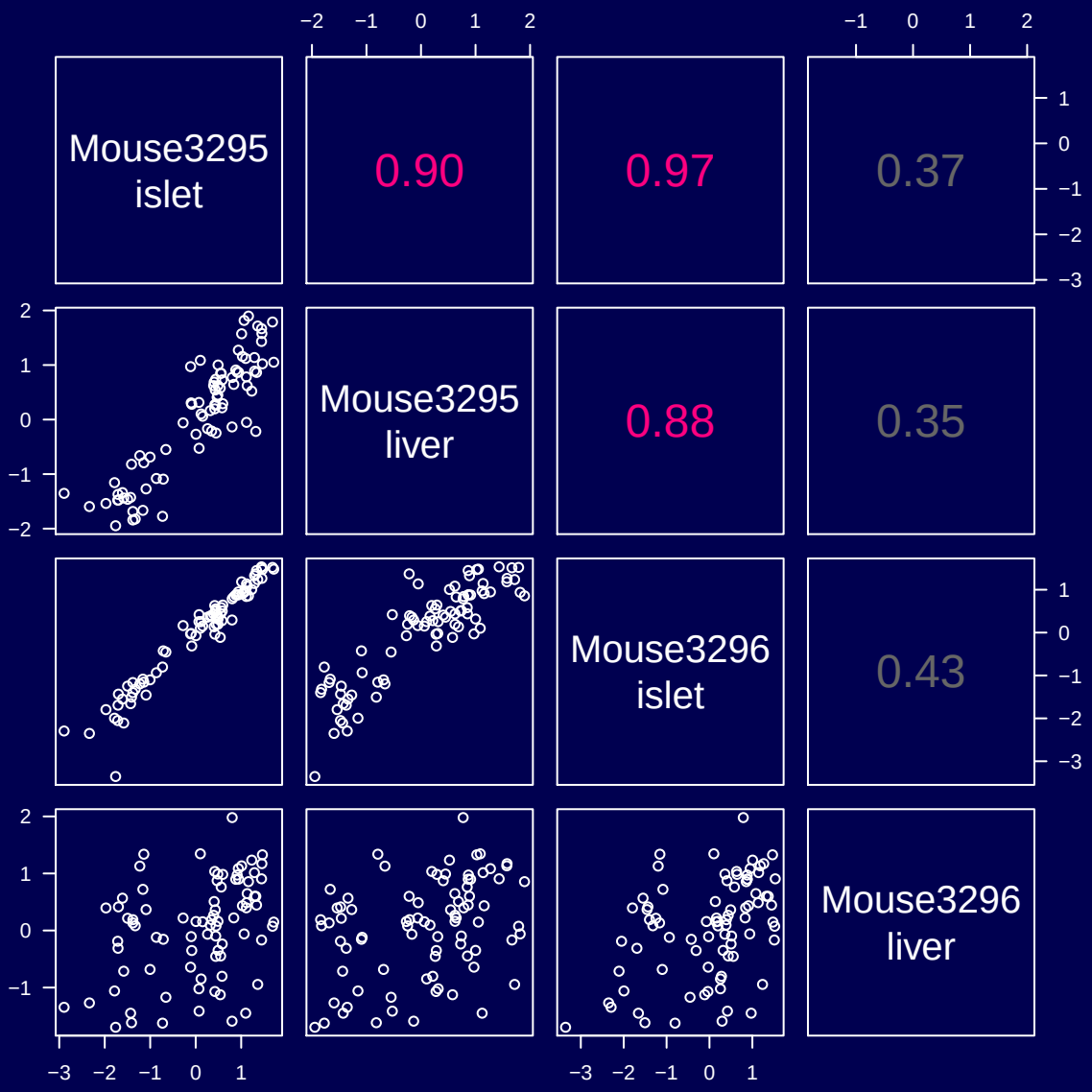
E vs E


Mouse3598 islet
−0.28
−0.24
0.84
Mouse3598 liver
0.87
−0.24
Mouse3599 islet
−0.27
Mouse3599 liver

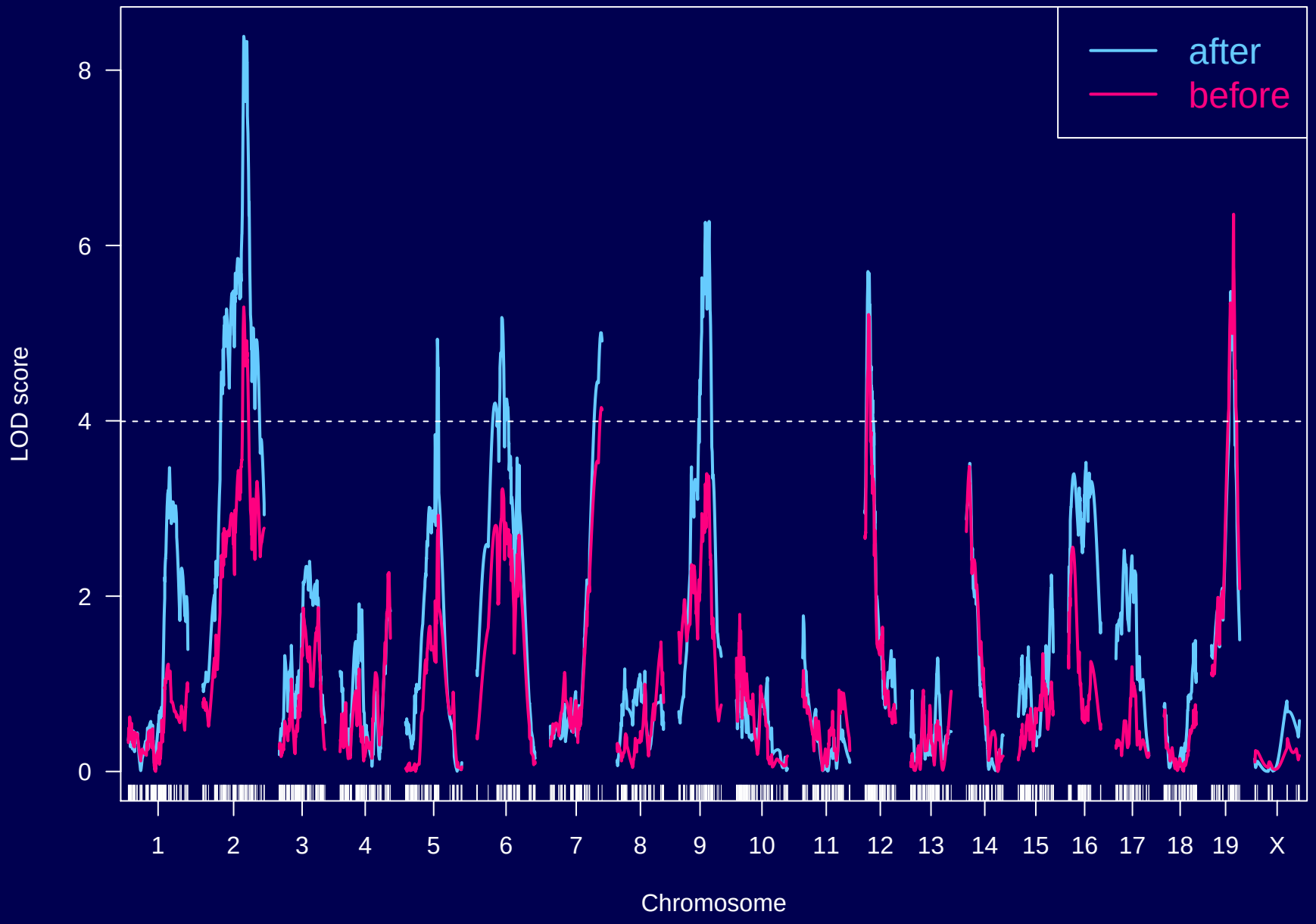
E vs E


Mouse3280 islet
0.80
−0.18
−0.15
Mouse3280 liver
−0.29
−0.09
Mouse3281 islet
0.85
Mouse3281 liver

E vs E


Mouse3295 islet
0.90
0.97
0.37
Mouse3295 liver
0.88
0.35
Mouse3296 islet
0.43
Mouse3296 liver

Insulin QTL


after
before
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

Summary

- Sample mix-ups happen
- With eQTL data, we can both identify and correct mix-ups
- There is great value in having expression on multiple tissues
- The general idea here has wide application for high-throughput data
- Very similar to MixupMapper (Westra et al., Bioinformatics 27:2104–2111, 2011)
  - Multiple tissues
  - Direct tissue-tissue comparisons
  - Predict genotype rather than expression phenotype

Acknowledgments

Alan Attie Mark Keller	Biochemistry, UW–Madison
Brian Yandell	Statistics and Horticulture, UW–Madison
Christina Kendziorski Aimee Teo Broman	Biostatistics & Medical Informatics, UW–Madison
Eric Schadt	Pacific Biosciences of California
Danielle Greenawalt Amit Kulkarni	Merck & Co., Inc.
Śaunak Sen	University of California, San Francisco

NIH: R01 GM074244, R01 DK066369