Sample mix-ups in eQTL data

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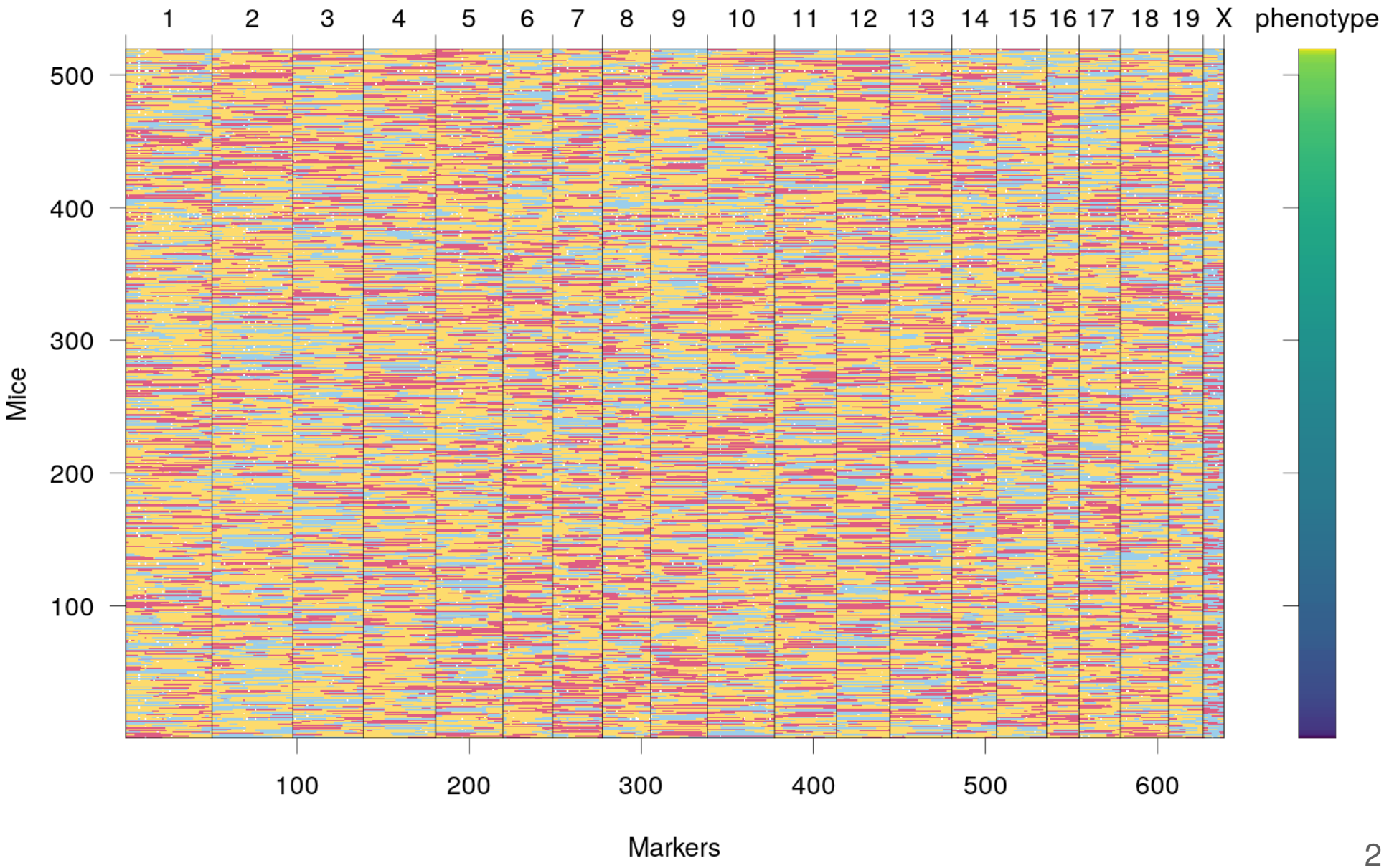
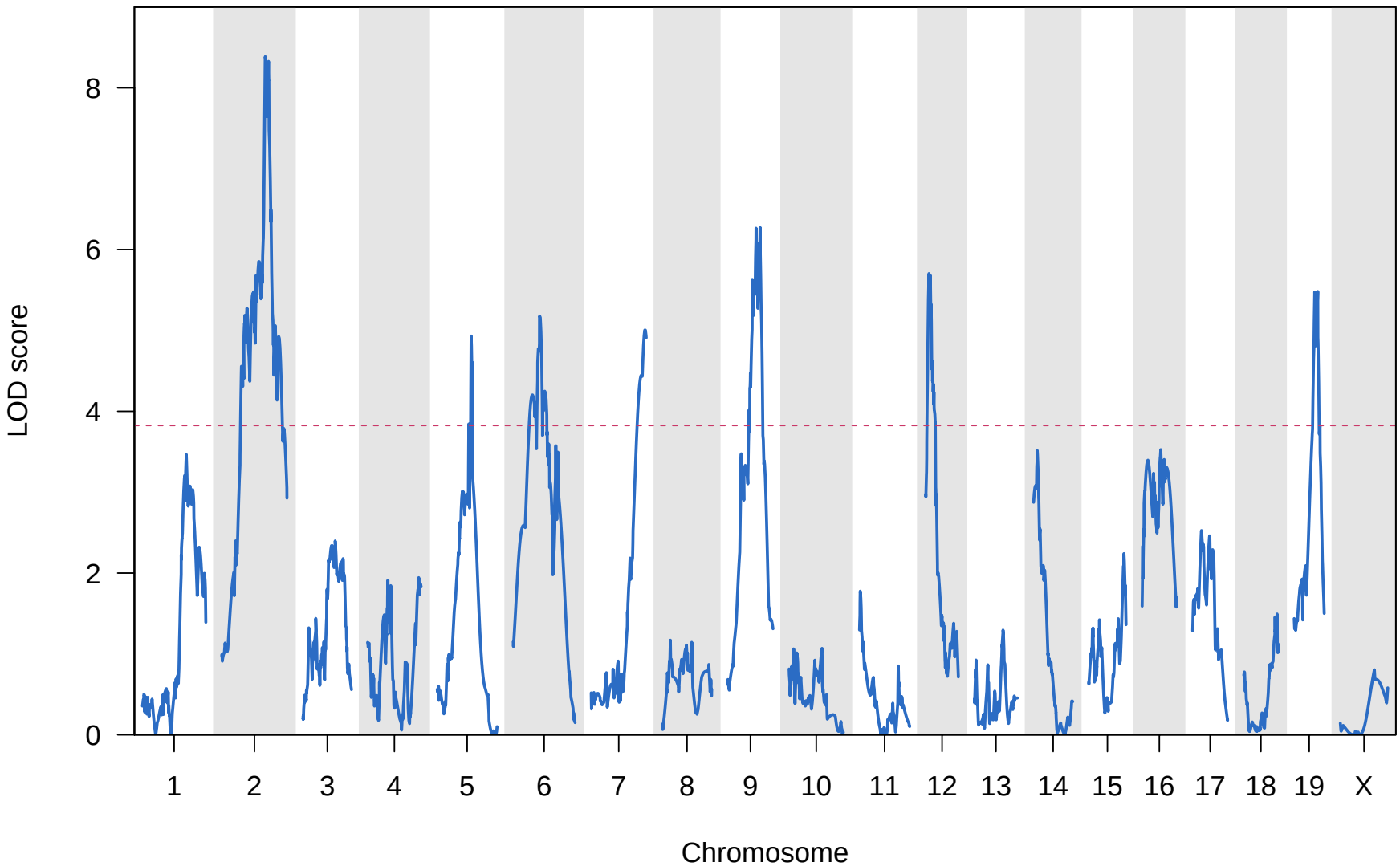
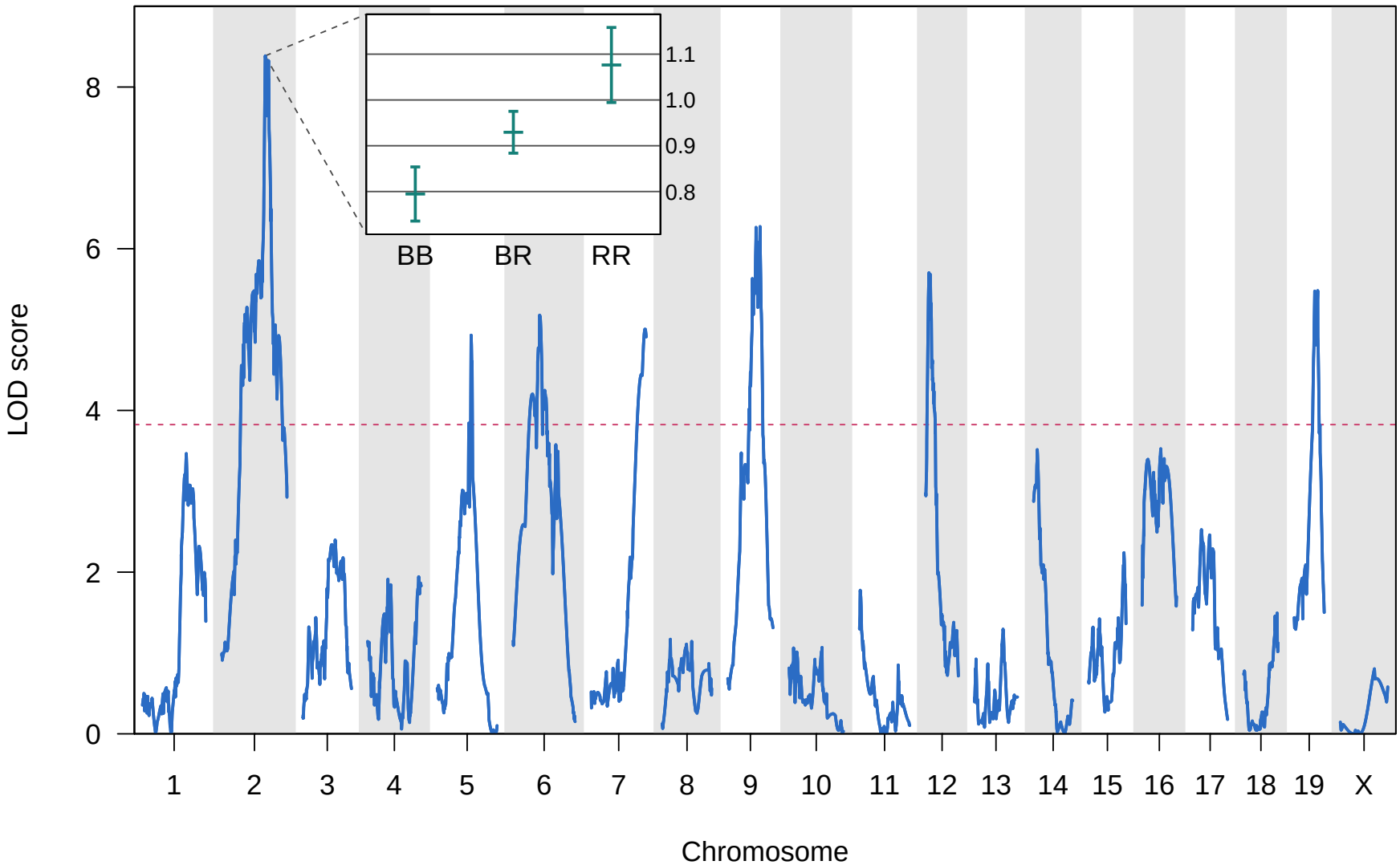
Data


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
phenotype
500
400
300
200
100
Mice
100
200
300
400
500
600
Markers

QTL mapping


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

QTL mapping


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
1.1
1.0
0.9
0.8
BB
BR
RR

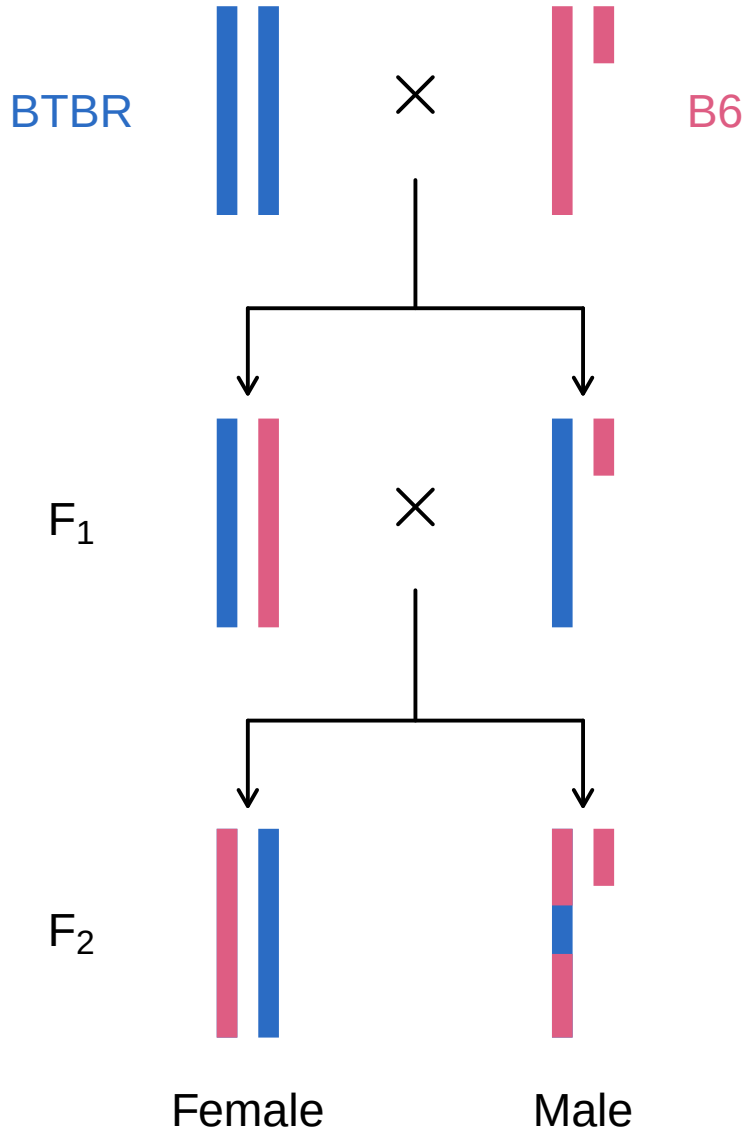
Attie project

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

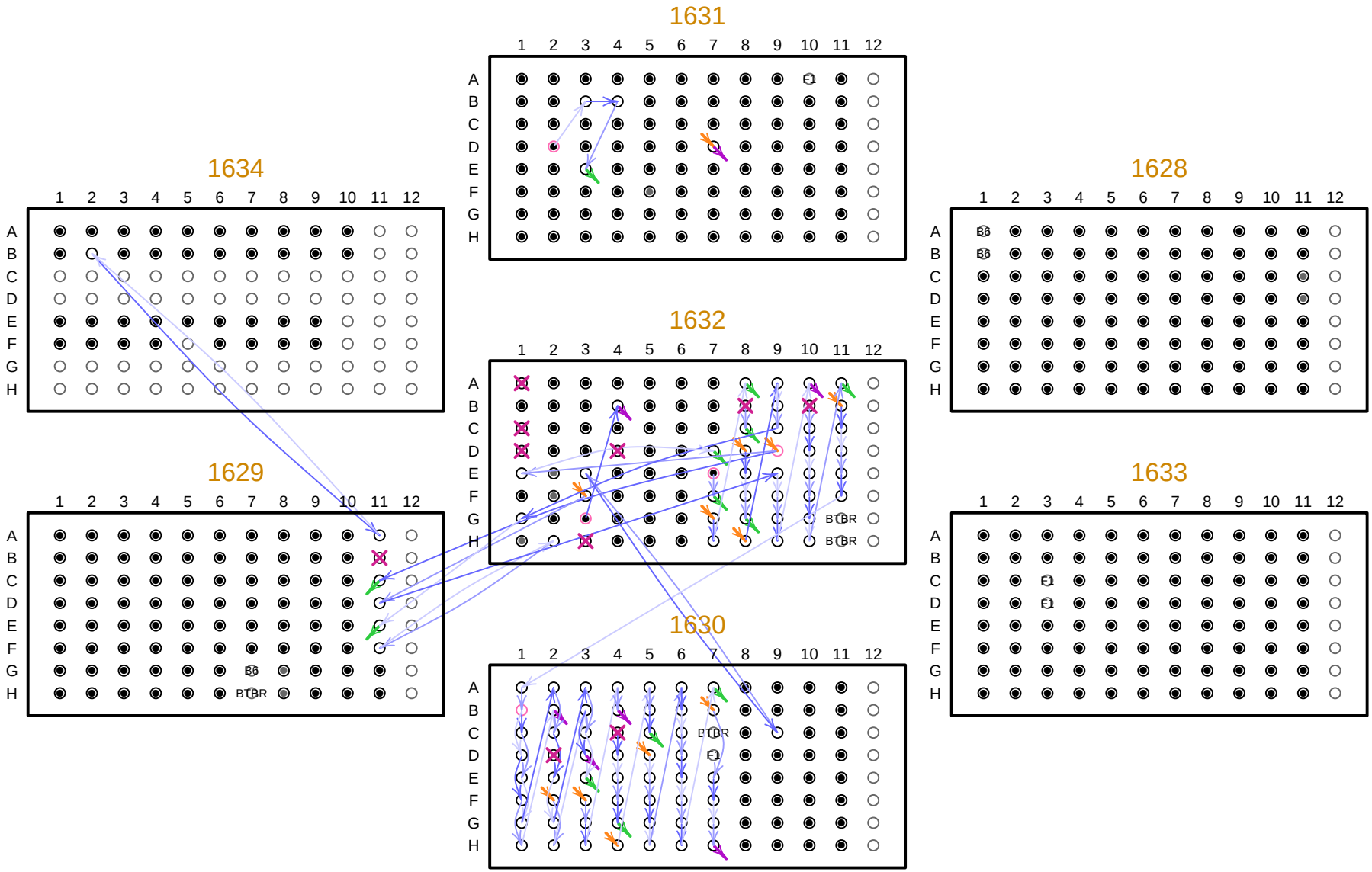
- Genotypes at 2057 SNPs (Affymetrix arrays)
- Gene expression in six tissues (Agilent arrays)
  - adipose
  - gastrocnemius muscle
  - hypothalamus
  - pancreatic islets
  - kidney
  - liver
- Numerous clinical phenotypes

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

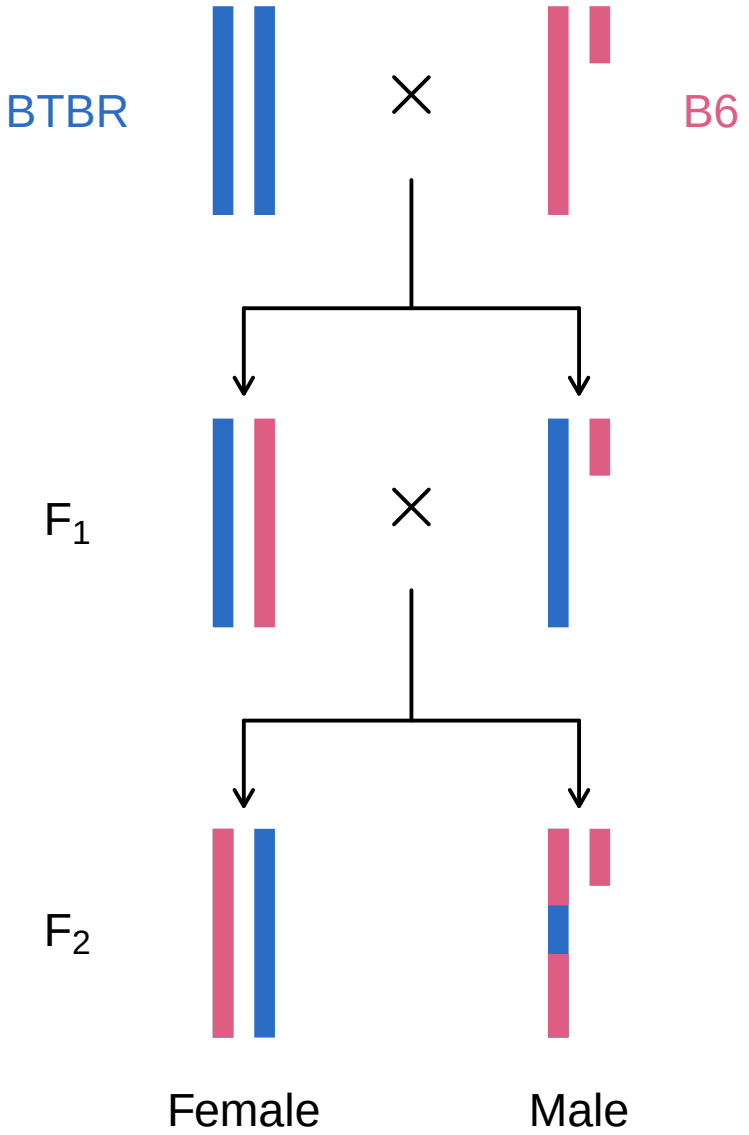
Sex and the X chr



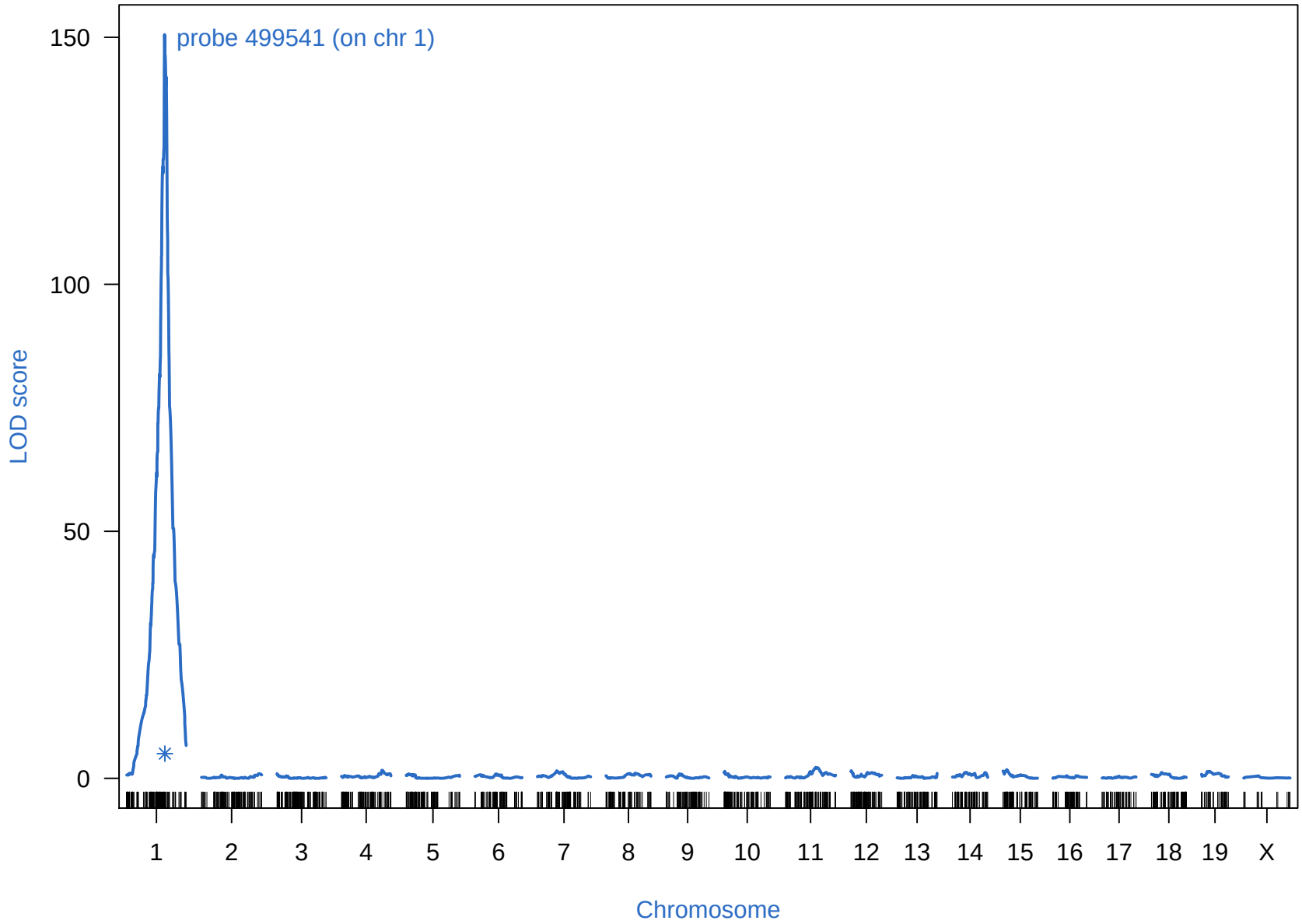
Genotype mix-ups



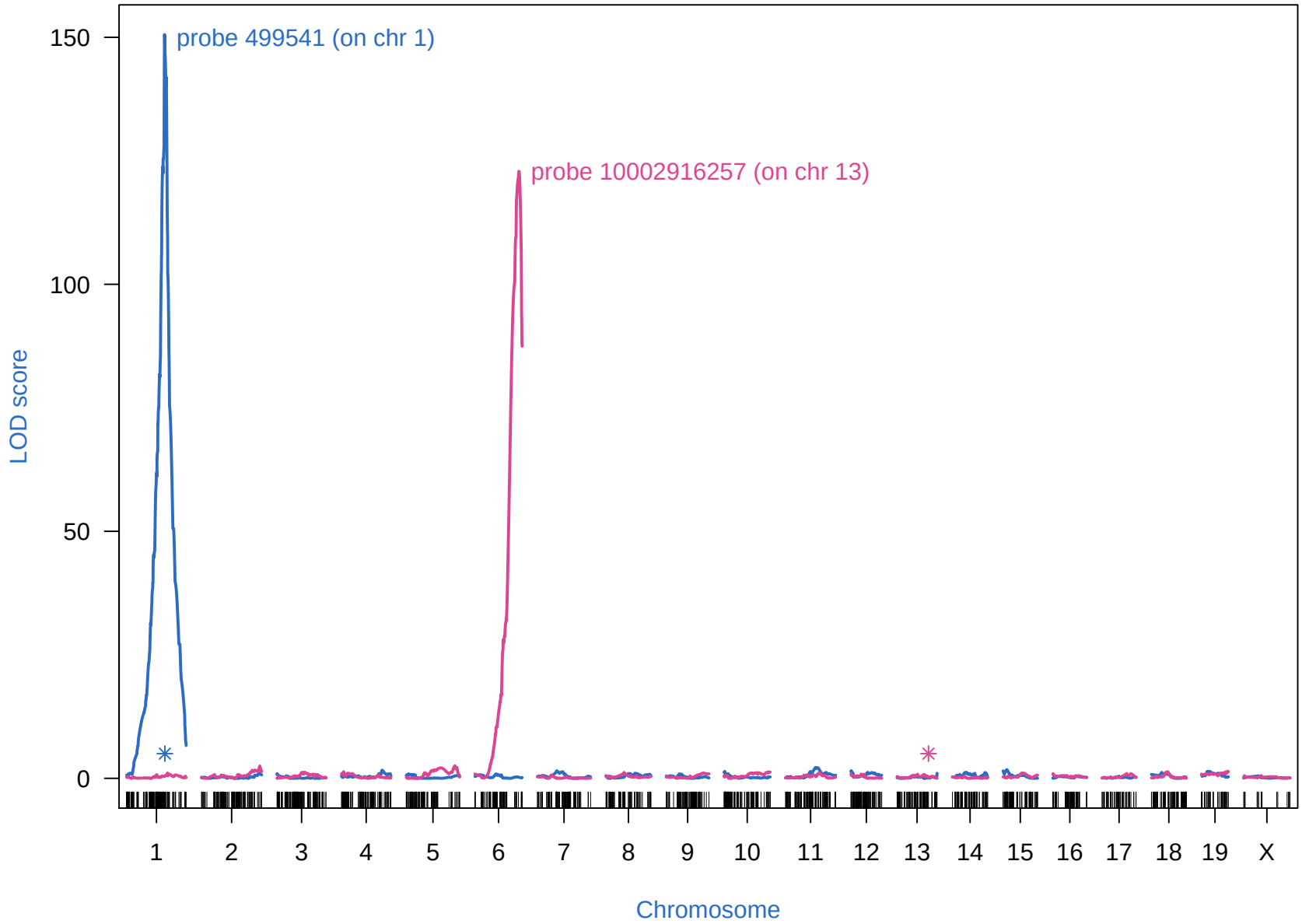
Sex and the X chr



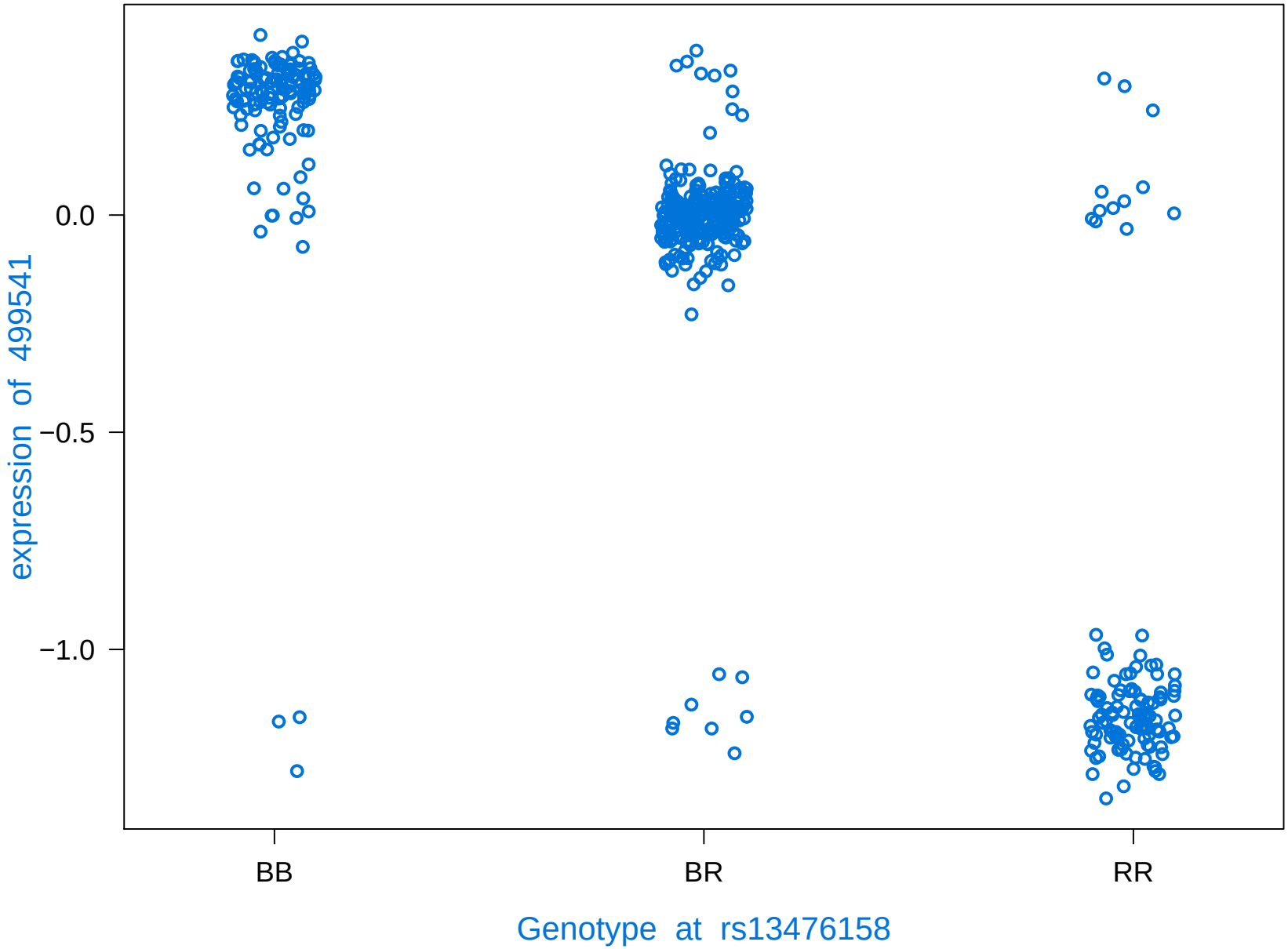
Strong eQTL


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

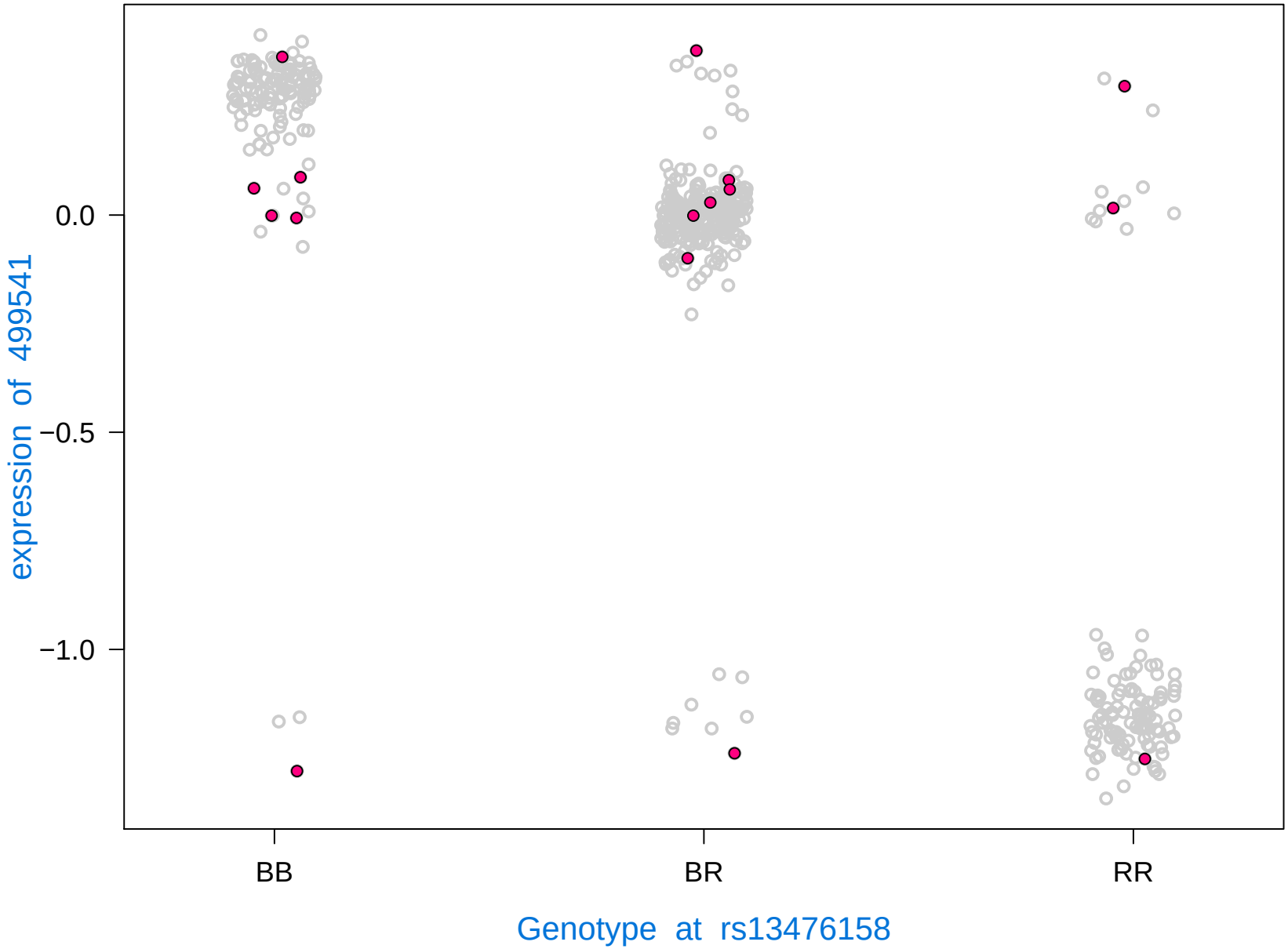
Strong eQTL


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

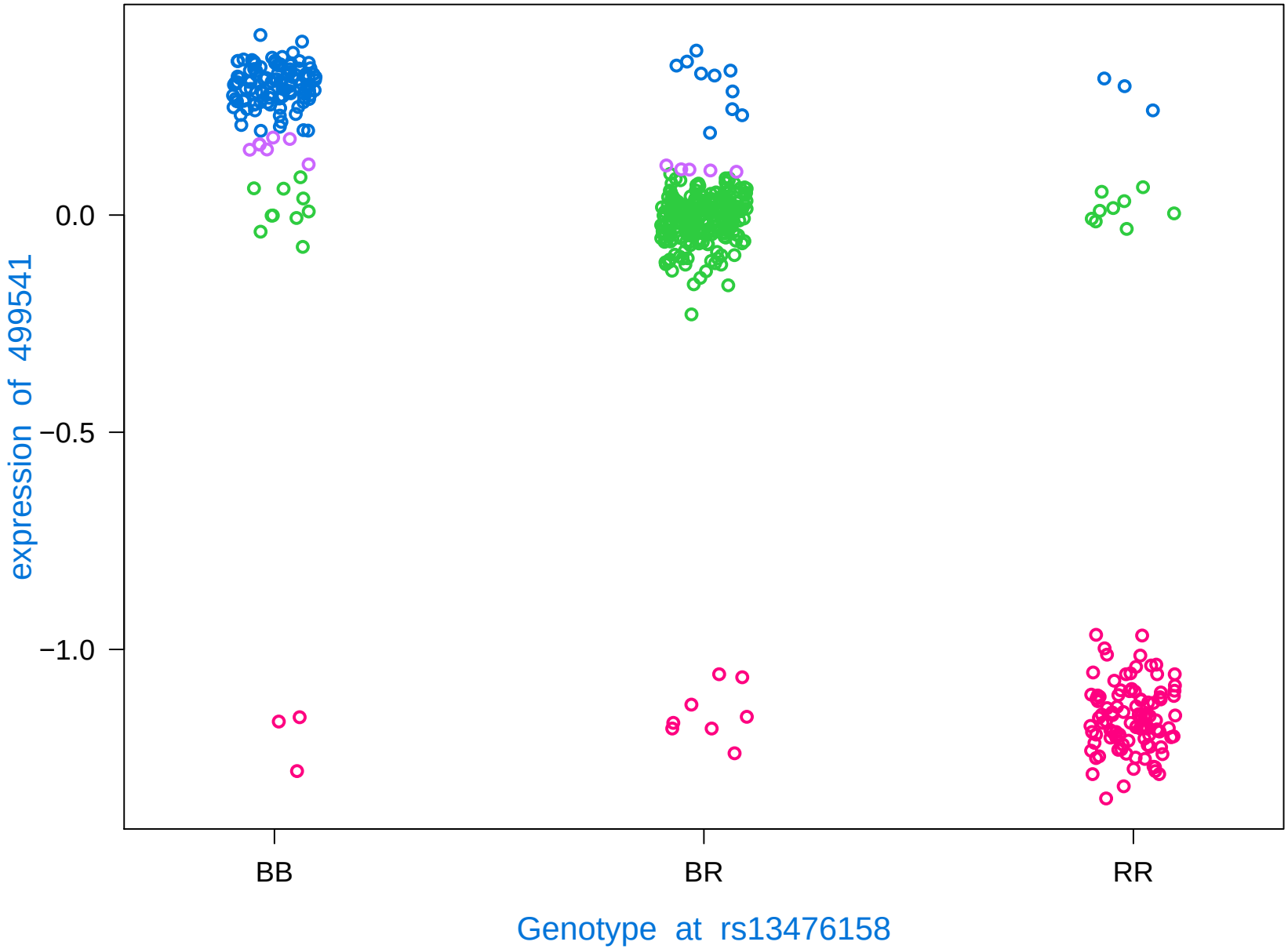
E vs G


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

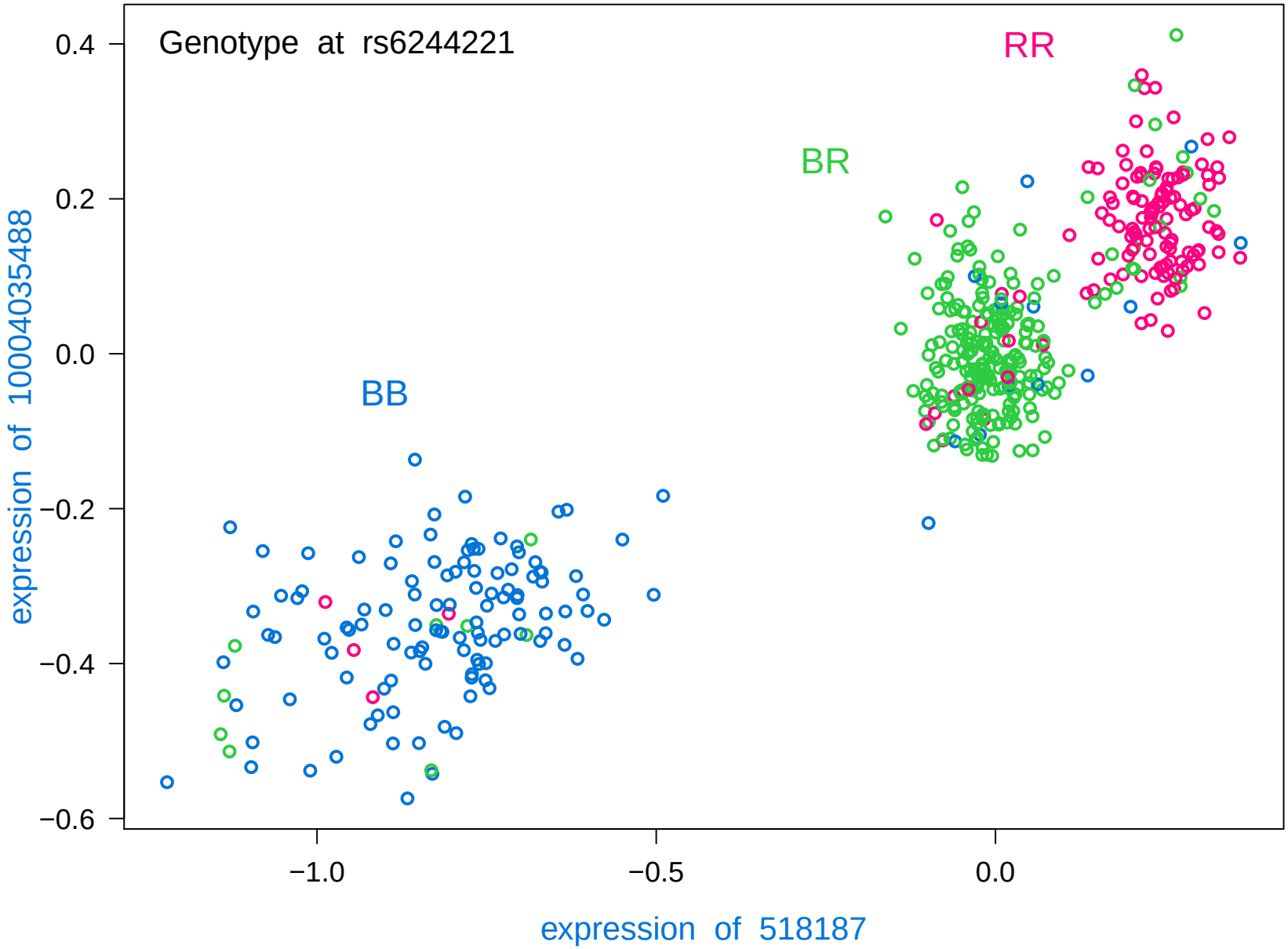
E vs G


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

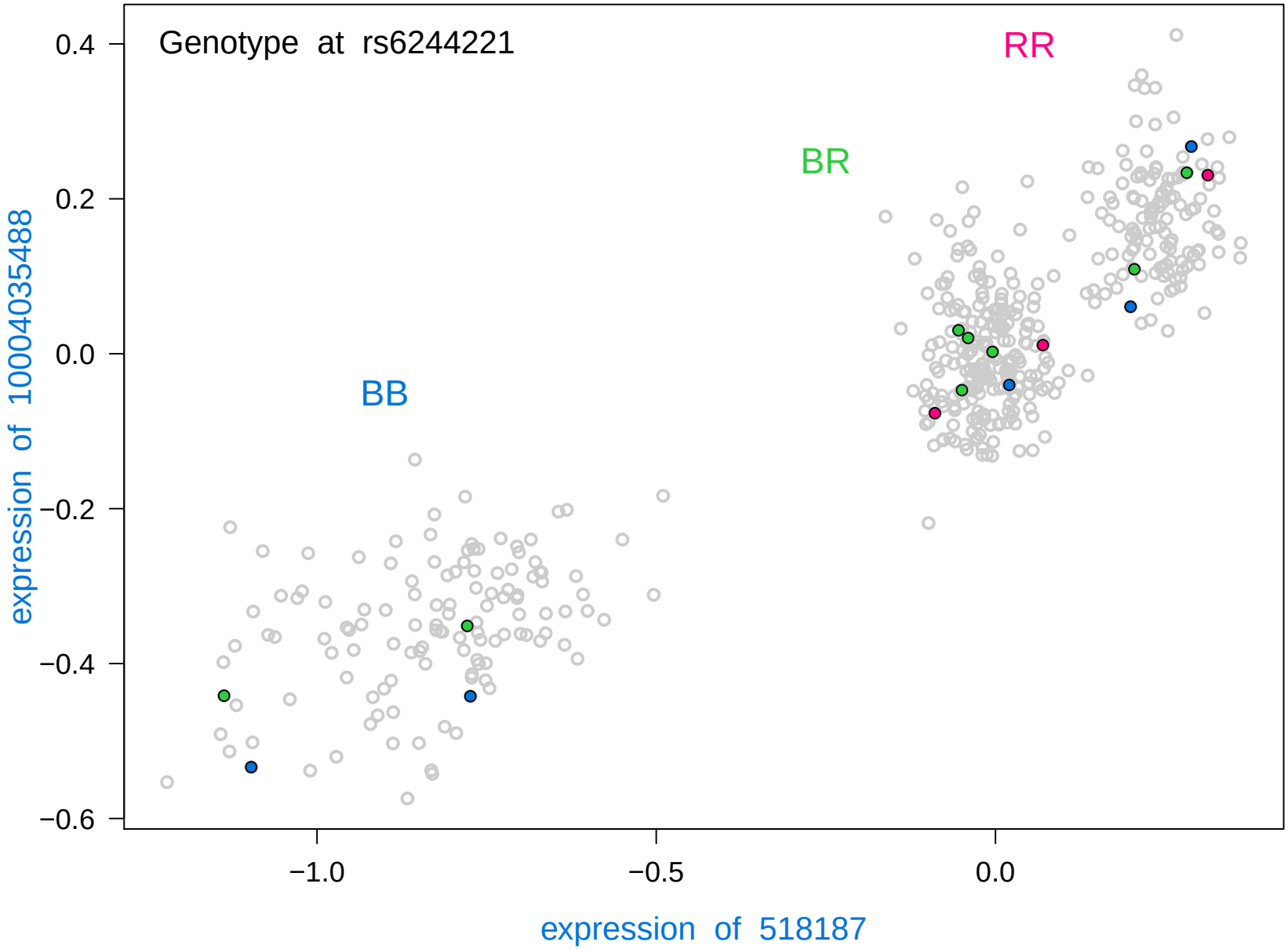
kNN classifier



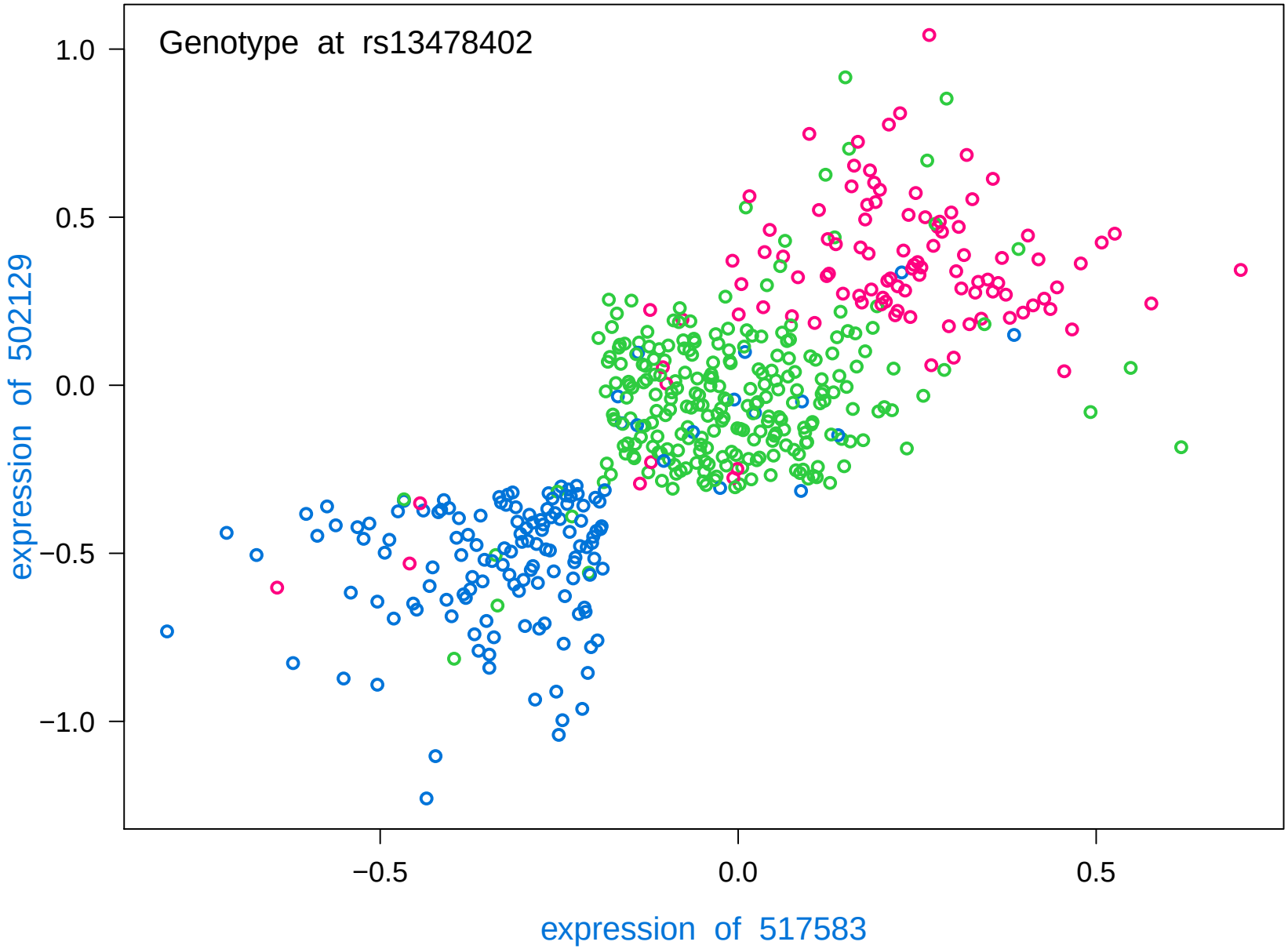
E vs G


Genotype at rs6244221
RR
BR
BB
0.4
0.2
0.0
−0.2
−0.4
−0.6
−1.0
−0.5
0.0
expression of 100040354 88
expression of 518187

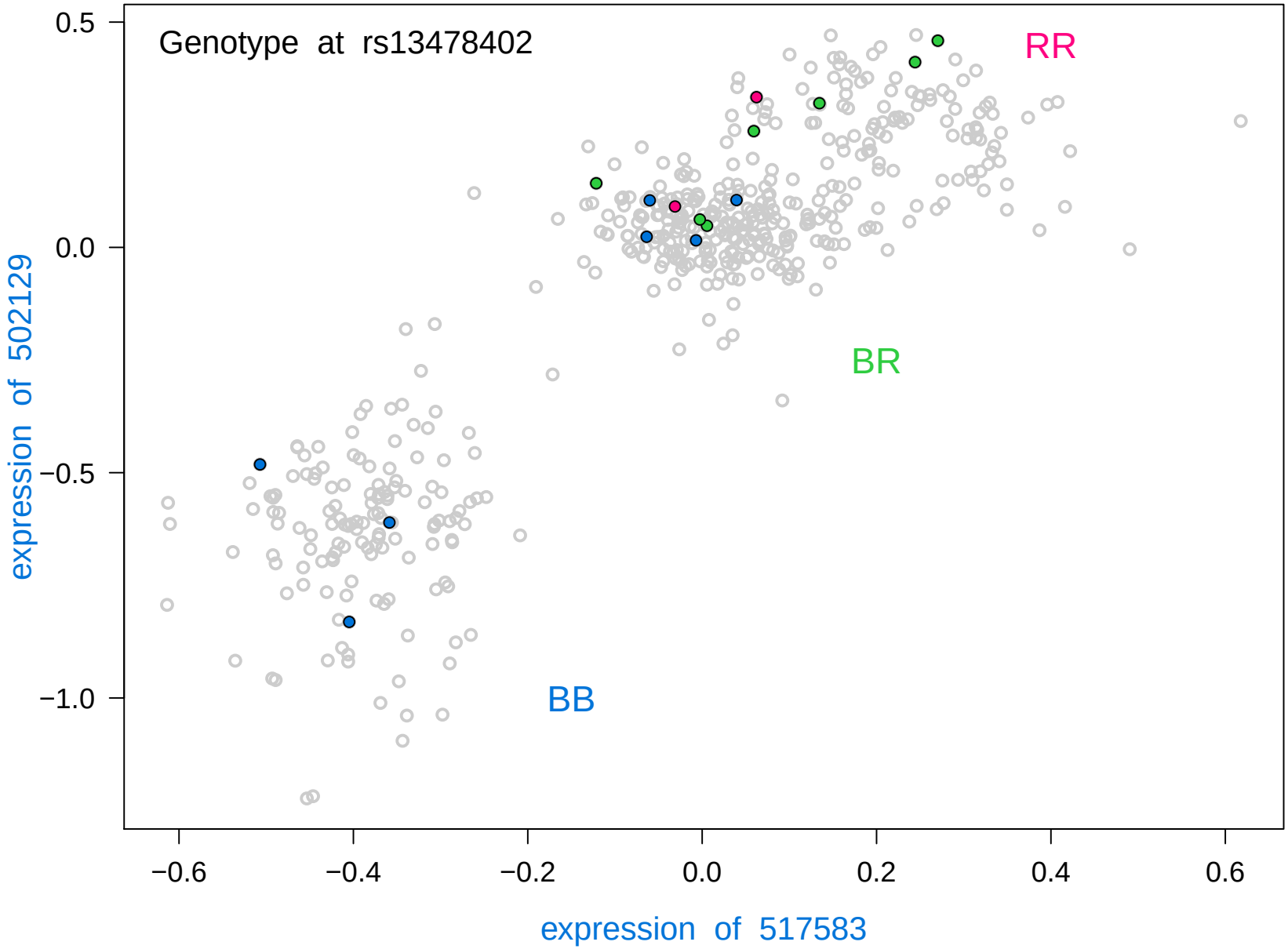
E vs G


Genotype at rs6244221
RR
BR
BB
0.4
0.2
0.0
−0.2
−0.4
−0.6
−1.0
−0.5
0.0
expression of 100040354 88
expression of 518187

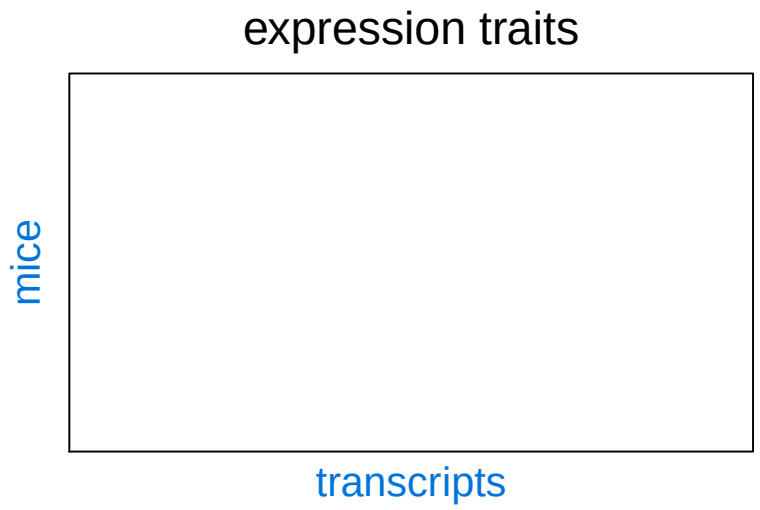
E vs G

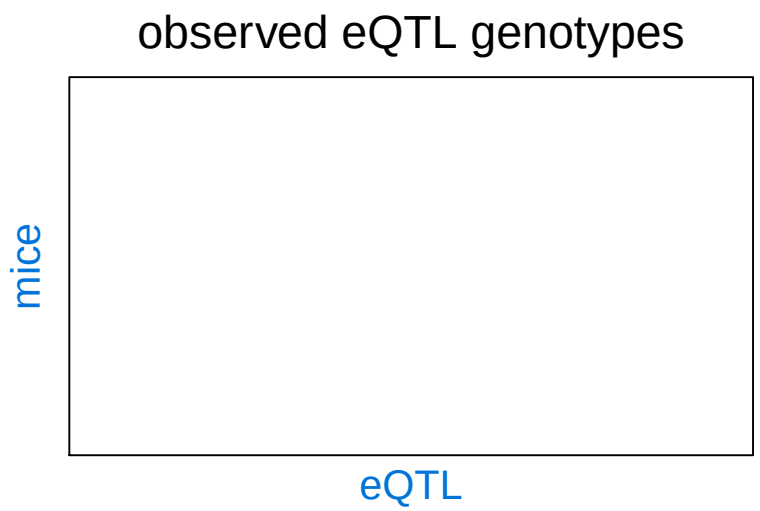

Genotype at rs13478402
1.0
0.5
0.0
−0.5
−1.0
expression of 502129
−0.5
0.0
0.5
expression of 517583

E vs G

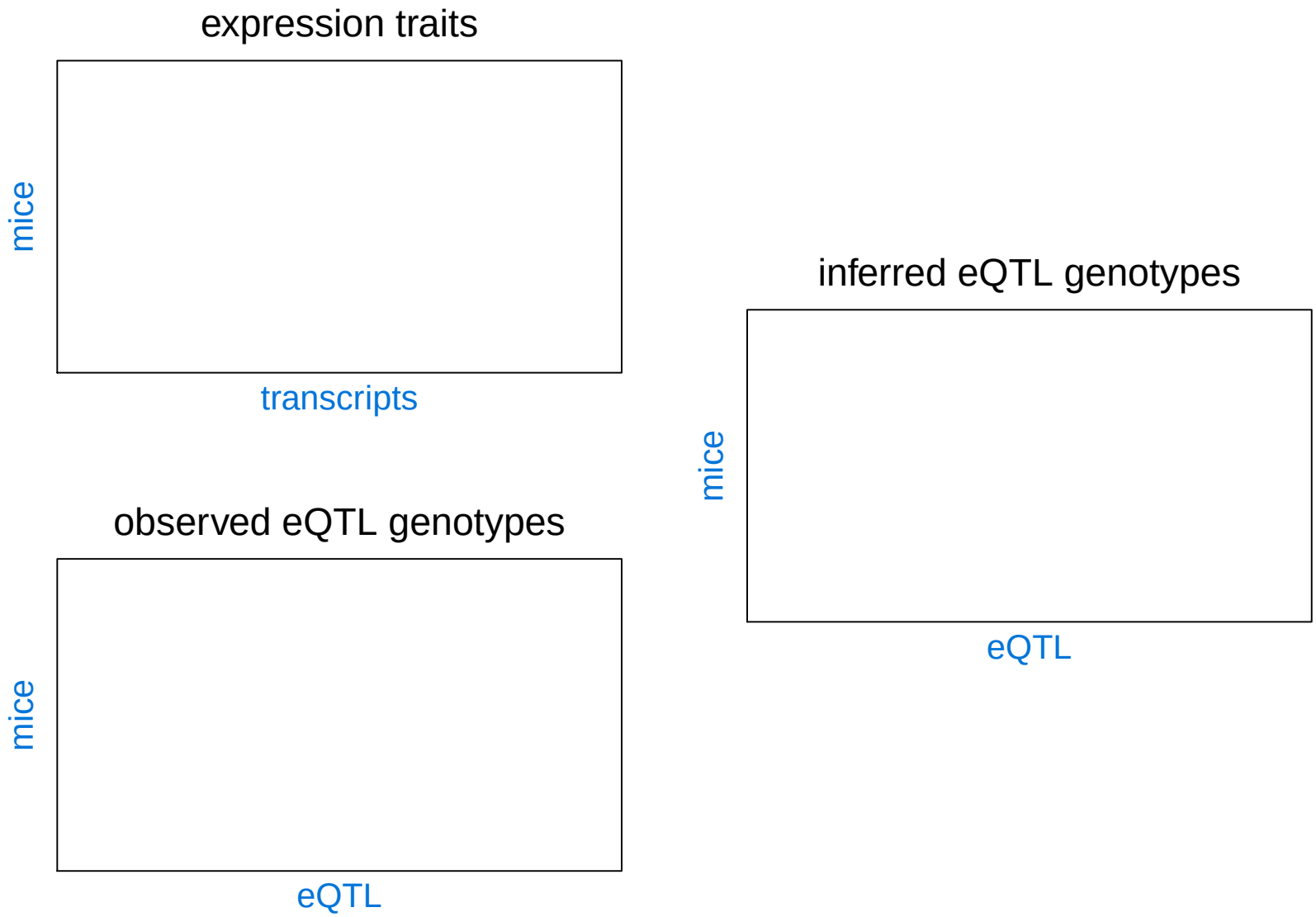

Genotype at rs13478402
RR
BR
BB
0.5
0.0
−0.5
−1.0
−0.6
−0.4
−0.2
0.0
0.2
0.4
0.6
expression of 502129
expression of 517583

Basic scheme

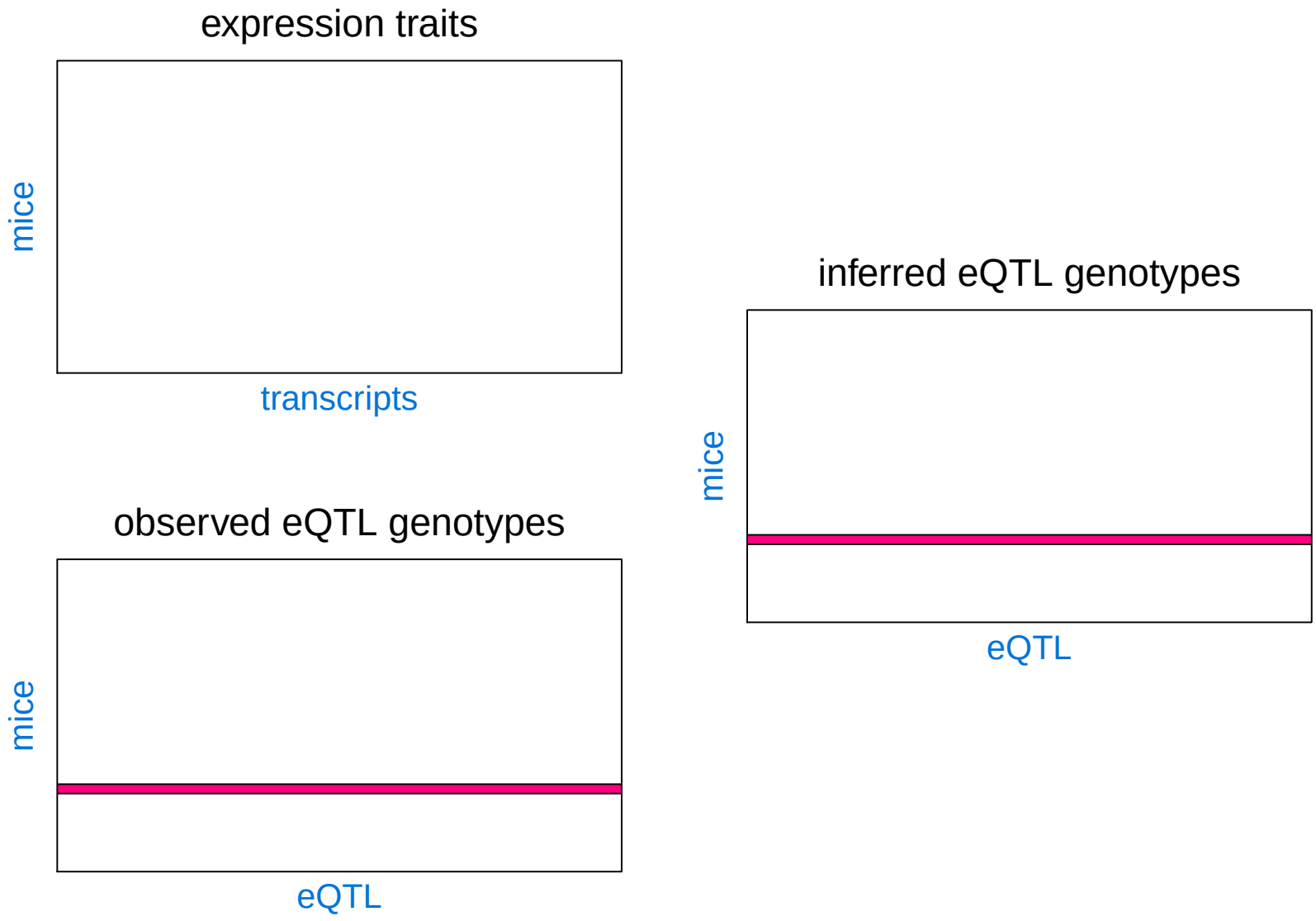




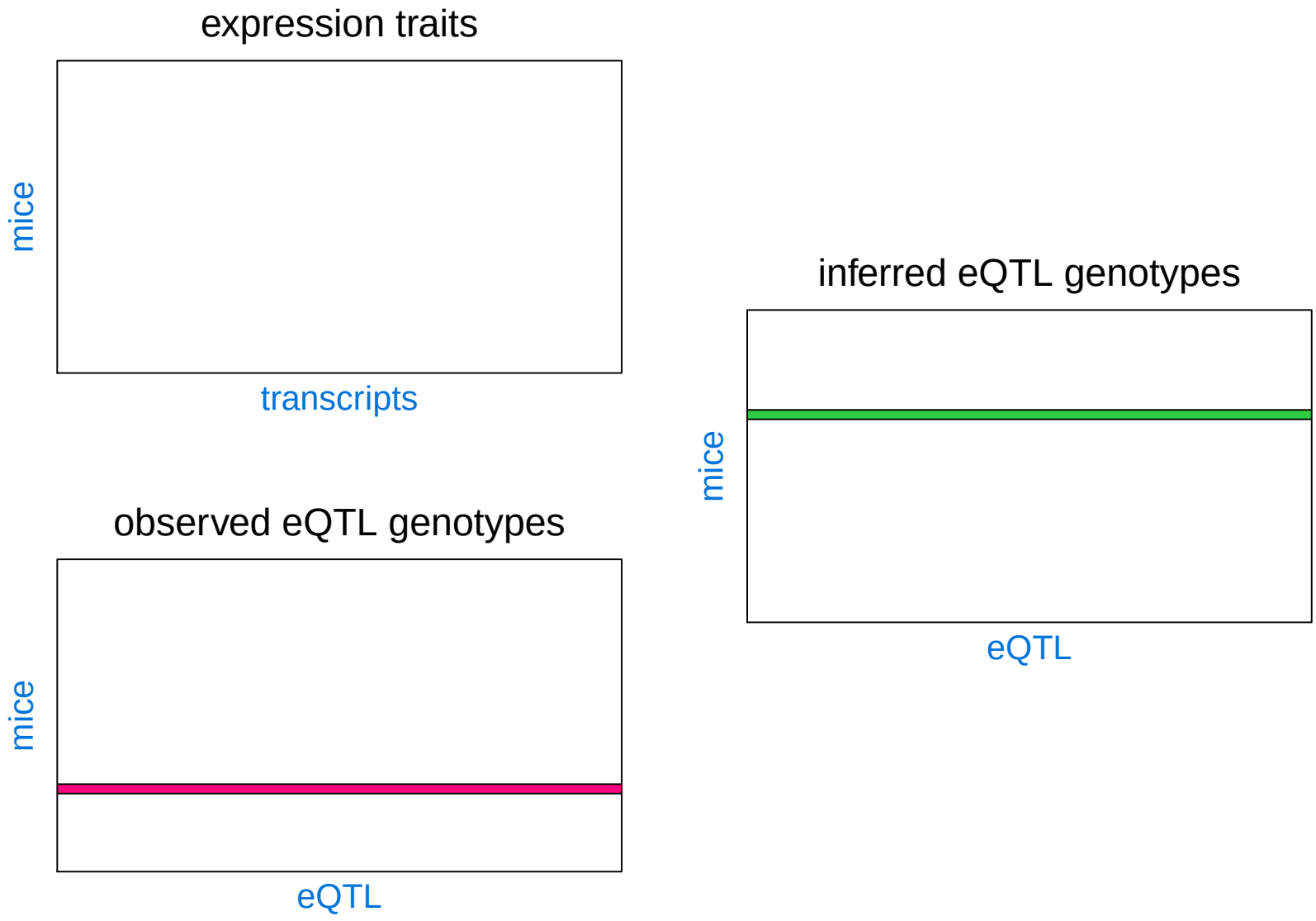
Basic scheme



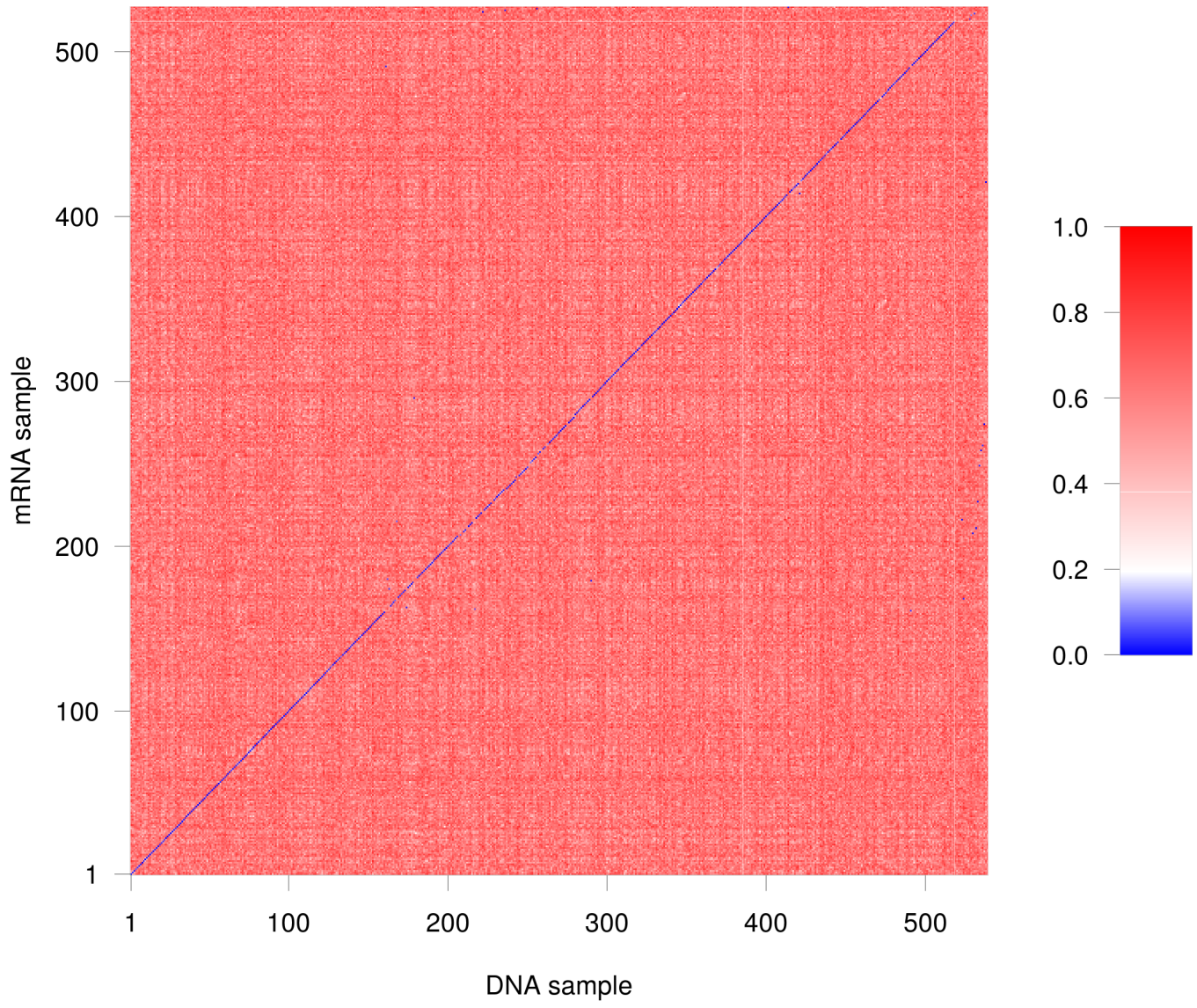
Basic scheme



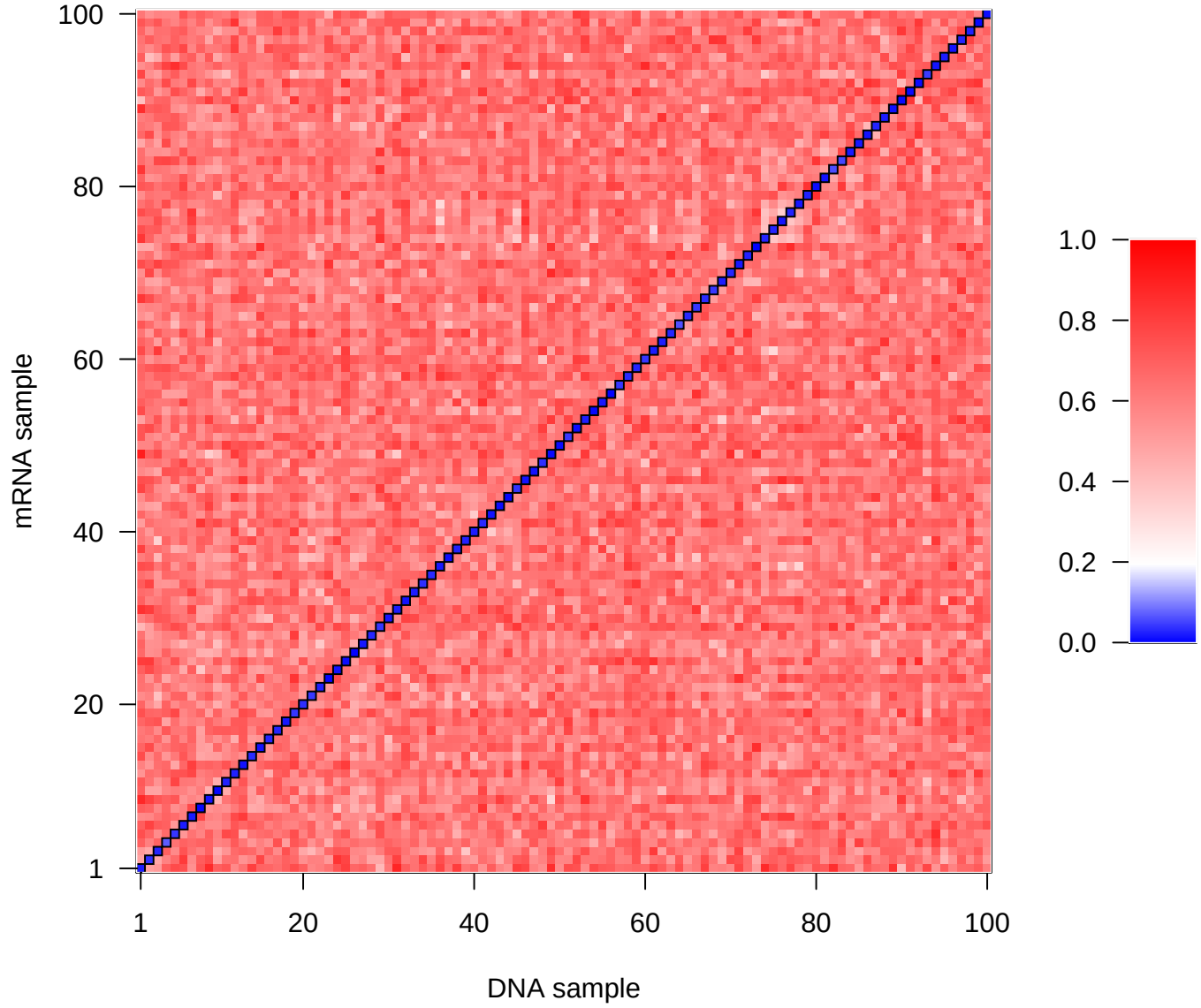
Basic scheme



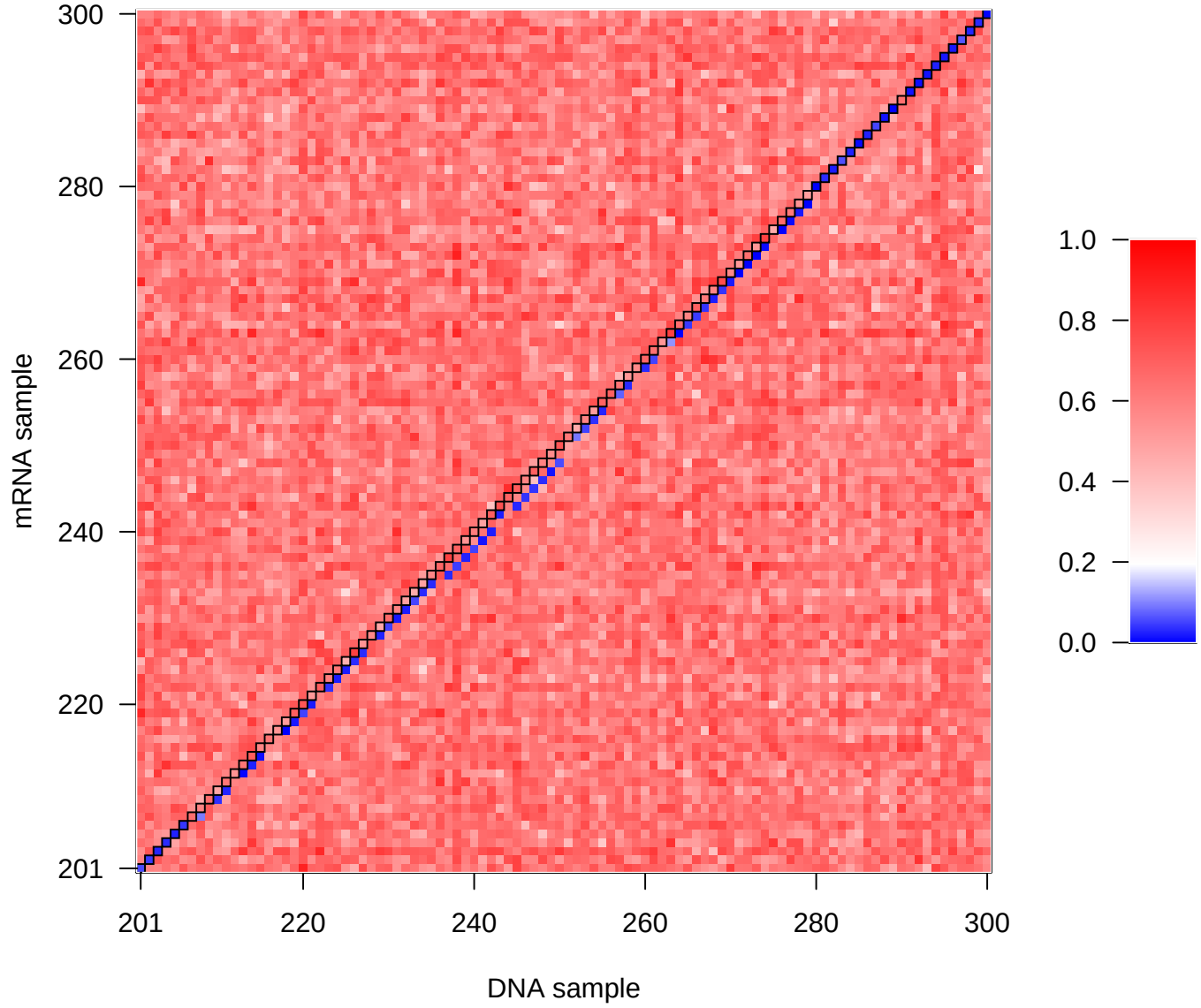
Prop’n mismatches



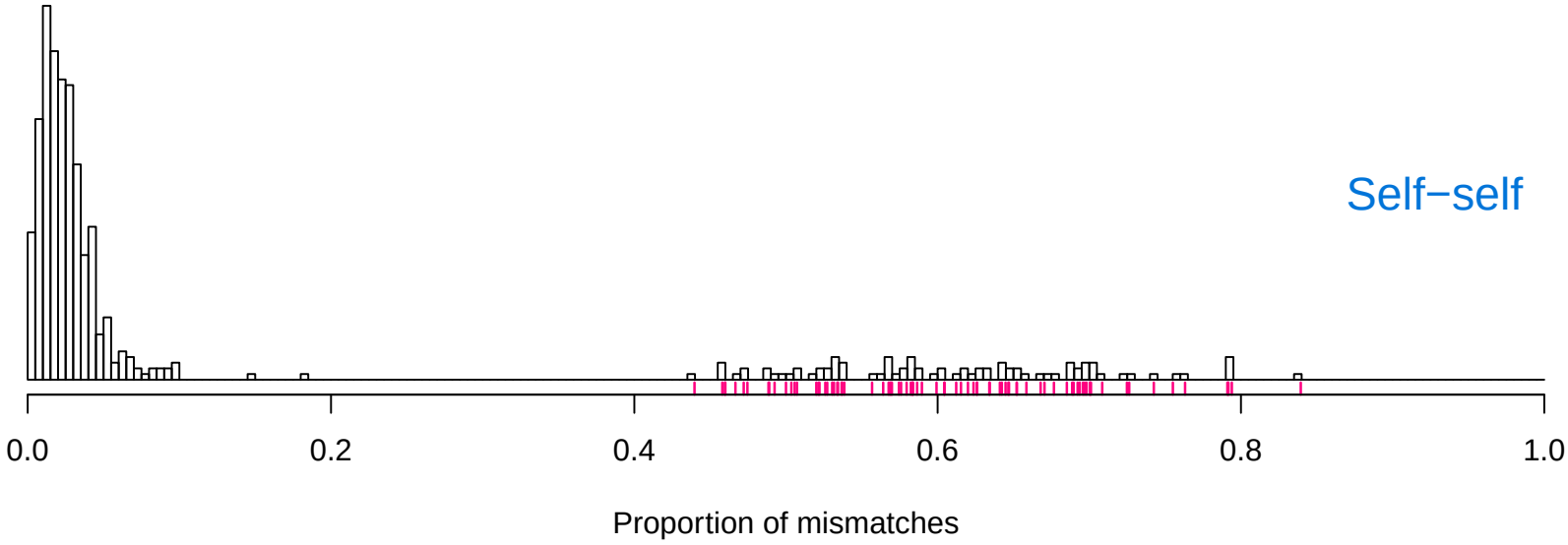
Prop’n mismatches

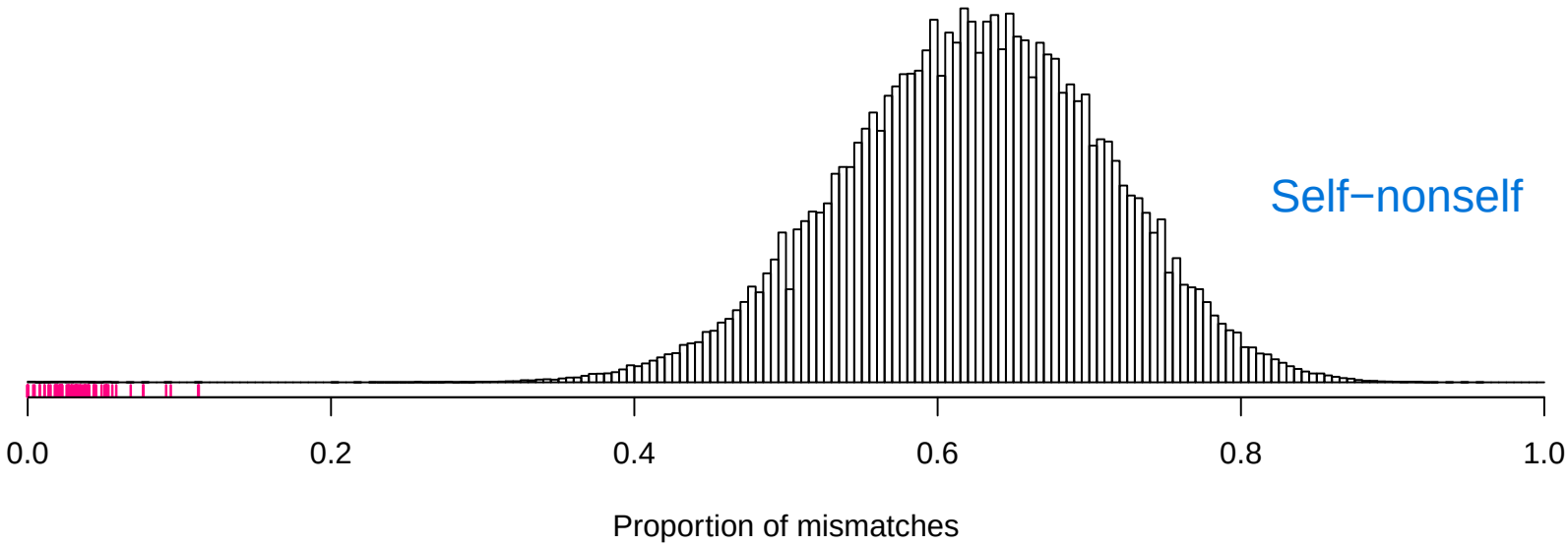


Prop’n mismatches

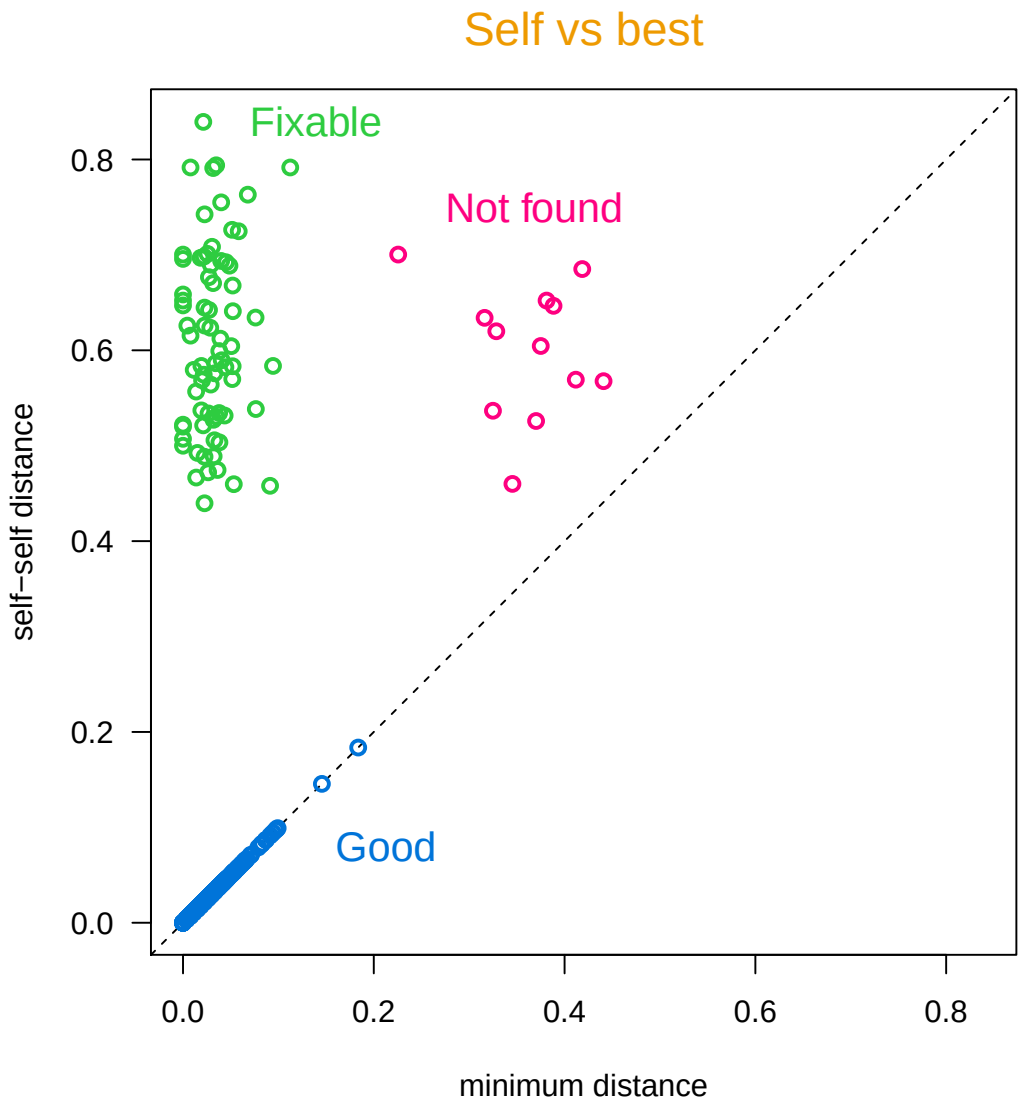


Prop’n mismatches





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

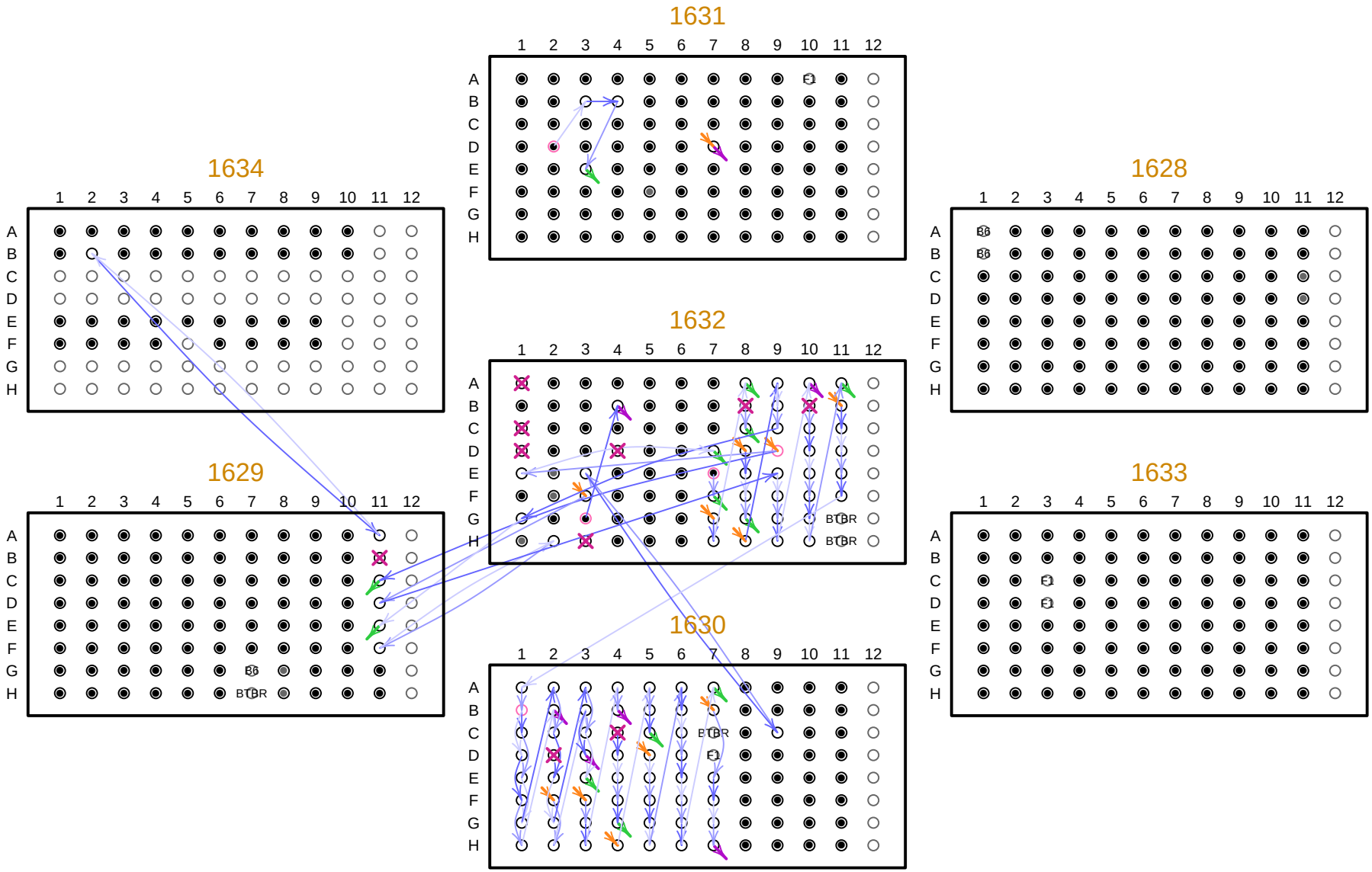
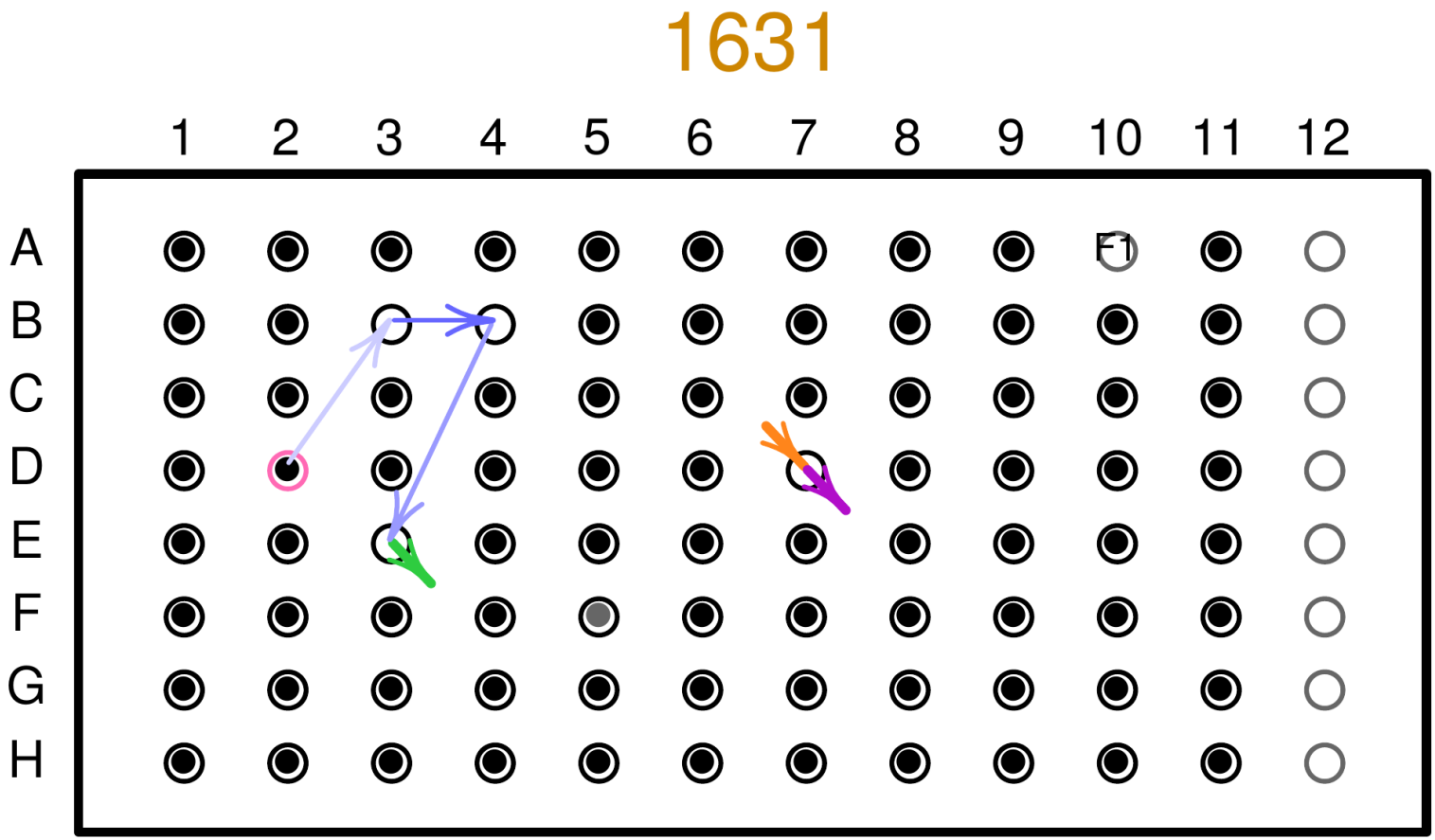


Plate 1631



Plates 1632 and 1630

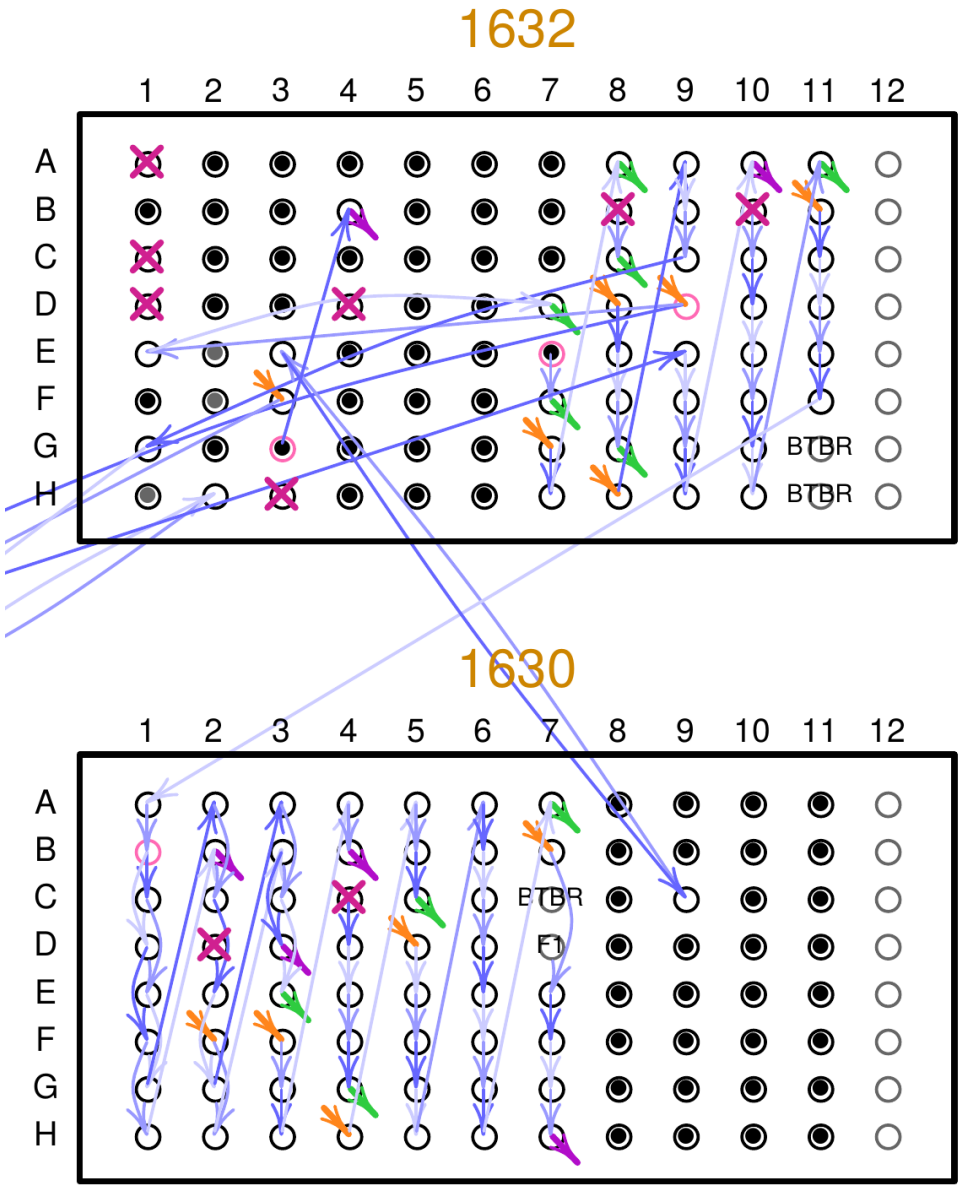
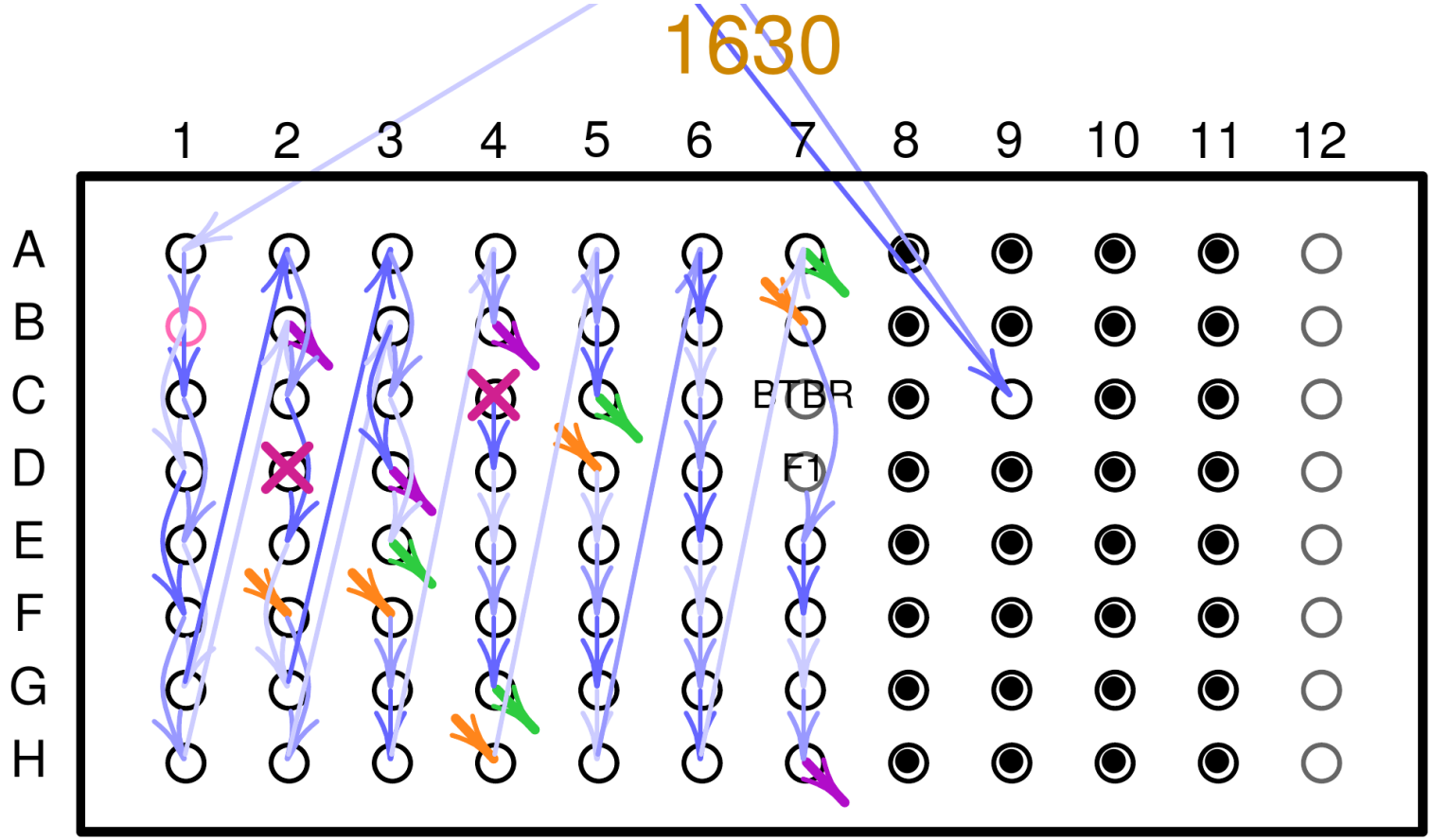


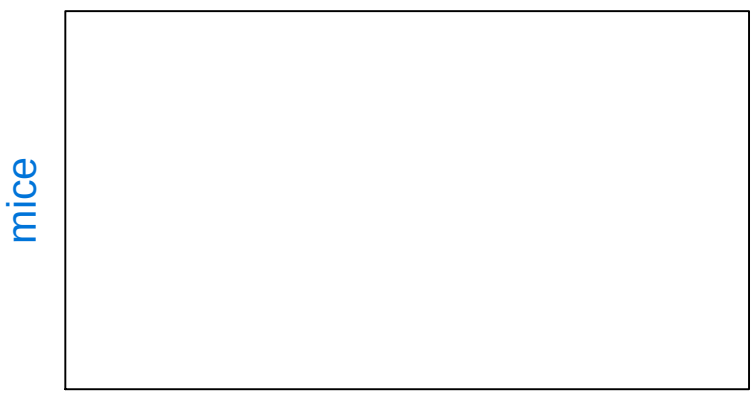
Plate 1630



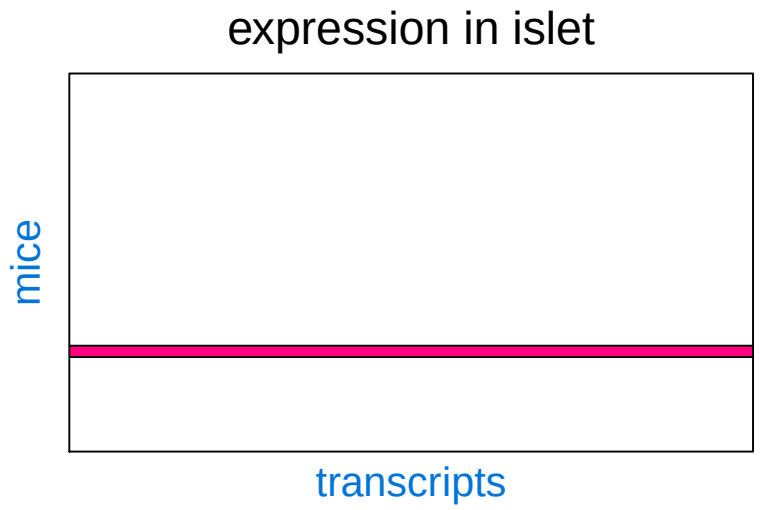
E vs E

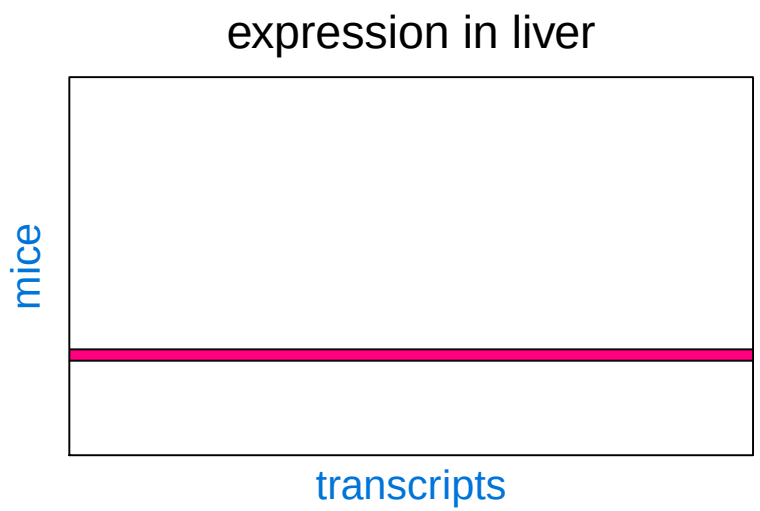
expression in islet

expression in liver



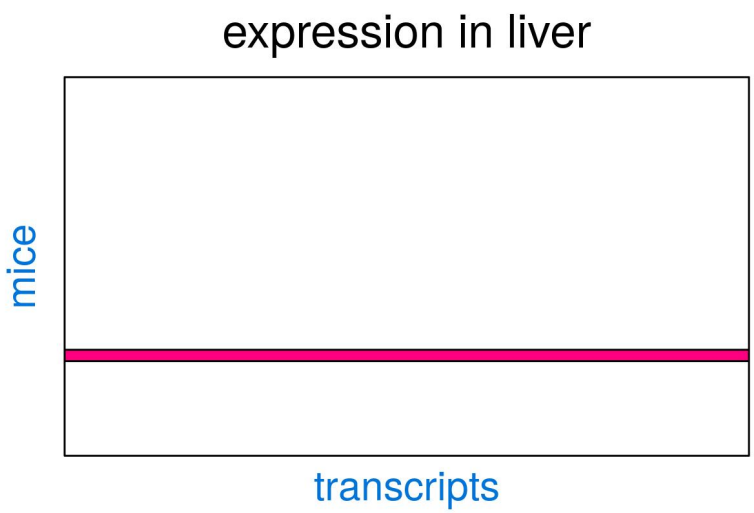
E vs E

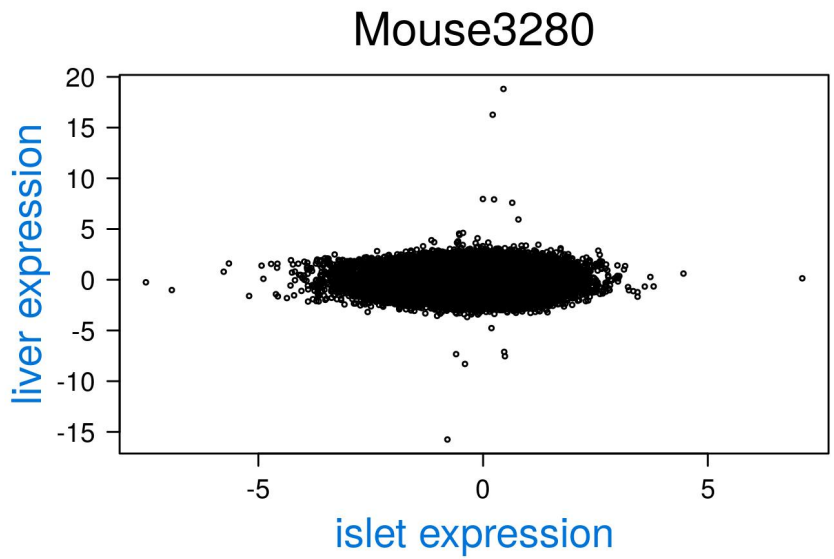

expression in islet
mice
transcripts


expression in liver
mice
transcripts

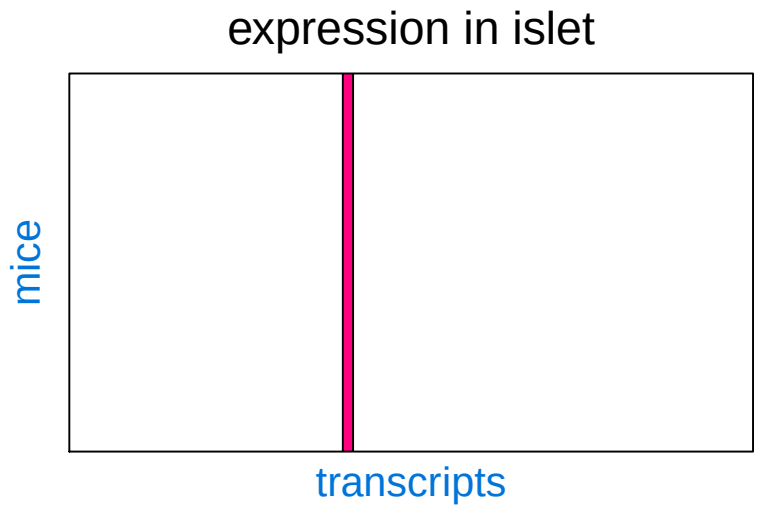
E vs E

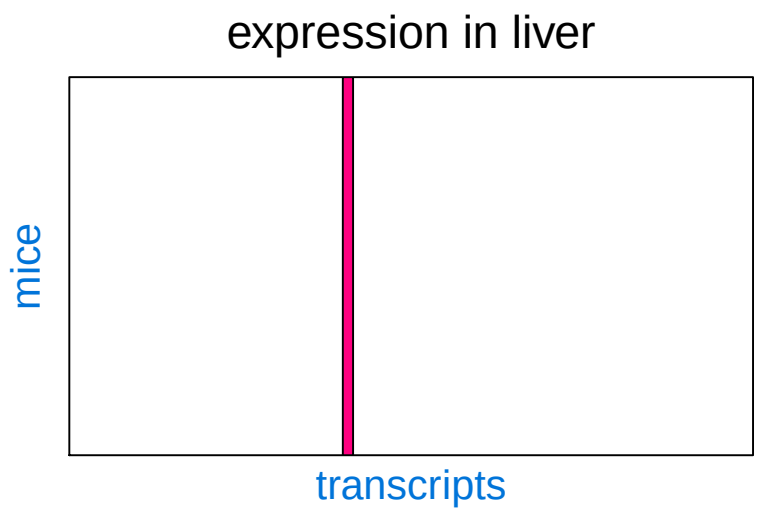

expression in islet
mice
transcripts

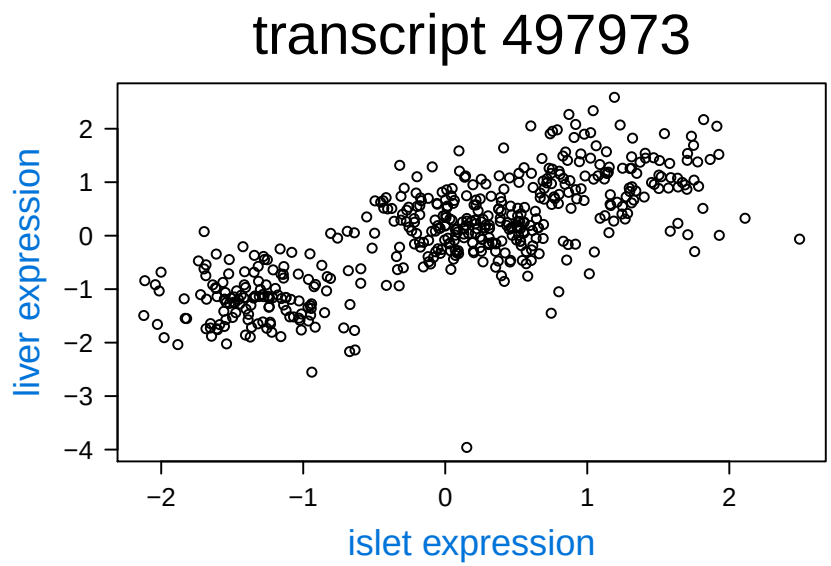

expression in liver
mice
transcripts


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

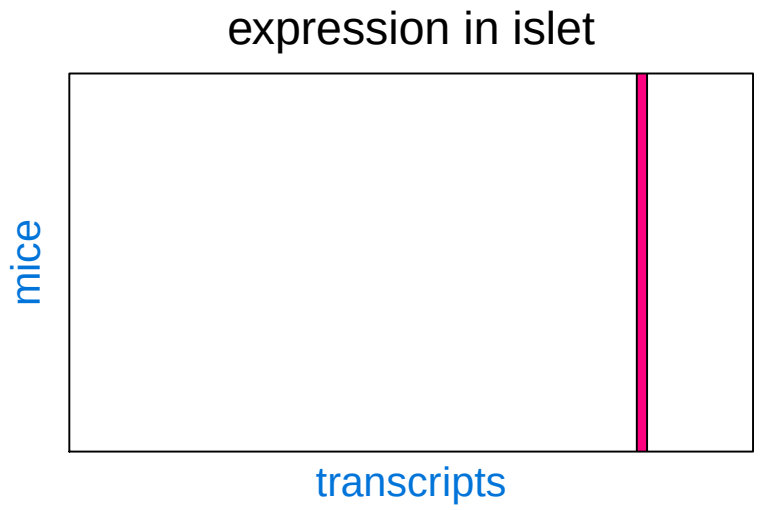
E vs E

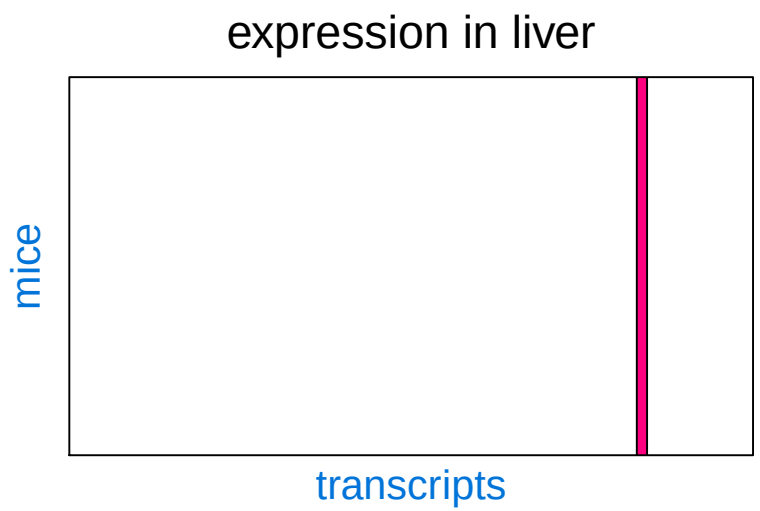

expression in islet
mice
transcripts

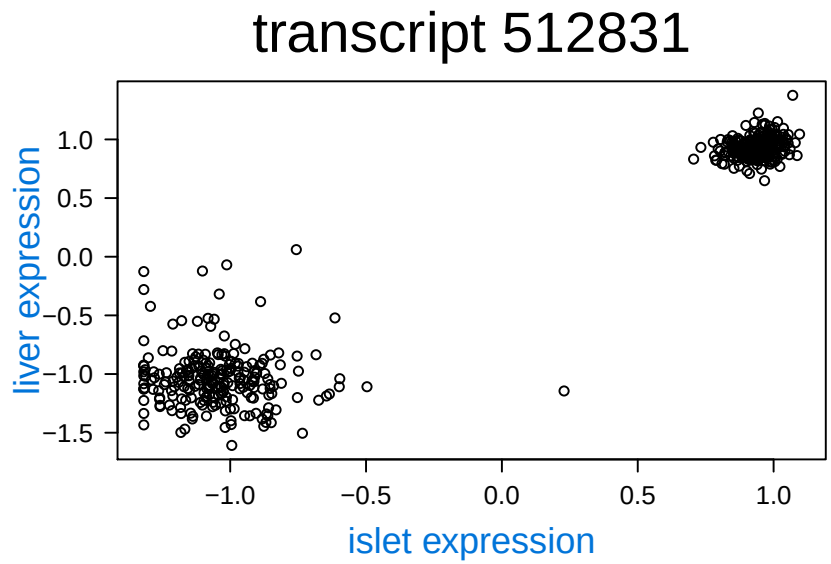

expression in liver
mice
transcripts


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

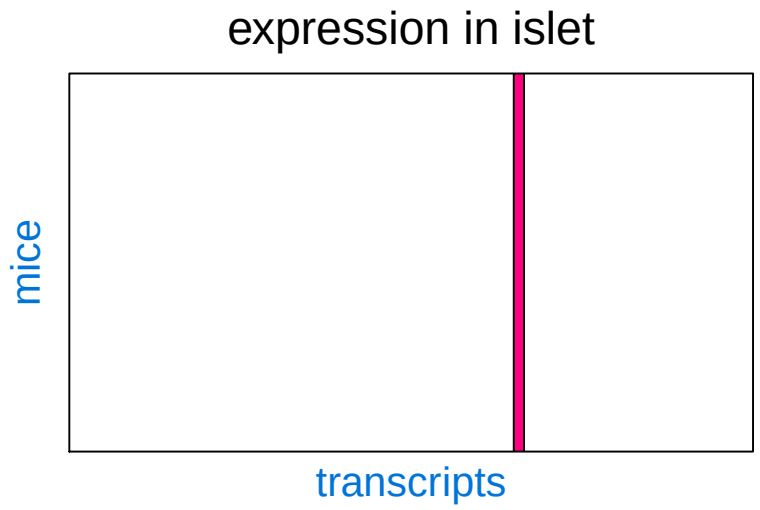
E vs E

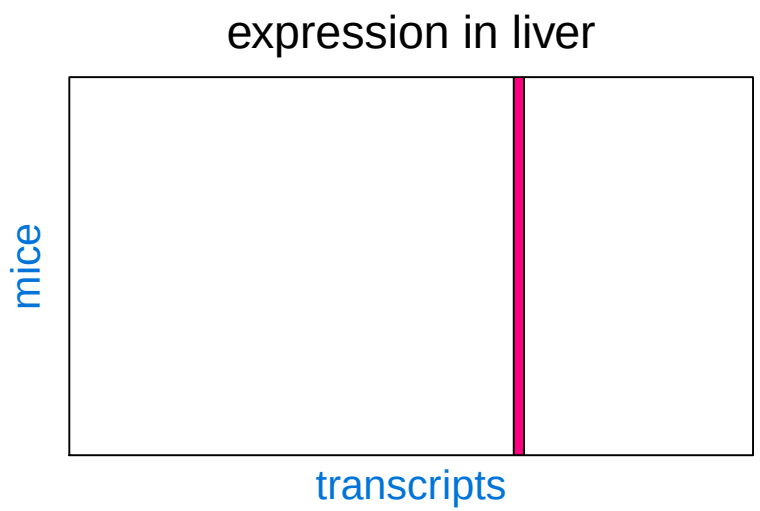

expression in islet
mice
transcripts

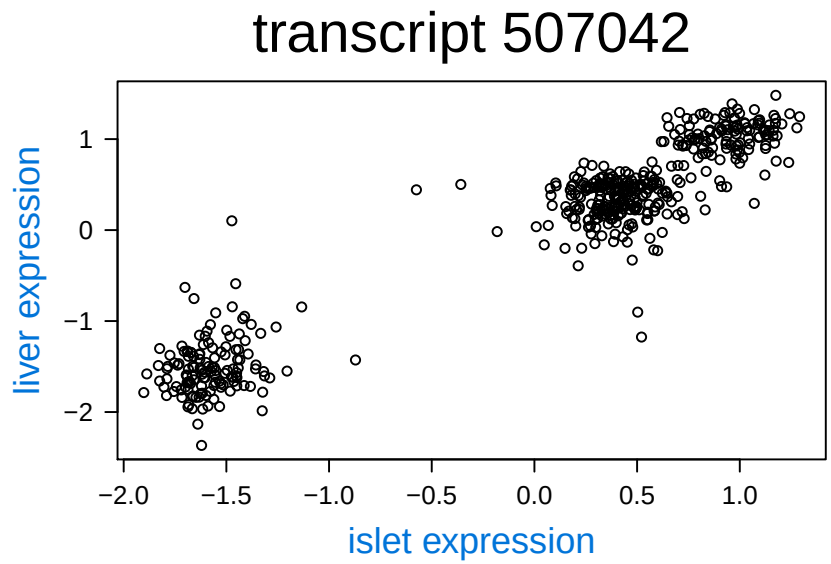

expression in liver
mice
transcripts


transcript 512831
liver expression
islet expression
1.0
0.5
0.0
−0.5
−1.0
−1.5
−1.0
−0.5
0.0
0.5
1.0

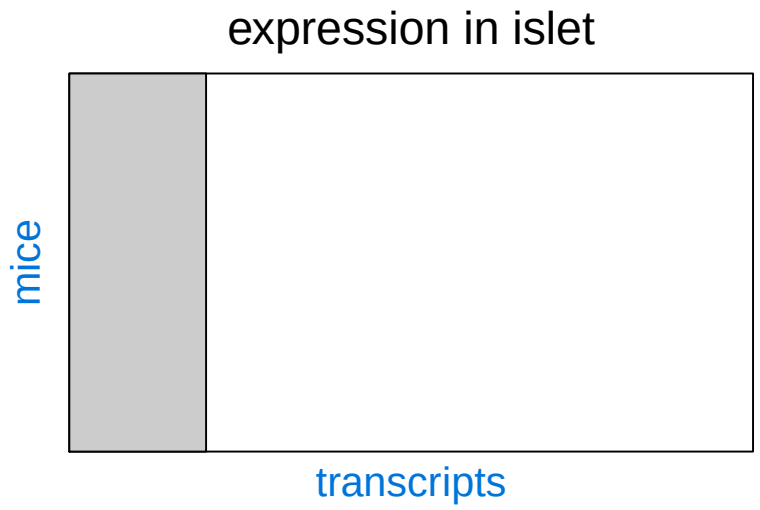
E vs E

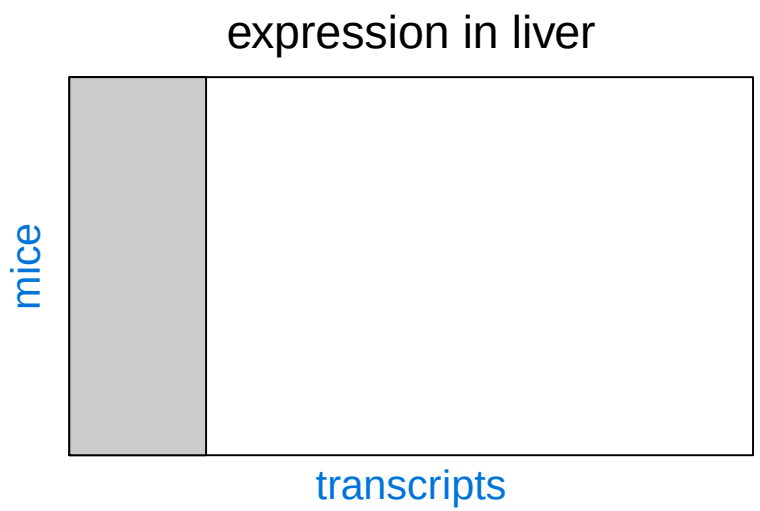

expression in islet
mice
transcripts


expression in liver
mice
transcripts

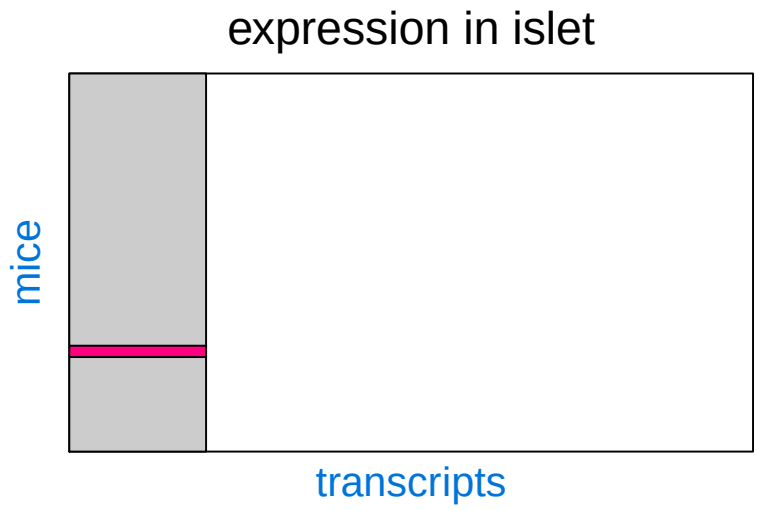

transcript 507042
liver expression
islet expression
1
0
−1
−2
−2.0
−1.5
−1.0
−0.5
0.0
0.5
1.0

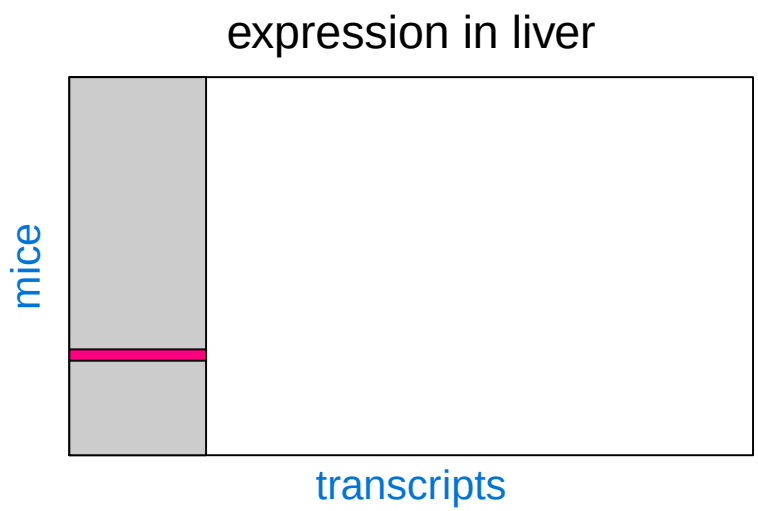
E vs E

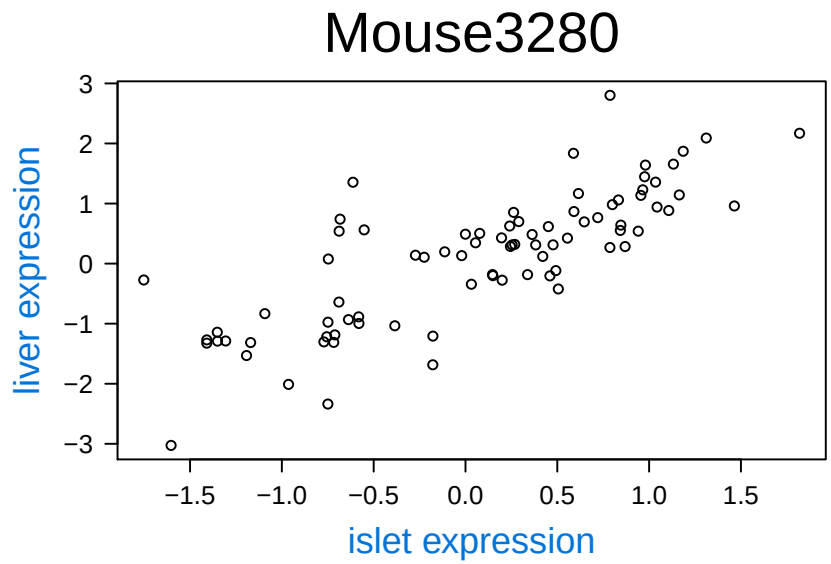

expression in islet
mice
transcripts


expression in liver
mice
transcripts

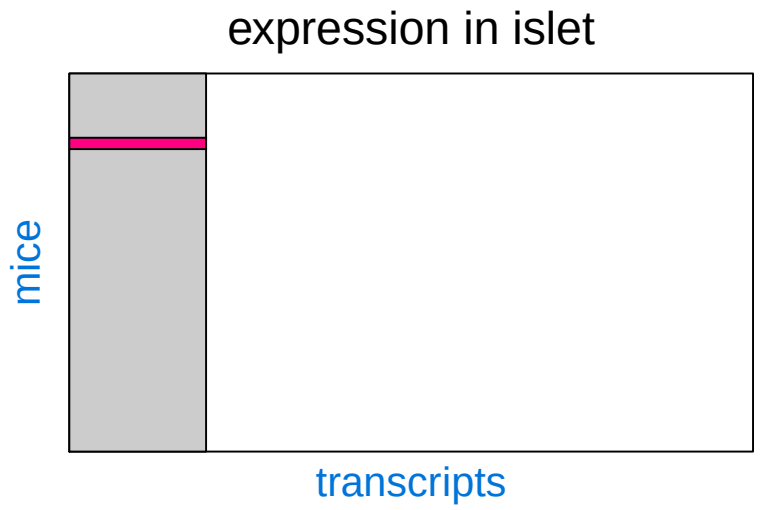
E vs E

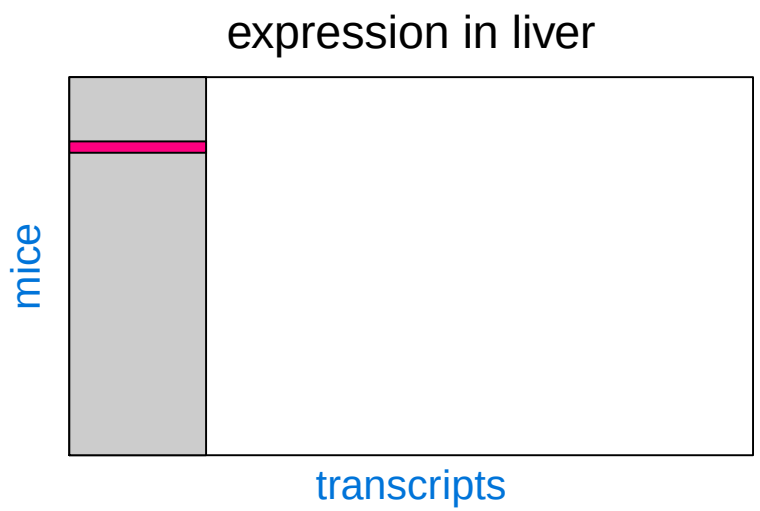

expression in islet
mice
transcripts

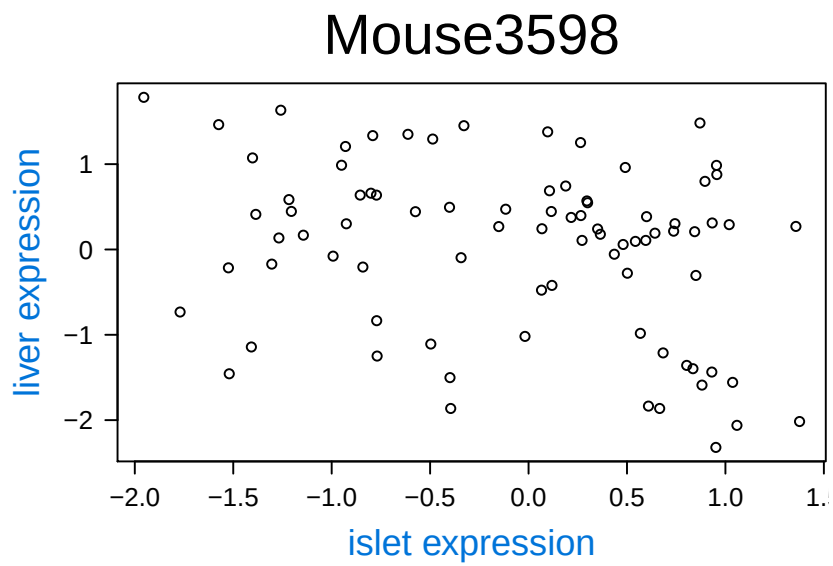

expression in liver
mice
transcripts


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

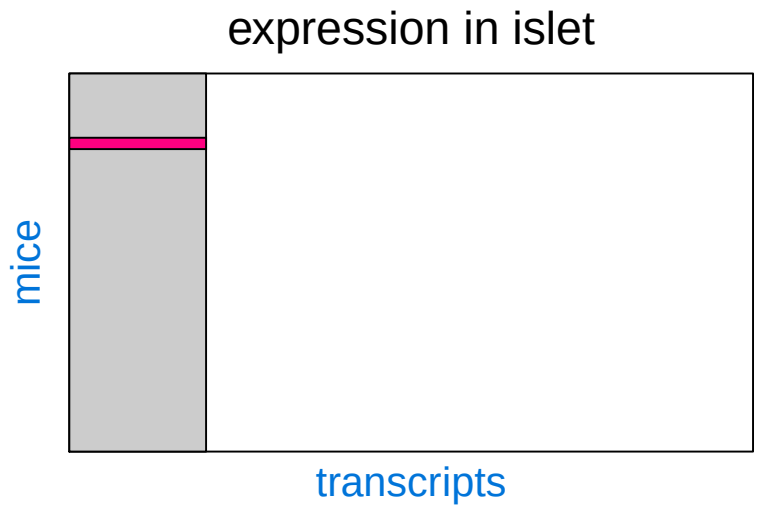
E vs E

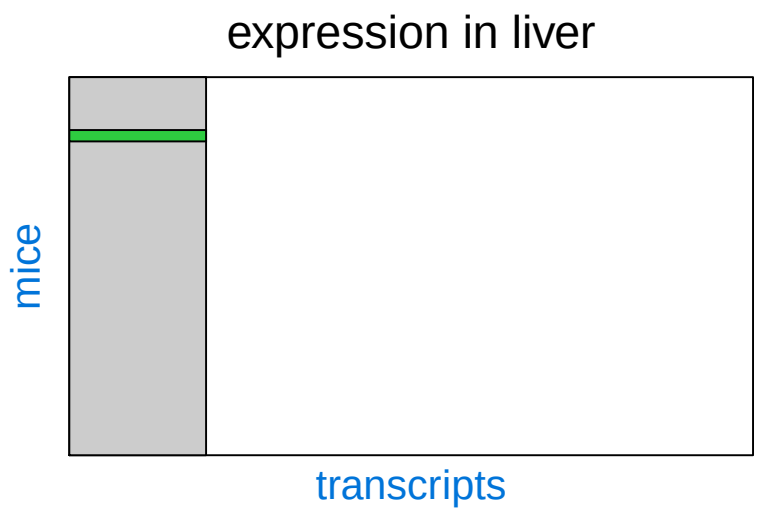

expression in islet
mice
transcripts

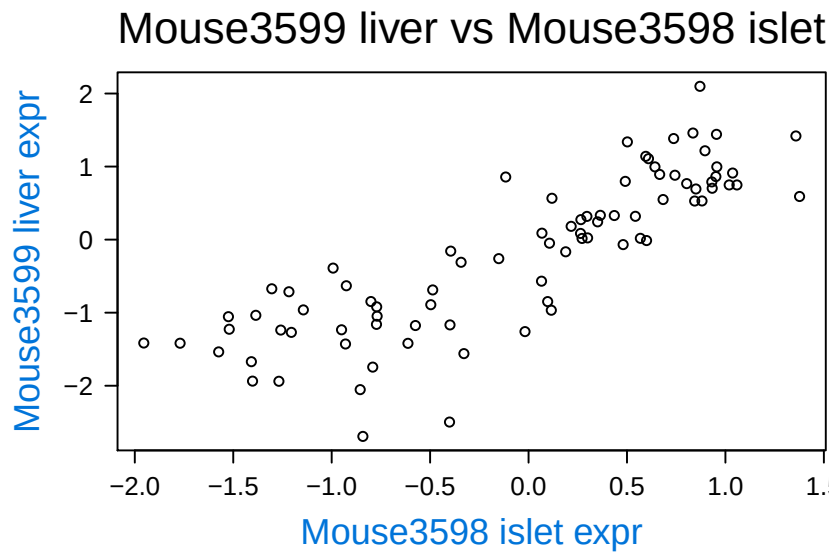

expression in liver
mice
transcripts


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

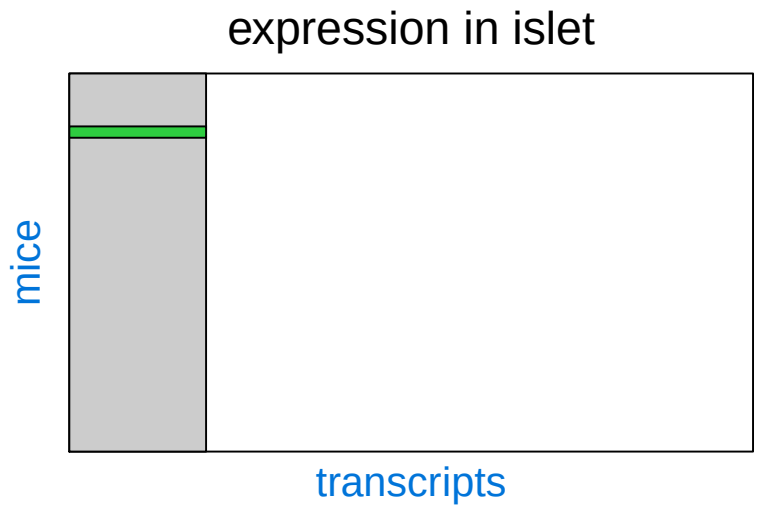
E vs E

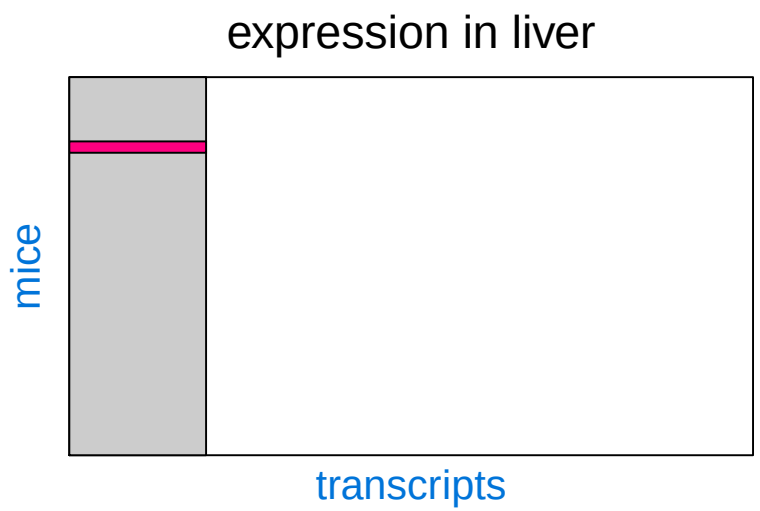

expression in islet
mice
transcripts

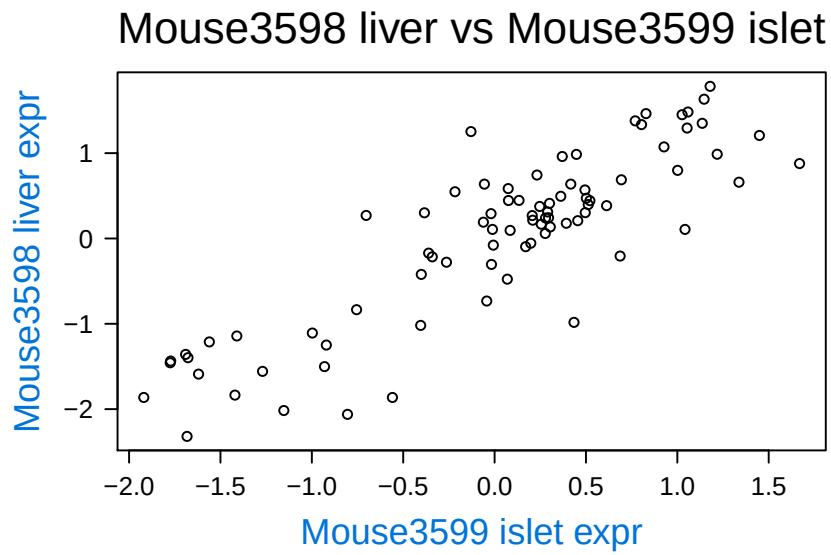

expression in liver
mice
transcripts


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

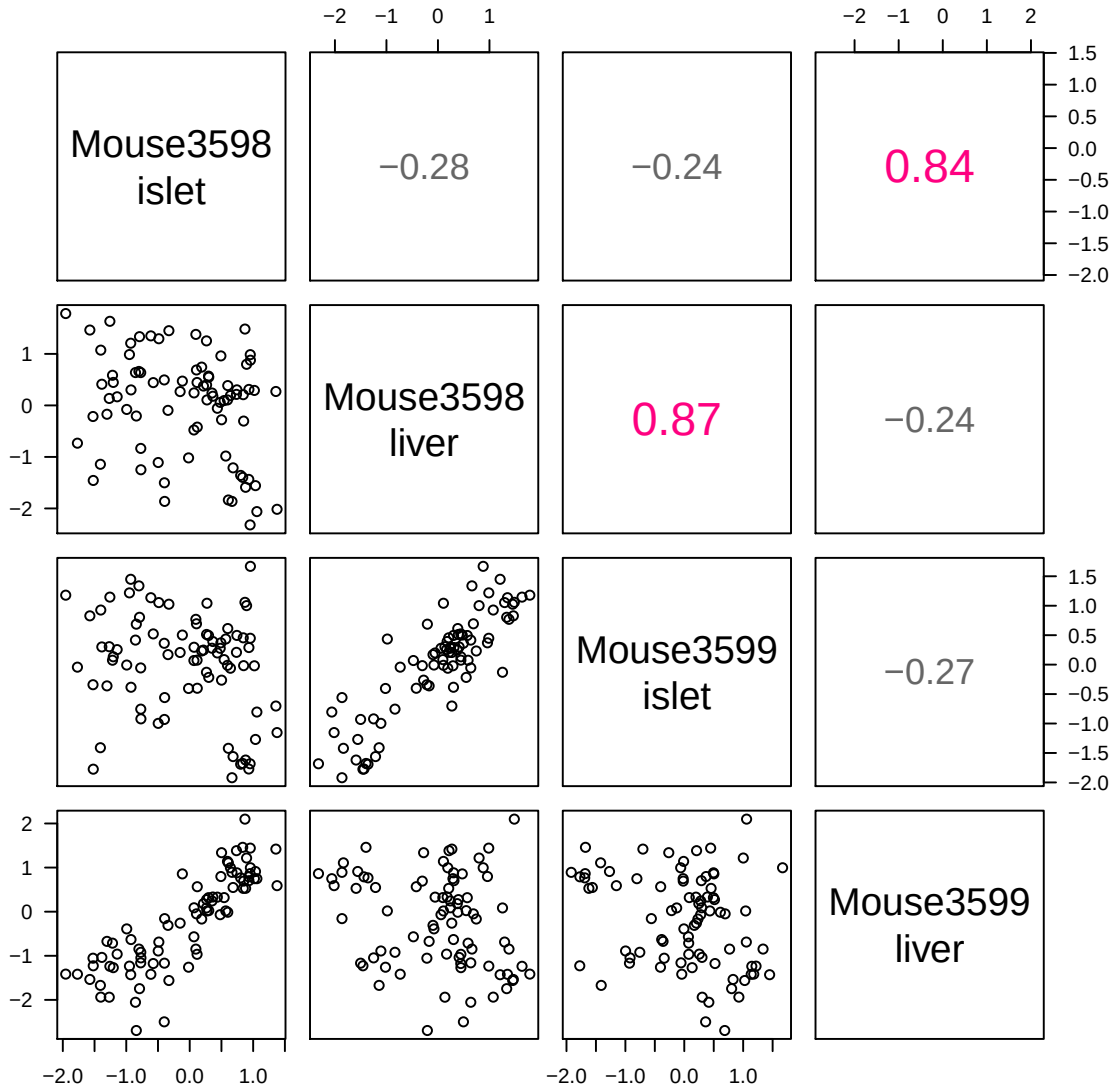
E vs E


expression in islet
mice
transcripts

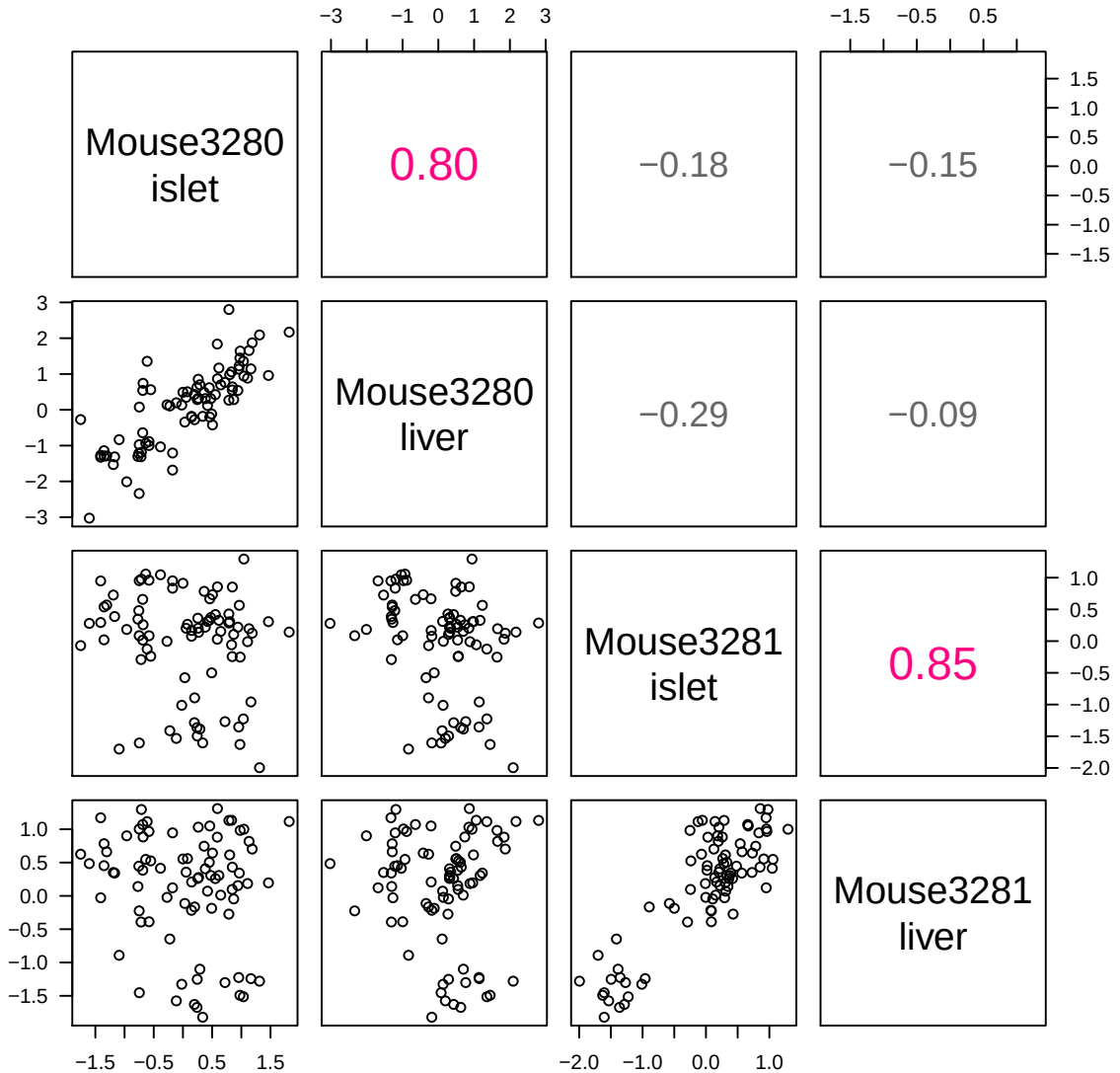

expression in liver
mice
transcripts


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

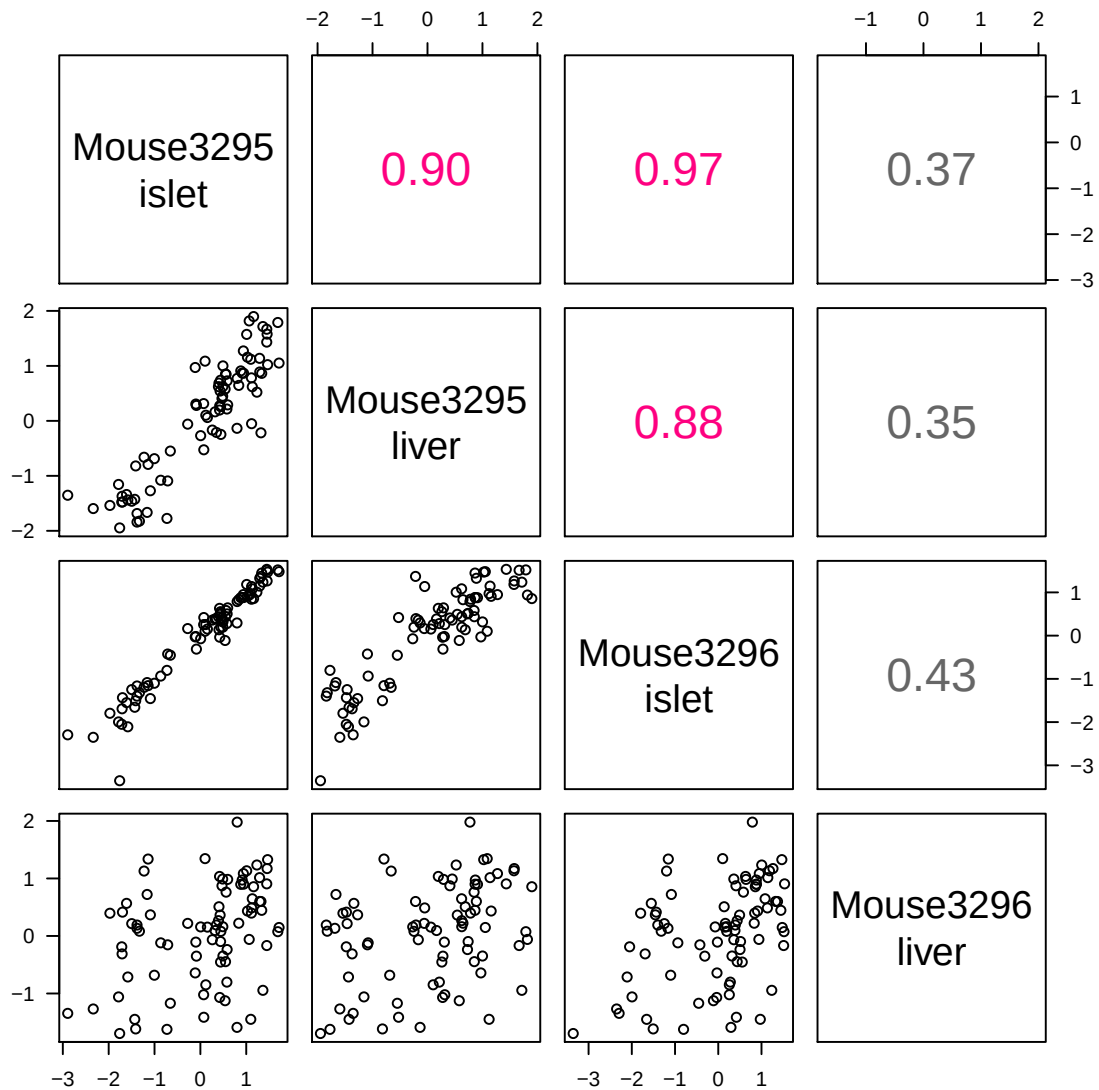
E vs E


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

E vs E

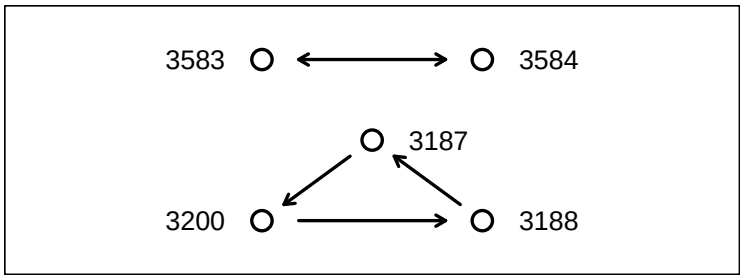

Mouse3280 islet
0.80
−0.18
−0.15
Mouse3280 liver
−0.29
−0.09
Mouse3281 islet
0.85
Mouse3281 liver

E vs E

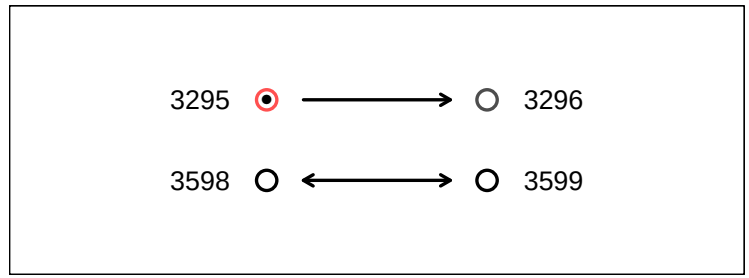

Mouse3295 islet
0.90
0.97
0.37
Mouse3295 liver
0.88
0.35
Mouse3296 islet
0.43
Mouse3296 liver

Expression mix-ups

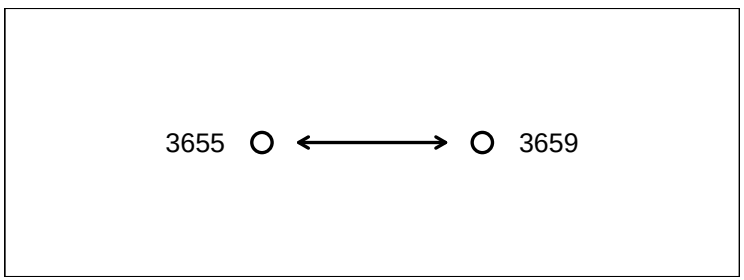
adipose



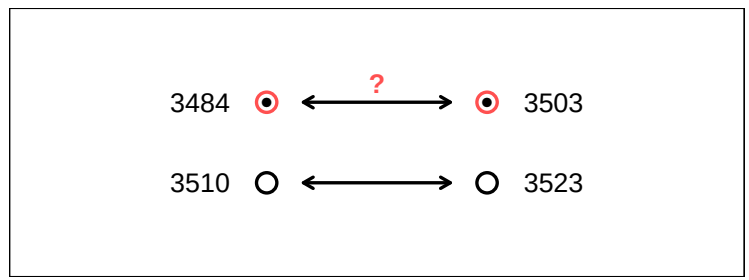
islet



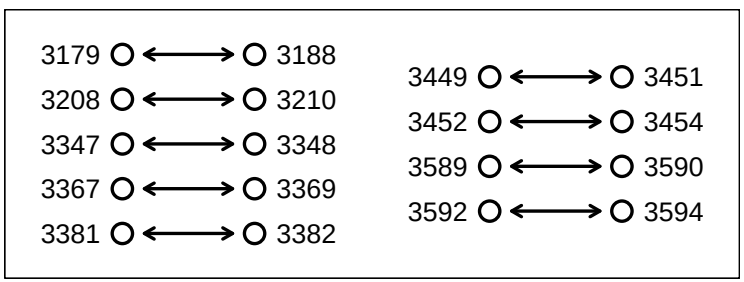
gastroc



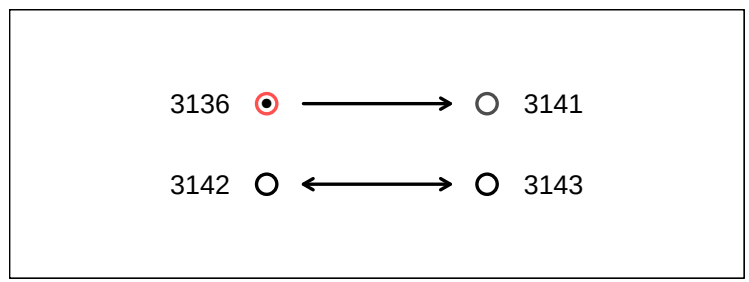
kidney



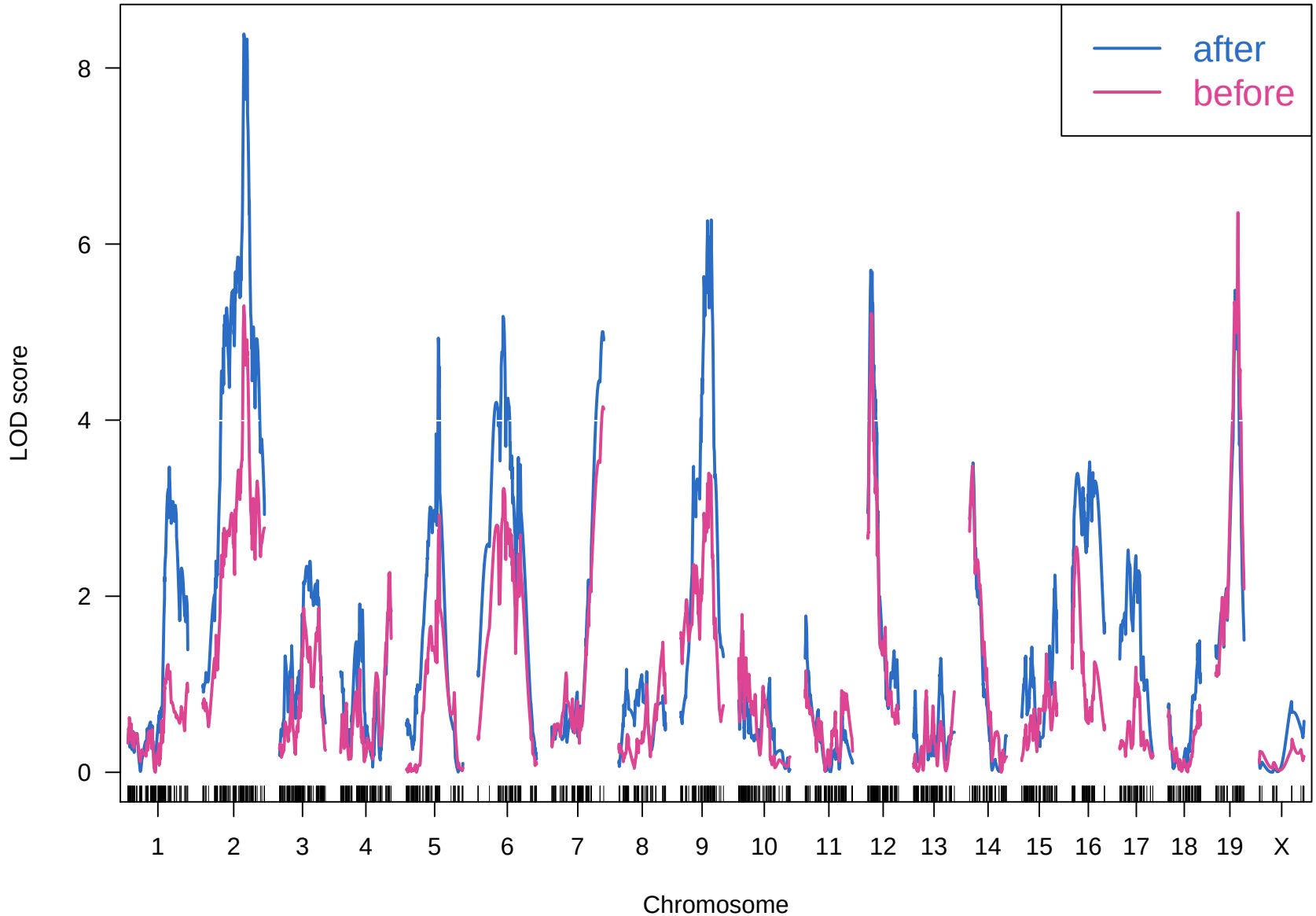
hypo



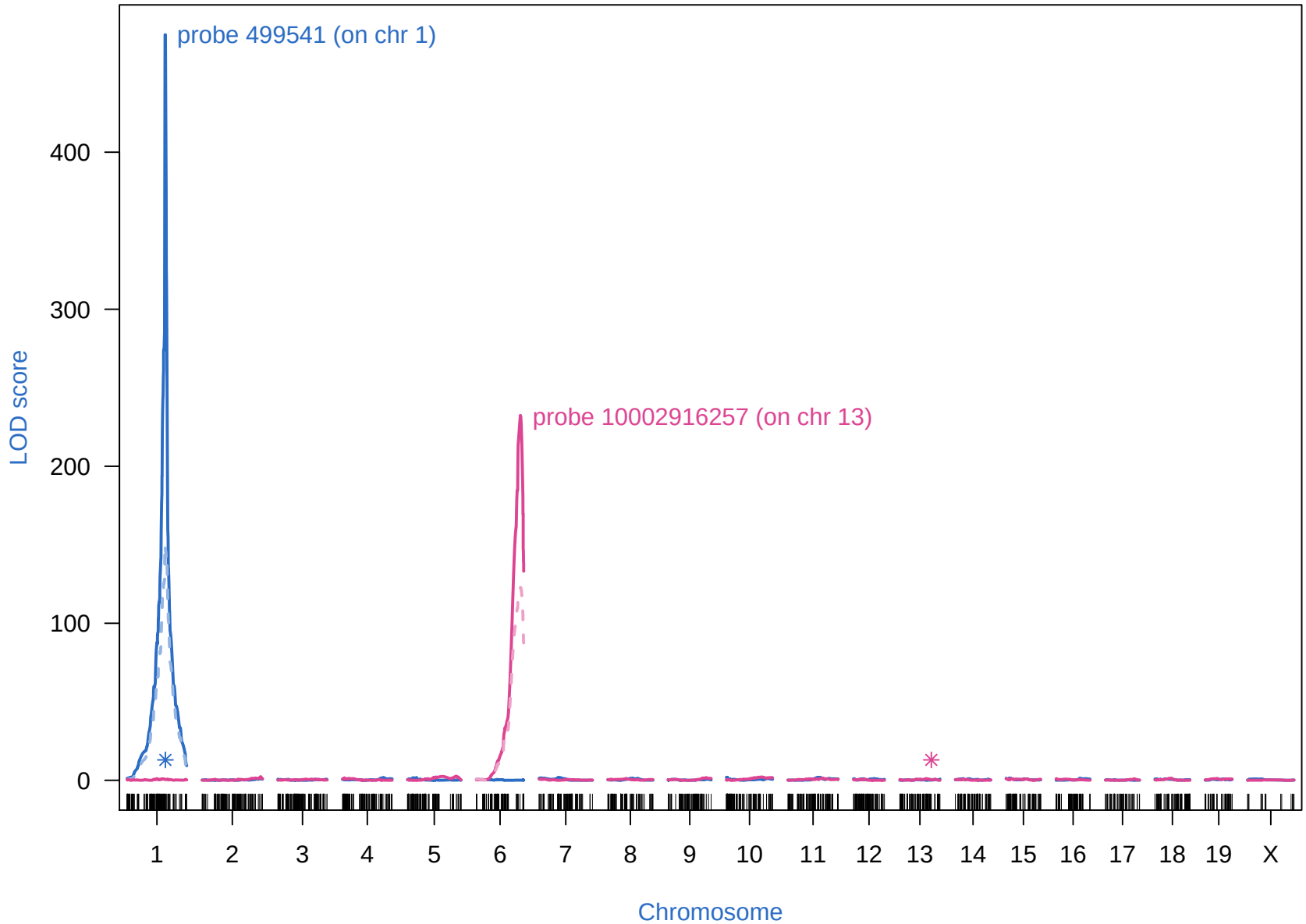
liver



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

Strong eQTL


probe 499541 (on chr 1)
probe 10002916257 (on chr 13)
LOD score
400
300
200
100
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

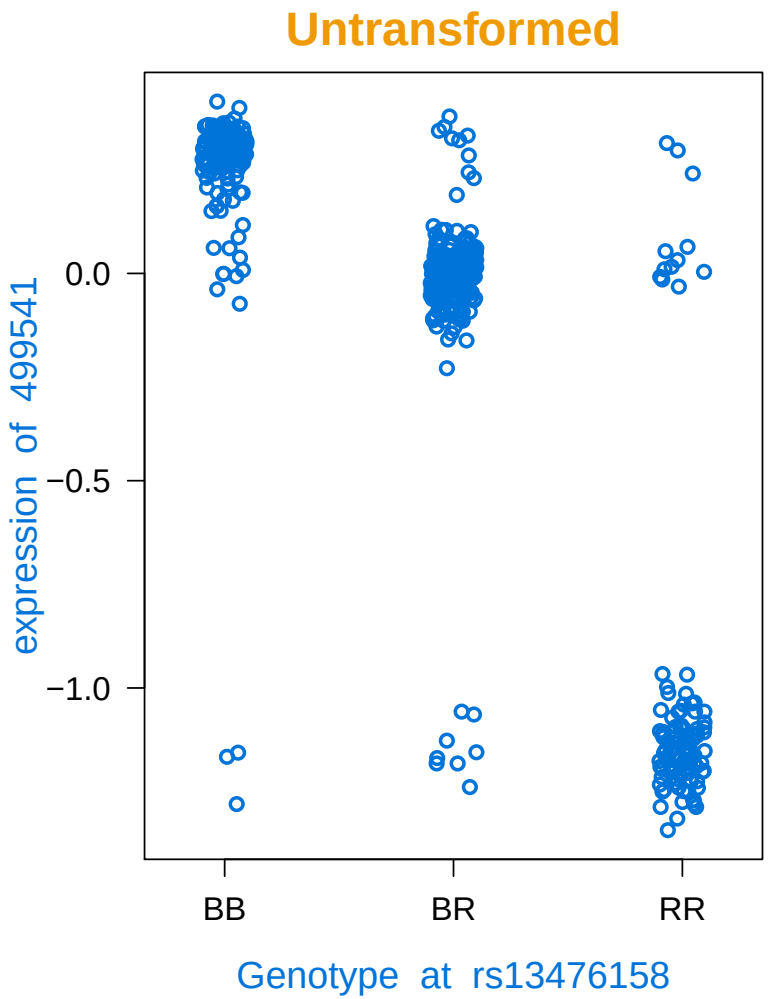
Summary

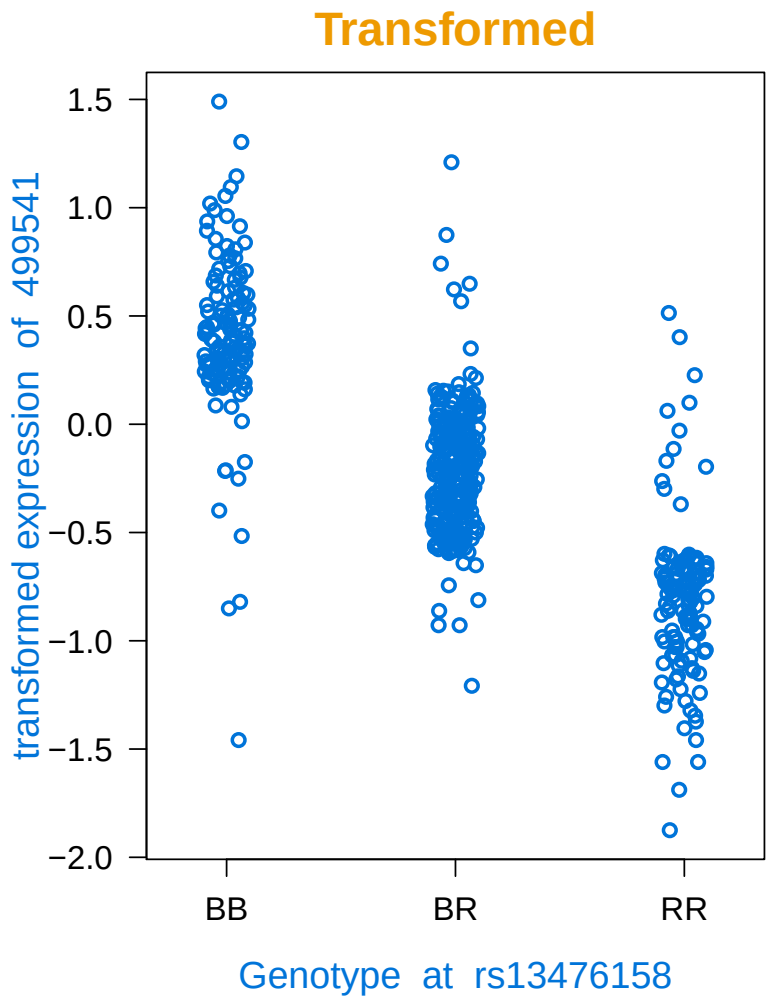
- Sample mix-ups happen
- With eQTL data, we can both identify and correct mix-ups
- There is great value in having expression on multiple tissues
- The general idea here has wide application for high-throughput data
- Broman et al. (2015) G3 5:2177-2186
  doi: 10.1534/g3.115.019778
- Related work:
  - Westra et al. (2011) Bioinformatics 27:2104–2111
  - Schadt et al. (2012) Nat Genet 44:603–608
  - Ekstrøm and Feenstra (2012) Stat Appl Genet Mol Biol 3:Article 13
  - Lynch et al. (2012) PLoS ONE 7:e41815

Lessons

- Don't fully trust anyone
  - Including yourself
- Make lots of plots
  - Don't rely on summary statistics, like LOD scores
  - Look at responses on the original scale
- Follow up all aberrations
- Take your time with data cleaning
  - A month, two months, a year?
- If you have big rectangles whose rows correspond, check that they actually correspond

E vs G

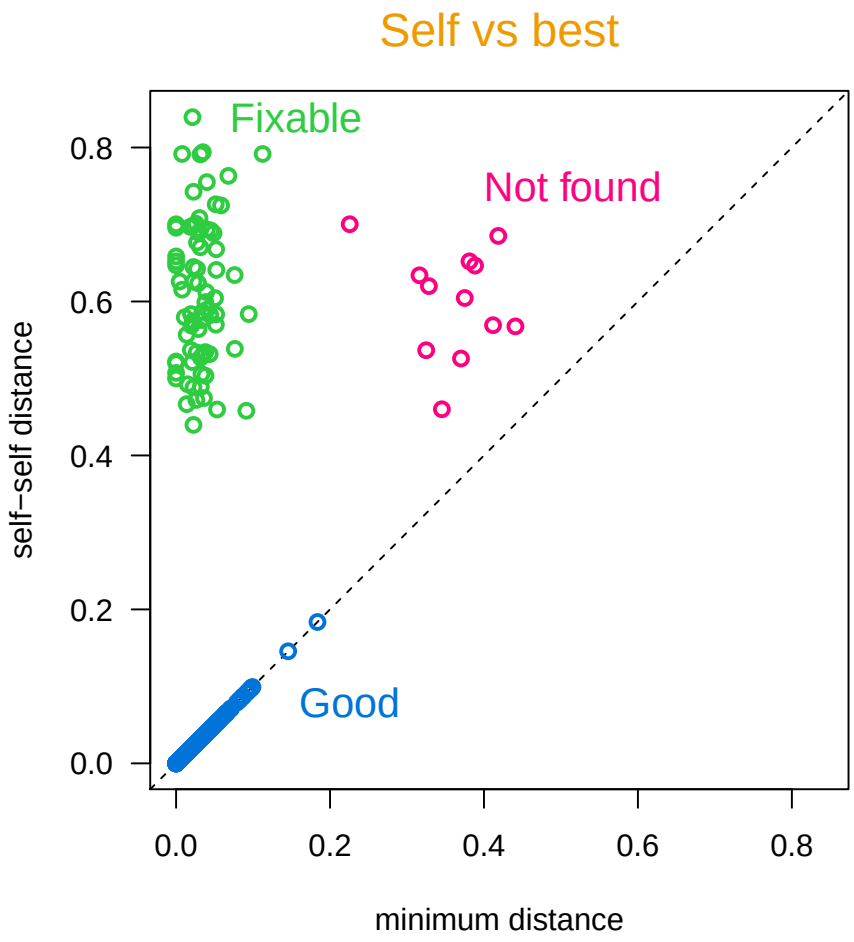

Untransformed
expression of 499541
0.0
−0.5
−1.0
BB
BR
RR
Genotype at rs13476158

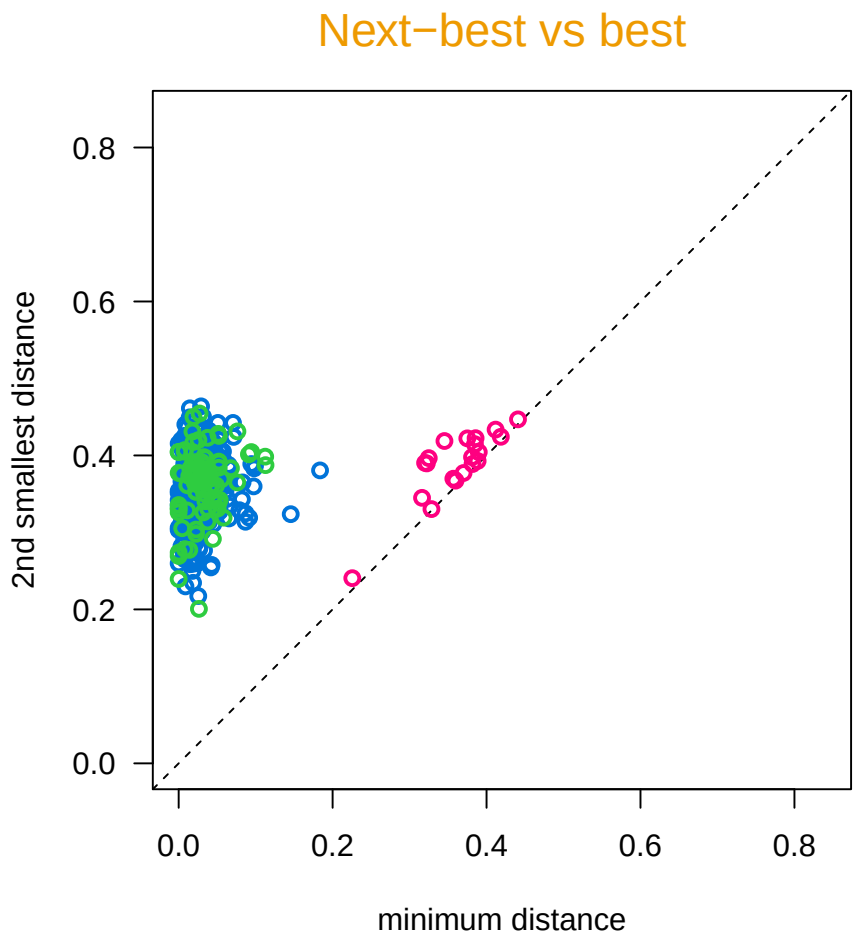

Transformed
transformed expression of 499541
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−2.0
BB
BR
RR
Genotype at rs13476158

Lessons

- Don't fully trust anyone
  - Including yourself
- Make lots of plots
  - Don't rely on summary statistics, like LOD scores
  - Look at responses on the original scale
- Follow up all aberrations
- Take your time with data cleaning
  - A month, two months, a year?
- If you have big rectangles whose rows correspond, check that they actually correspond

Decisions


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


Next−best vs best
2nd smallest distance
minimum distance
0.0
0.2
0.4
0.6
0.8