Quantitative Genomics and Genetics

BTRY 4830/6830; PBSB.5201.03

Optional Lecture 3: Alternative tests in GWAS

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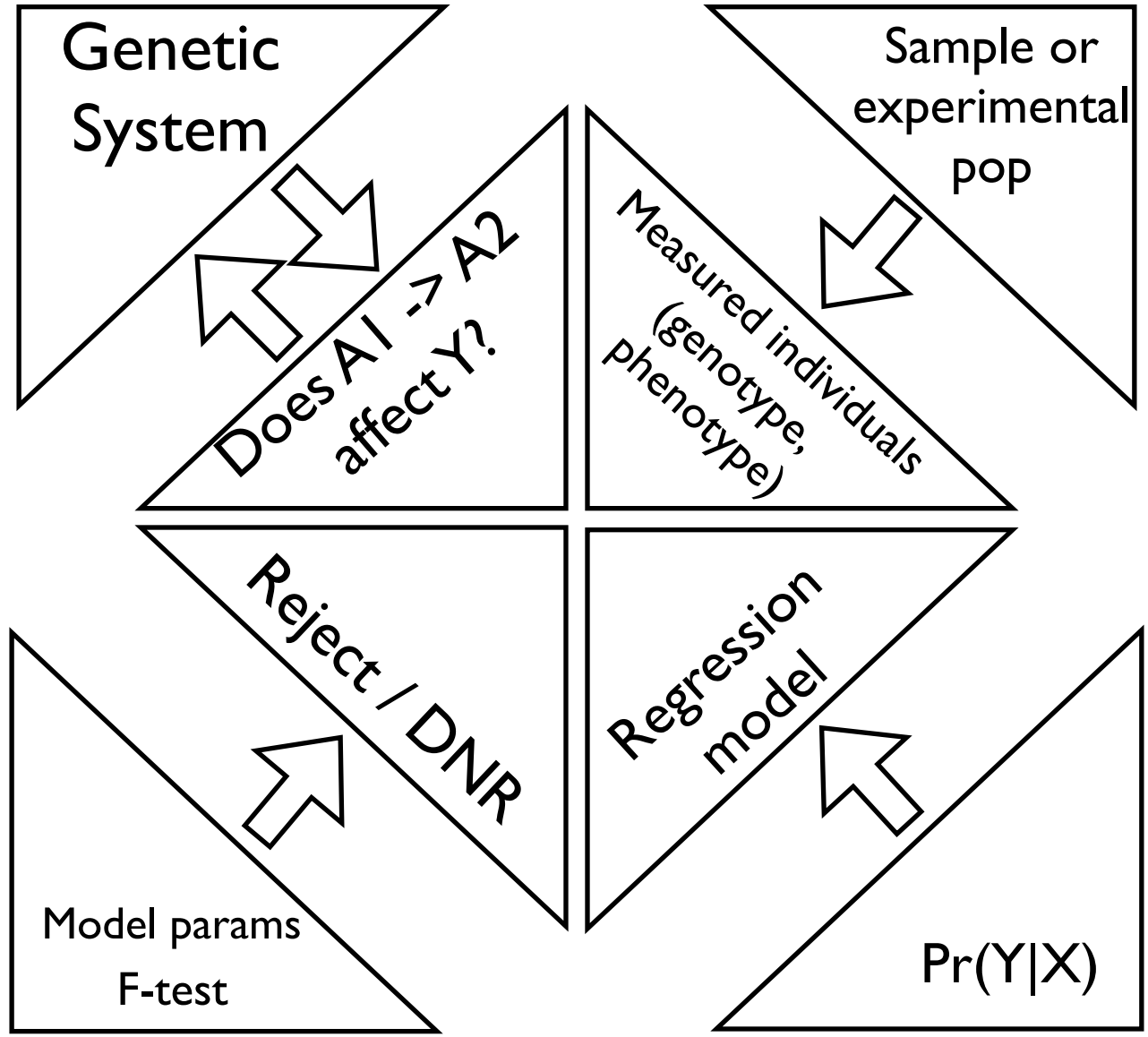
Summary of Optional Lecture 3

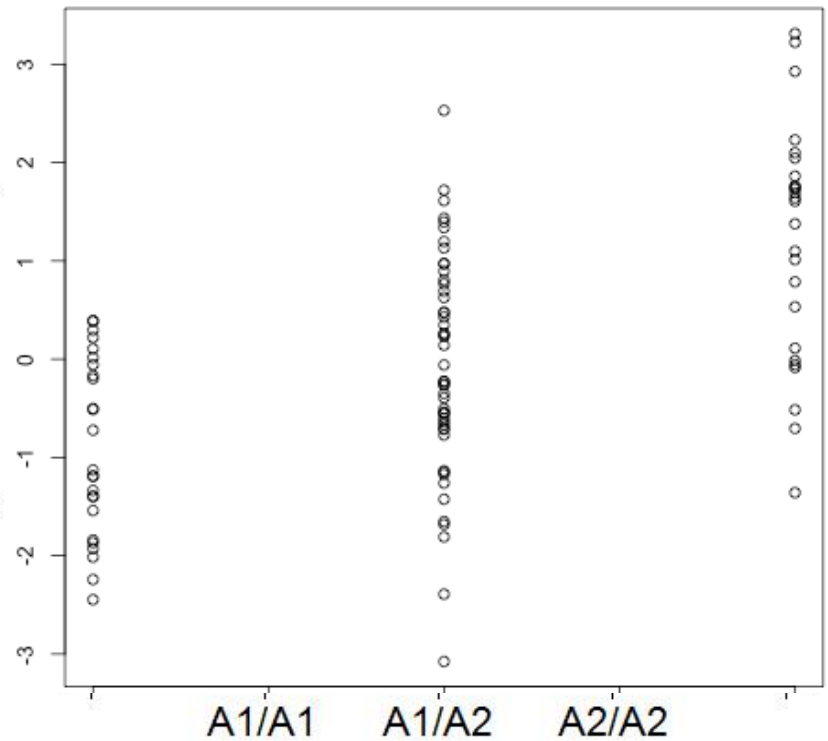
- Today we will discuss applying alternative tests in GWAS!

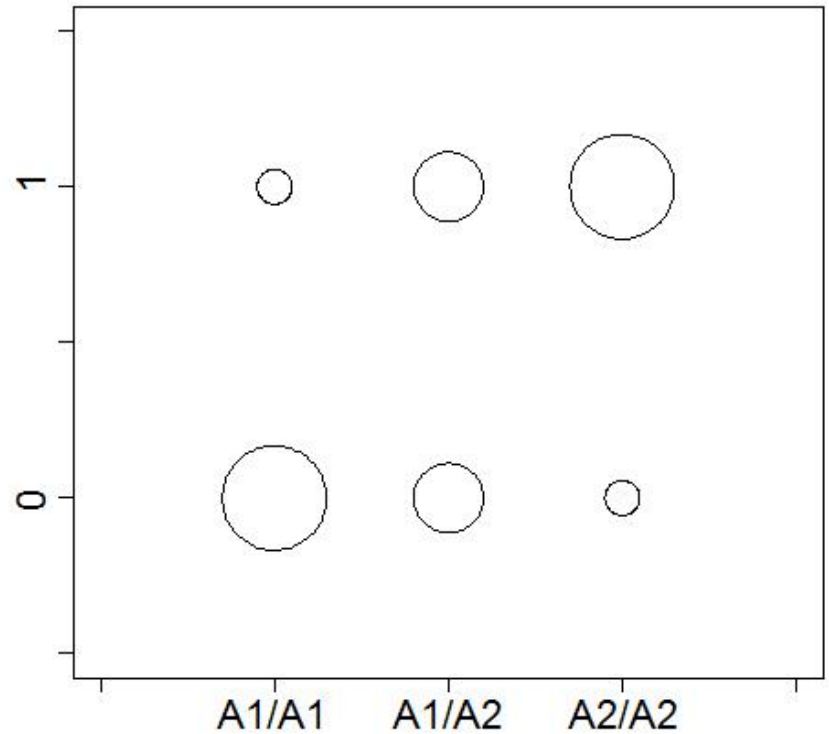
Conceptual Overview



Case / Control Phenotypes

- Let's contrast the situation, let's contrast data we might model with a linear regression model versus case / control data:





Alternative tests in GWAS I

- Since our basic null / alternative hypothesis construction in GWAS covers a large number of possible relationships between genotypes and phenotypes, there are a large number of tests that we could apply in a GWAS
- e.g. t-tests, ANOVA, Wald's test, non-parametric permutation based tests, Kruskal-Wallis tests, other rank based tests, chi-square, Fisher's exact, Cochran-Armitage, etc. (see PLINK for a somewhat comprehensive list of tests used in GWAS)
- When can we use different tests? The only restriction is that our data conform to the assumptions of the test (examples?)
- We could therefore apply a diversity of tests for any given GWAS

Alternative tests in GWAS II

- Should we use different tests in a GWAS (and why)? Yes we should - the reason is different tests have different performance depending on the (unknown) conditions of the system and experiment, i.e. some may perform better than others
- In general, since we don't know the true conditions (and therefore which will be best suited) we should run a number of tests and compare results
- How to compare results of different GWAS is a fuzzy case (=no non-conditional rules) but a reasonable approach is to treat each test as a distinct GWAS analysis and compare the hits across analyses using the following rules:
  - If all methods identify the same hits (=genomic locations) then this is good evidence that there is a causal polymorphism
  - If methods do not agree on the position (e.g. some are significant, some are not) we should attempt to determine the reason for the discrepancy (this requires that we understand the tests and experience)

Alternative tests in GWAS III

- We do not have time in this course to do a comprehensive review of possible tests (keep in mind, every time you learn a new test in a statistics class, there is a good chance you could apply it in a GWAS!)
- Let's consider a few examples alternative tests that could be applied
- Remember that to apply these alternative tests, you will perform *N* alternative tests for each marker-phenotype combinations, where for each case, we are testing the following hypotheses with different (implicit) codings of *X* (!!):

$$H_0 : Cov(Y, X) = 0$$

$$H_A : Cov(Y, X) \neq 0$$

Alternative test examples I

- First, let's consider a case-control phenotype and consider a chi-square test (which has deep connections to our logistic regression test under certain assumptions but it has slightly different properties!)

- To construct the test statistic, we consider the counts of genotype-phenotype combinations (left) and calculate the expected numbers in each cell (right):

	Case	Control	
A_1A_1	n_{11}	n_{12}	$n_{1.}$
A_1A_2	n_{21}	n_{22}	$n_{2.}$
A_2A_2	n_{31}	n_{32}	$n_{3.}$
	$n_{.1}$	$n_{.2}$	n

	Case	Control	
A_1A_1	$(n_{.1}n_{1.})/n$	$(n_{.2}n_{1.})/n$	$n_{1.}$
A_1A_2	$(n_{.1}n_{2.})/n$	$(n_{.2}n_{2.})/n$	$n_{2.}$
A_2A_2	$(n_{.1}n_{3.})/n$	$(n_{.2}n_{3.})/n$	$n_{3.}$
	$n_{.1}$	$n_{.2}$	n

- We then construct the following test statistic:

$$LRT = -2ln\Lambda = -2\sum_{i=1}^{3}\sum_{j=1}^{2} n_{ij} ln\left(\frac{n_i}{n_{.i}n_{j.}}\right)$$

- Where the (asymptotic) distribution when the null hypothesis is true is:

$$\chi^2_{d.f.=2} \qquad \text{d.f.} = (\#\text{columns-1})(\#\text{rows-1}) = 2$$

Alternative test examples II

- Second, let's consider a Fisher's exact test
- Note the the LRT for the null hypothesis under the chi-square test was only asymptotically exact, i.e. it is exact as sample size *n* approaches infinite but it is not exact for smaller sample sizes (although we hope it is close!)
- Could we construct a test that is exact for smaller sample sizes? Yes, we can calculate a Fisher's test statistic for our sample, where the distribution under the null hypothesis is exact for any sample size (I will let you look up how to calculate this statistic and the distribution under the null on your own):

	Case	Control
A_1A_1	n_{11}	n_{21}
A_1A_2	n_{21}	n_{22}
A_2A_2	n_{31}	n_{32}

- Given this test is exact, why would we ever use Chi-square / what is a rule for when we should use one versus the other?

Alternative test examples III

- Third, let's ways of grouping the cells, where we could apply either a chi-square or a Fisher's exact test
- For MAF = A1, we can apply a "recessive" (left) and "dominance" test (right):

	Case	Control
A_1A_1	n_{11}	n_{12}
$A_1A_2 \cup A_2A_2$	n_{21}	n_{22}

	Case	Control
$A_1A_1 \cup A_1A_2$	n_{11}	n_{12}
A_2A_2	n_{21}	n_{22}

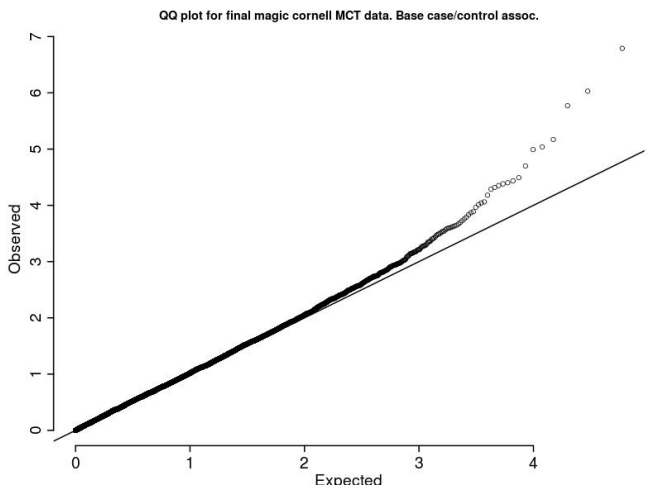
- We could also apply an "allele test" (note these test names are from PLINK):

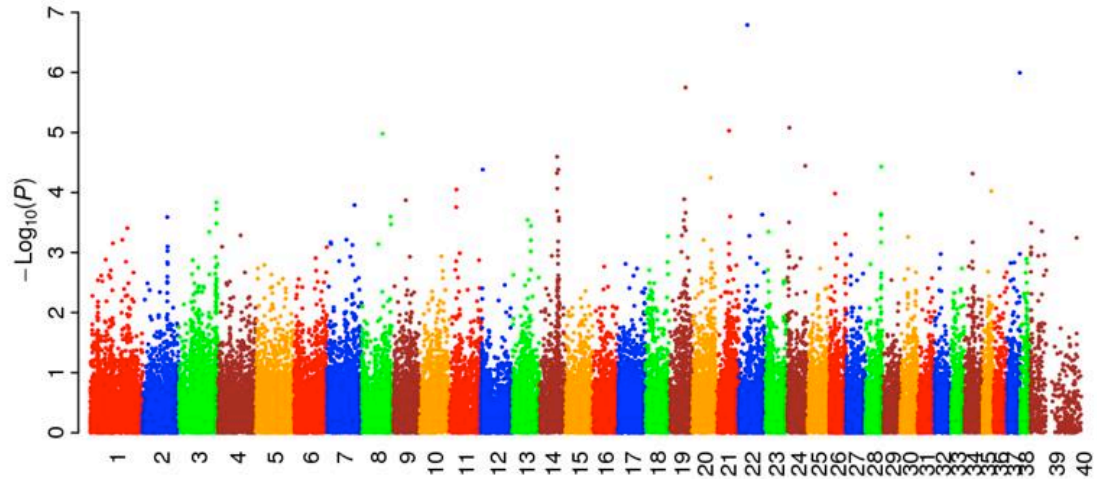
	Case	Control
A_1	n_{11}	n_{12}
A_2	n_{21}	n_{22}

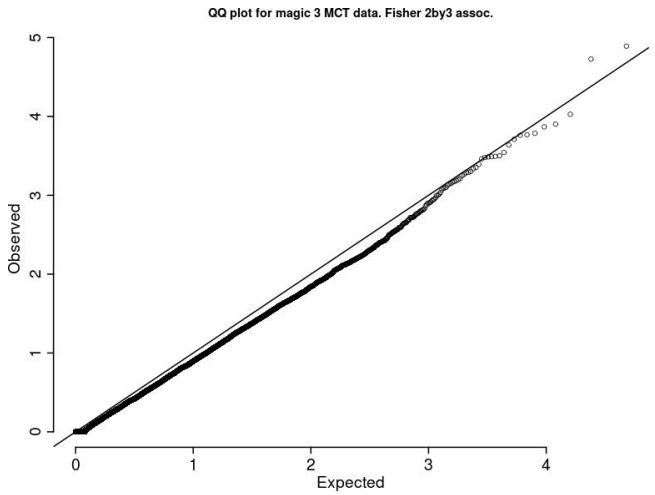
- When should we expect one of these tests to perform better than the others?

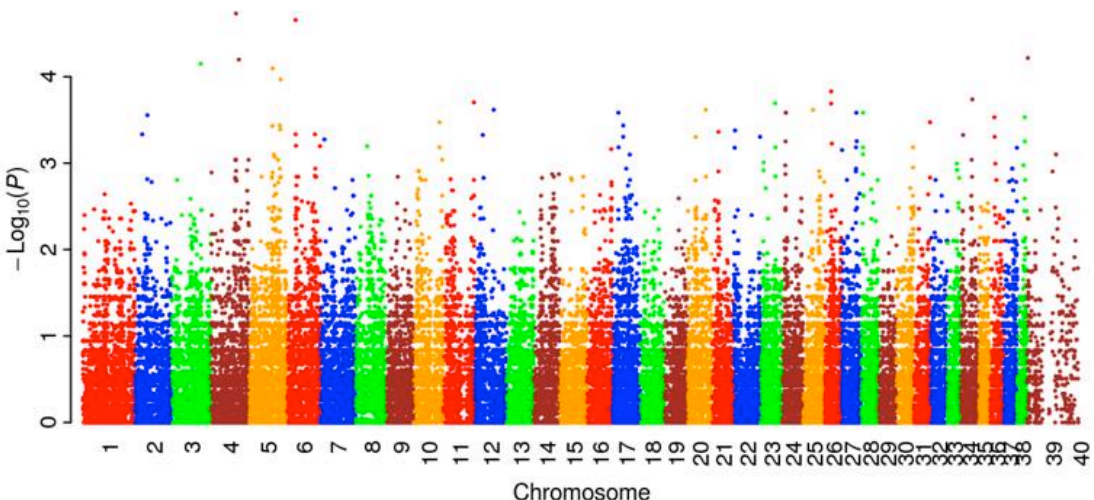
Comparing results of multiple analyses of the same GWAS data I

- I've run my initial analyses using several tests and produced the following (now what!?):









Comparing results of multiple analyses of the same GWAS data II

- The best case is that the same markers (SNPs) pass a multiple test correction regardless of the testing approach used, i.e. the result is robust to testing approach.
- In cases where this does not happen (most) it becomes helpful to understand why test results could be different:
  - Are tests capturing additive vs. dominance effects?
  - Are tests less powerful than others or depend on certain assumptions being true? Are they handling missing data in different ways?
  - Are particular covariates altering the results if included/excluded? Why might this be?
  - Does it depend on how you partition the data (e.g. batch effects)?
- This can help narrow down the set of tests you feel are the most informative. In general, a good publishing strategy is limiting yourself to one or two tests that both give you significant results that you believe!

That's it for today

- See you next time!