Uses and abuses of tests

- Report the P-value
- Report a confidence interval
- Consider the model
- Consider the study design
- Be careful about data snooping

Was the result significant?

- In genetics, people often talk about

"suggestive"	$5\% < P < 10\%$
"significant"	$1\% < P < 5\%$
"highly significant"	$P < 1\%$

  I despise this!

- Hard-and-fast rules are bad

  P = 4.8% is essentially the same as P = 5.3%.

- Give the actual P-value, and treat it as a measure of evidence.

Was the result important?

- Statistically significant is not the same as important.
- A difference is "statistically significant" if it cannot reasonably be ascribed to chance variation.
- With lots of data, small (and unimportant) differences can be statistically significant.
- With very little data, quite important differences will fail to be significant.
- Always report a confidence interval!

  Consider: 0.5 ± 0.1 vs. 100 ± 40

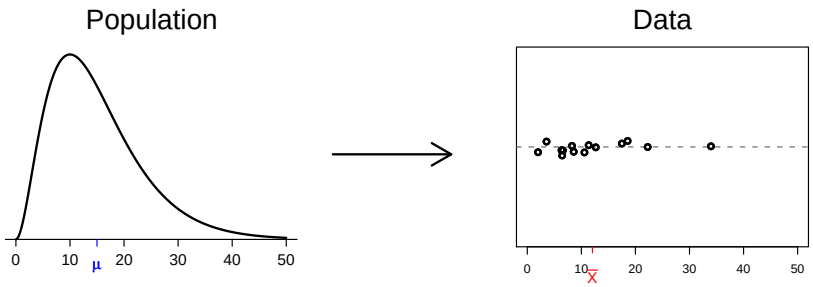
Failure to reject

- Failure to reject the null hypothesis does not mean you should accept the null hypothesis.
- The means of two populations can always reasonably be slightly different—it's impossible to prove, "They are the same," though we can say, "They are not too different."
- Think about the power of the statistical test.
- Look at the confidence interval.

Statisticians as cops

- Don't think of statistics as a barrier to publishing important work.
- Rather, think of statistics as help for avoiding publishing garbage.
- Statistics can help you to avoid wasting time (and money) following false leads.

The role of the model



- Statistical tests and confidence intervals concern inferences about a (possibly hypothetical) population on the basis of data.
- Model: $X_1, \ldots, X_n$ independent with mean μ and SD σ.
- For a well-designed (randomized) experiment, this is usually not a worry.
- Be suspicious about statistical tests with censuses and convenience samples.

Does the difference prove the point?

- A test of significance doesn't check the design of the study.
- With observational studies or poorly controlled experiments, the proof of statistical significance may not prove what you want.
- Example: consider the tick/deer leg experiment. It may be that ticks are not attracted to deer-gland-substance but rather despise the scent of latex gloves and deer-gland-substance masks it.
- Example: In a study of gene expression, if cancer tissue samples were always processed first, while normal tissue samples were kept on ice, the observed differences might not have to do with normal/cancer as with iced/not iced.
- Don't forget the science in the cloud of data and statistics.

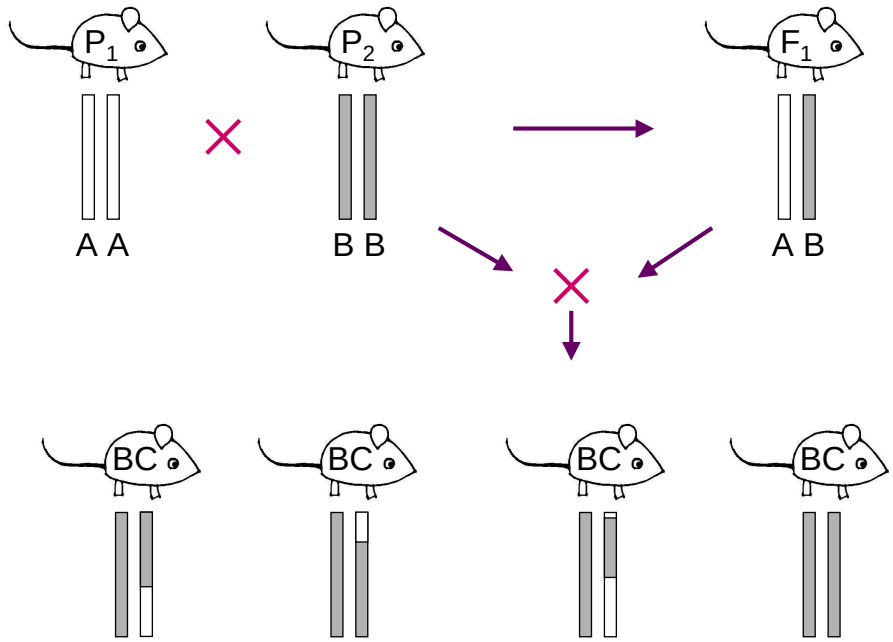
Data snooping / Multiple testing

- Generally we perform more than one statistical test at once.
- If you are performing many statistical tests, and then reporting the interesting ones, take care!

  You need to adjust for the fact that you are performing many tests.
- Sometimes investigators study their data, and then apply formal statistical tests only to features that appear interesting (and likely statistically significant).

  Take care! They should adjust for the statistical tests that they applied informally, in snooping through their data.
- Ideally, such multiple statistical tests are treated as exploratory, and the interesting results are confirmed with independent data.

Backcross experiment



Data and Goals

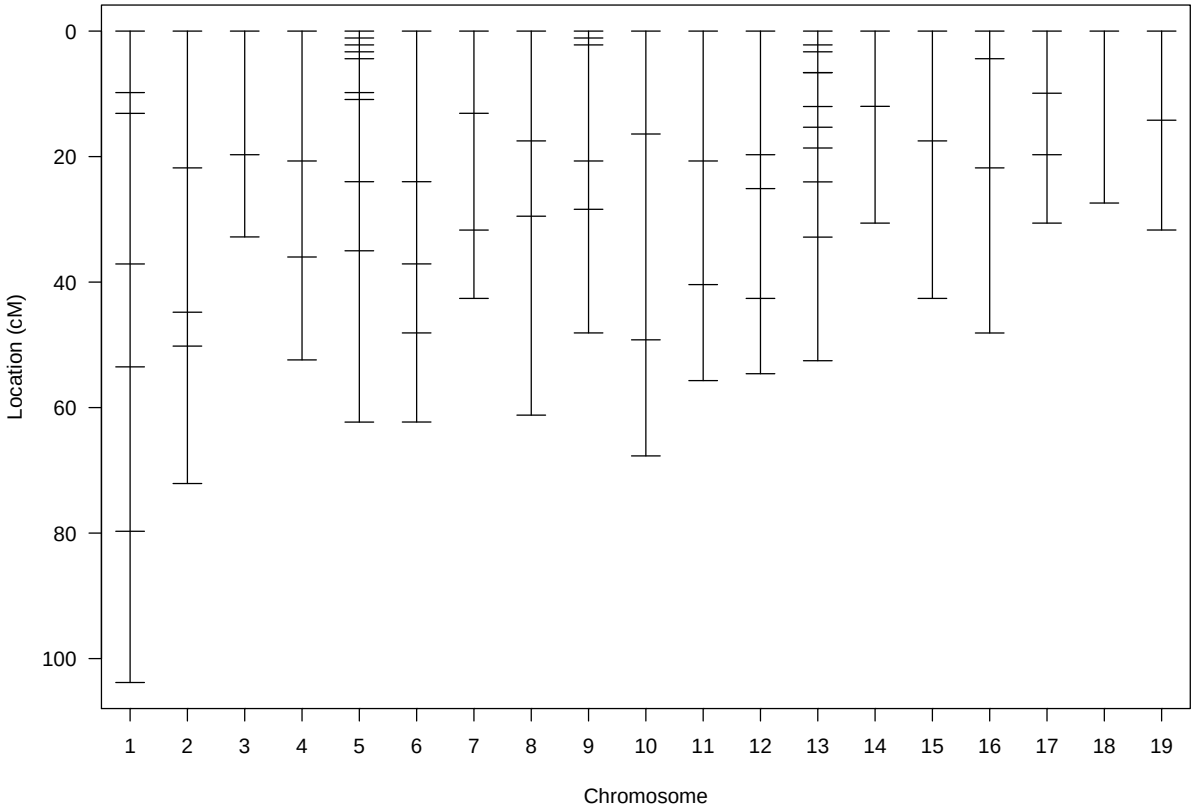
Phenotypes: y_i = phenotype for mouse i

Genotypes: x_{ij} = 1/0 if mouse i is BB/AB at marker j (for a backcross)

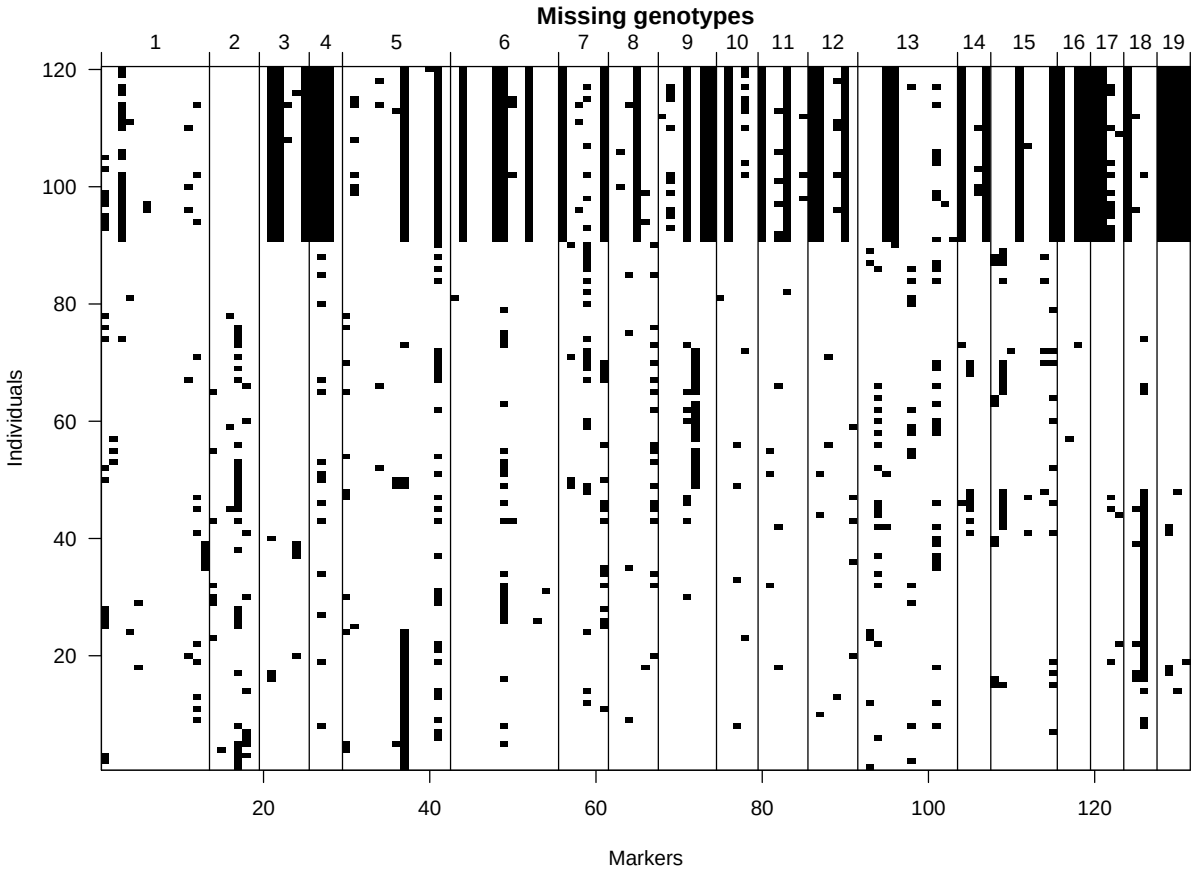
Genetic map: Locations of markers

Goals:

- Identify the (or at least one) genomic regions (QTLs) that contribute to variation in the phenotype.
- Form confidence intervals for QTL locations.
- Estimate QTL effects.


Genetic map
Location (cM)
0
20
40
60
80
100
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Chromosome

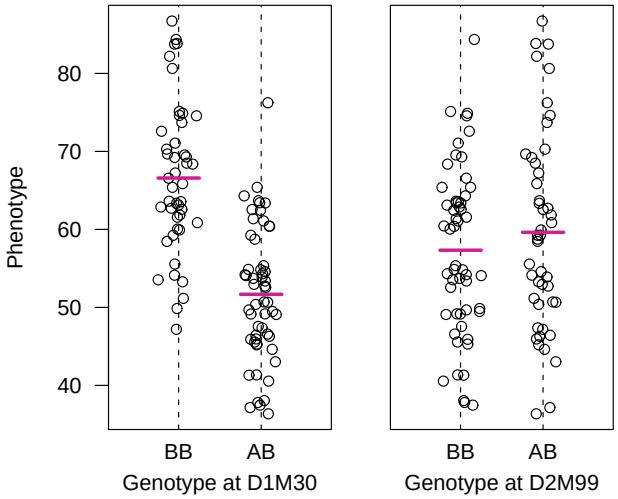
11

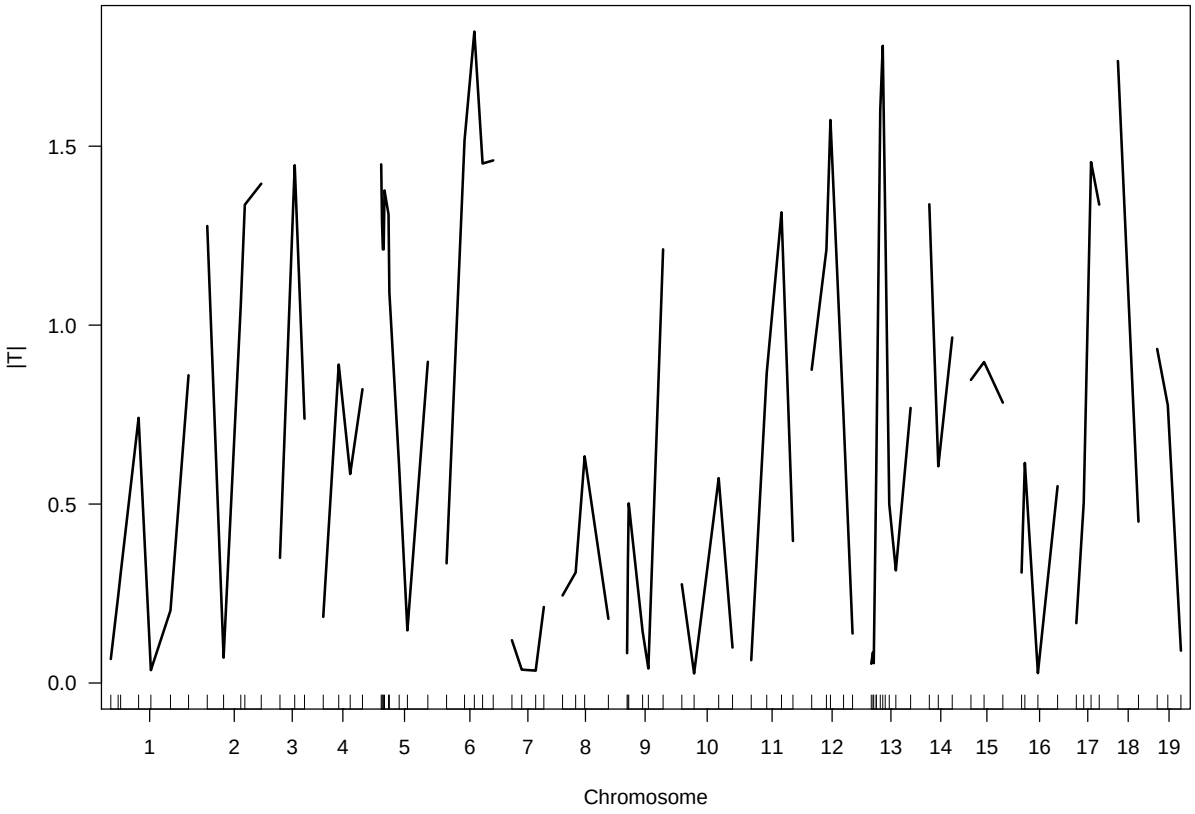

Missing genotypes
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Individuals
120
100
80
60
40
20
20
40
60
80
100
120
Markers

12

The simplest method: t-tests

- Split mice into groups according to genotype at a marker.
- Do a t-test
- Repeat for each marker.





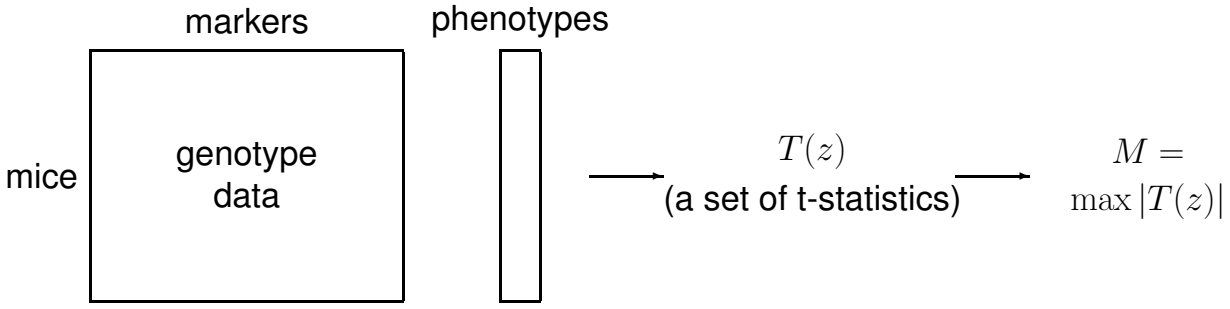
Adjustment for multiple tests

- We performed a t-test at each of 91 markers. (The markers are, of course, associated.)
- The maximum t-statistic was 3.05. What P-value do we assign to this?

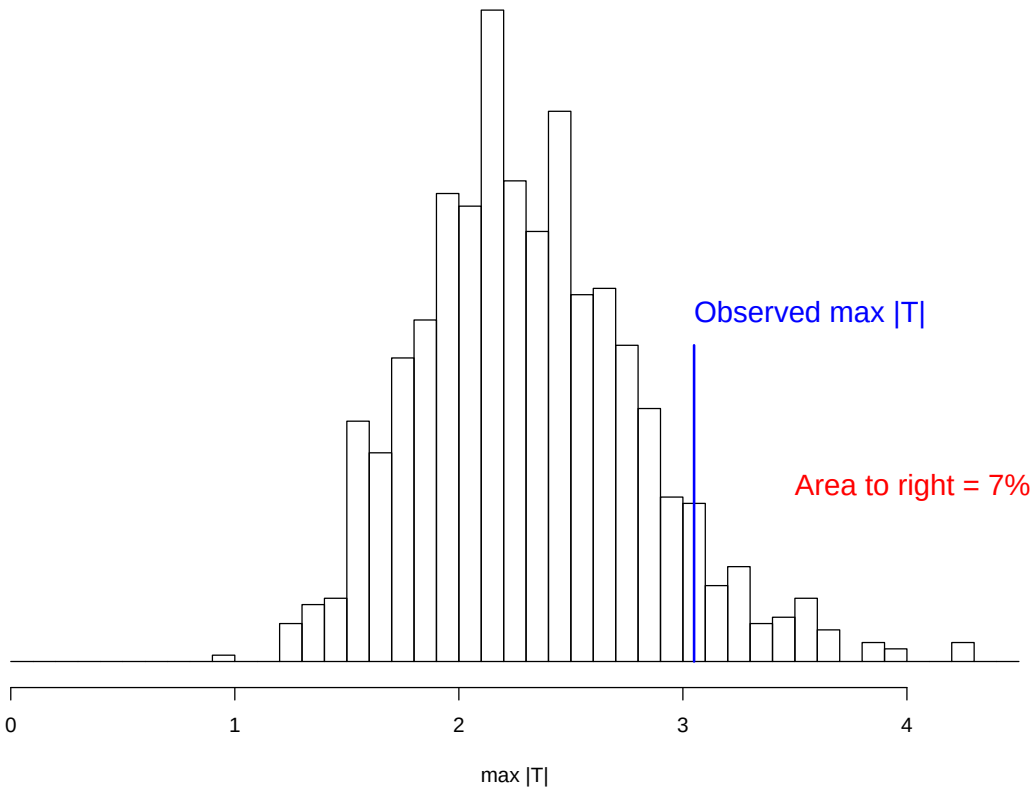
  Nominal P-value = Percentile of |T| (under null hypothesis) = 0.002

  Adjusted P-value = Percentile of maximum |T| (under null hypothesis of no QTLs anywhere)
- How to get at the distribution of the maximum |T|, genome-wide? I like permutation tests. They require heavy computation, but they're trustworthy.

Permutation tests



- Permute/shuffle the phenotypes; keep the genotype data intact.
- Calculate $|T^\star(z)| \longrightarrow M^\star = \max_z |T^\star(z)|$
- We wish to compare the observed M to the distribution of $M^\star$.
- $\Pr(M^\star \geq M)$ is a genome-wide P-value.
- The 95th %ile of $M^\star$ is a genome-wide critical value
- We can't look at all $n!$ possible permutations, but a random set of 1000 is feasible and provides reasonable estimates of P-values and critical values



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