Center for Genomics Research and Innovation

H3ABioNet

Genome-Wide Association Study (GWAS): Association Analysis

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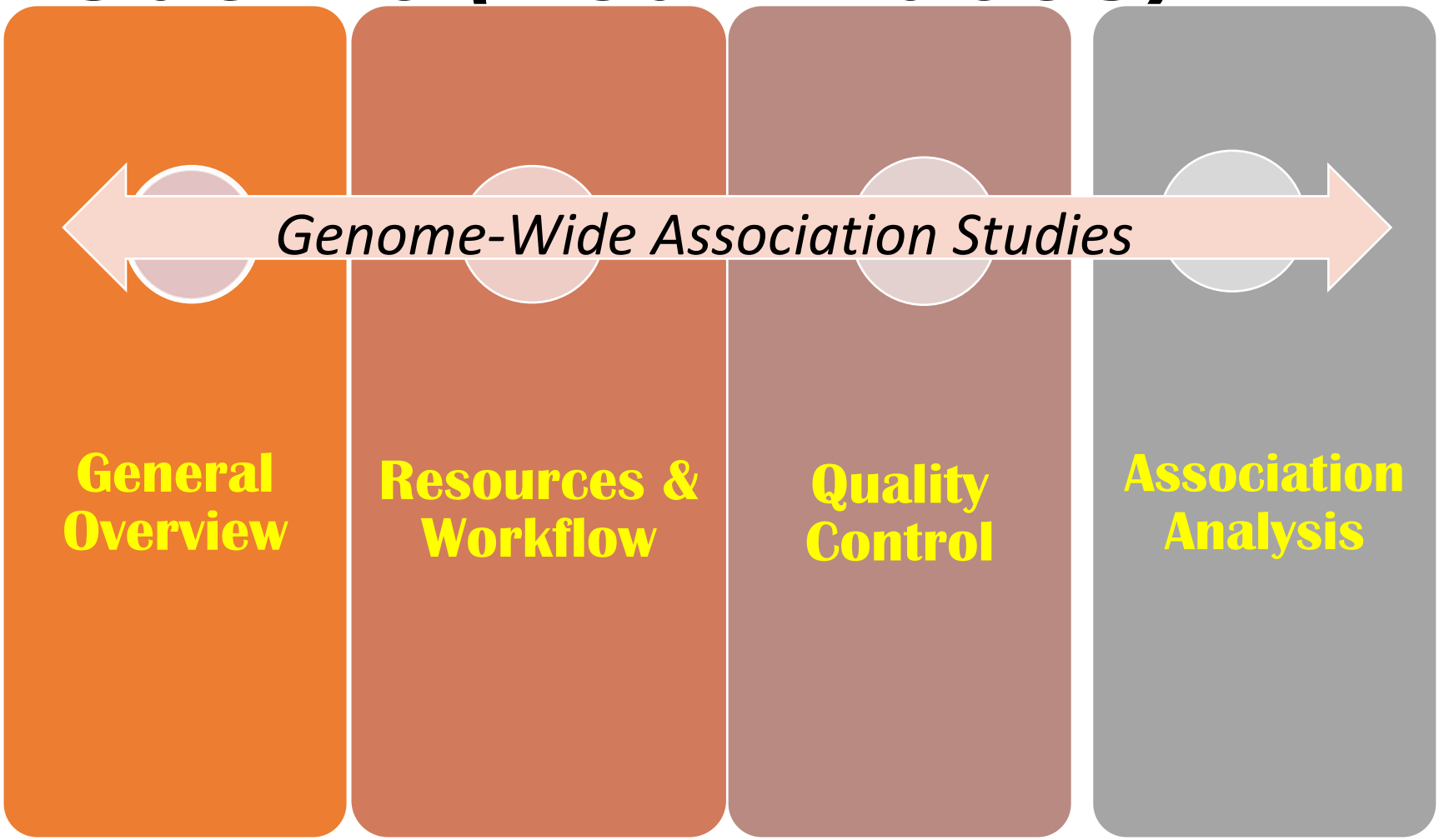
Outline (Four Videos)

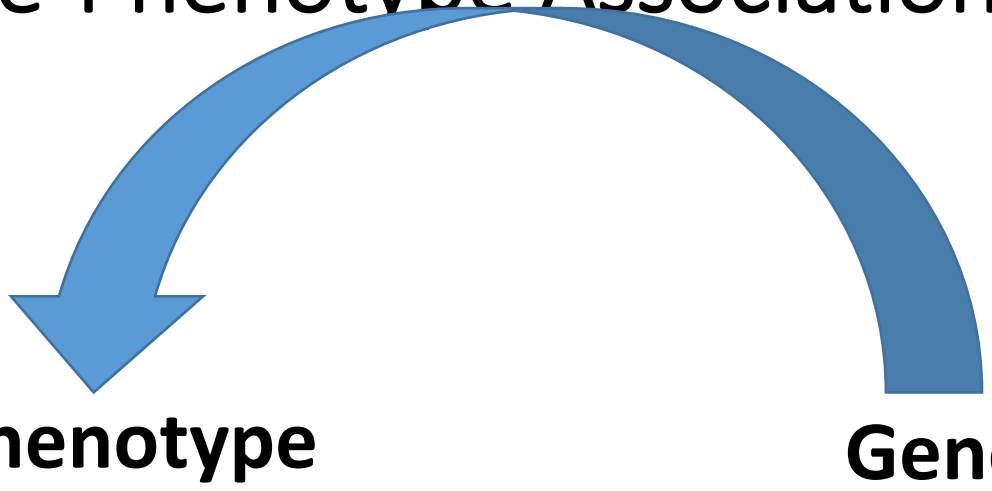


Intended Learning Outcomes

By the end of the session, students will be able to

- Describe the statistical models for identifying phenotype-genotype associations.
- Identify appropriate model for adjusting for potential confounding when performing genetic association study.
- Interpret plots from genetics association study

Genotype-Phenotype Associations



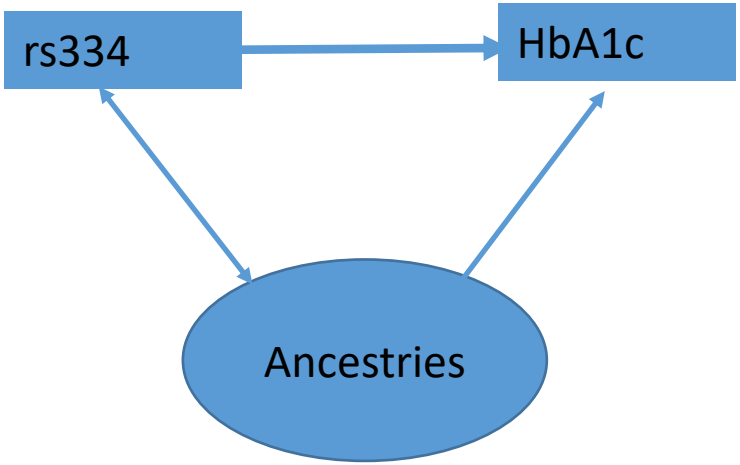
- **Case-control GWAS**

- Identify SNPs where one allele is significantly more common in cases than controls
- The SNP is *associated* with disease
- Logistic regression

Continuous trait GWAS

- Fit **linear regression** model for each (SNP, phenotype) pair

Mixed Model



- A major concern in GWAS is the need to account for the complicated dependence-structure of the data both between loci as well as between individuals. (Adjust for the confounding variable)

- For example, ethnic groups (and subgroups) often share distinct dietary habits and other lifestyle characteristics that leads to many traits of interest being correlated with ancestry and/or ethnicity

- The linear mixed model (LMM) is a powerful way to control covariation arising from complex correlation

Testing for association

- All methods produce a test statistic and a *p* value indicating how significant the association/correlation appears to be
  - i.e. how likely it was to have occurred by chance

- In GWAS, we require stringent significance levels (e.g. $p = 5 \times 10^{-8}$) to overcome the multiple testing problem incurred when we test many SNPs throughout the genome
  - If testing 1 million SNPs using $p = 0.05$, we would obtain 50,000 'significant' results just by chance!

  - Bonferroni correction

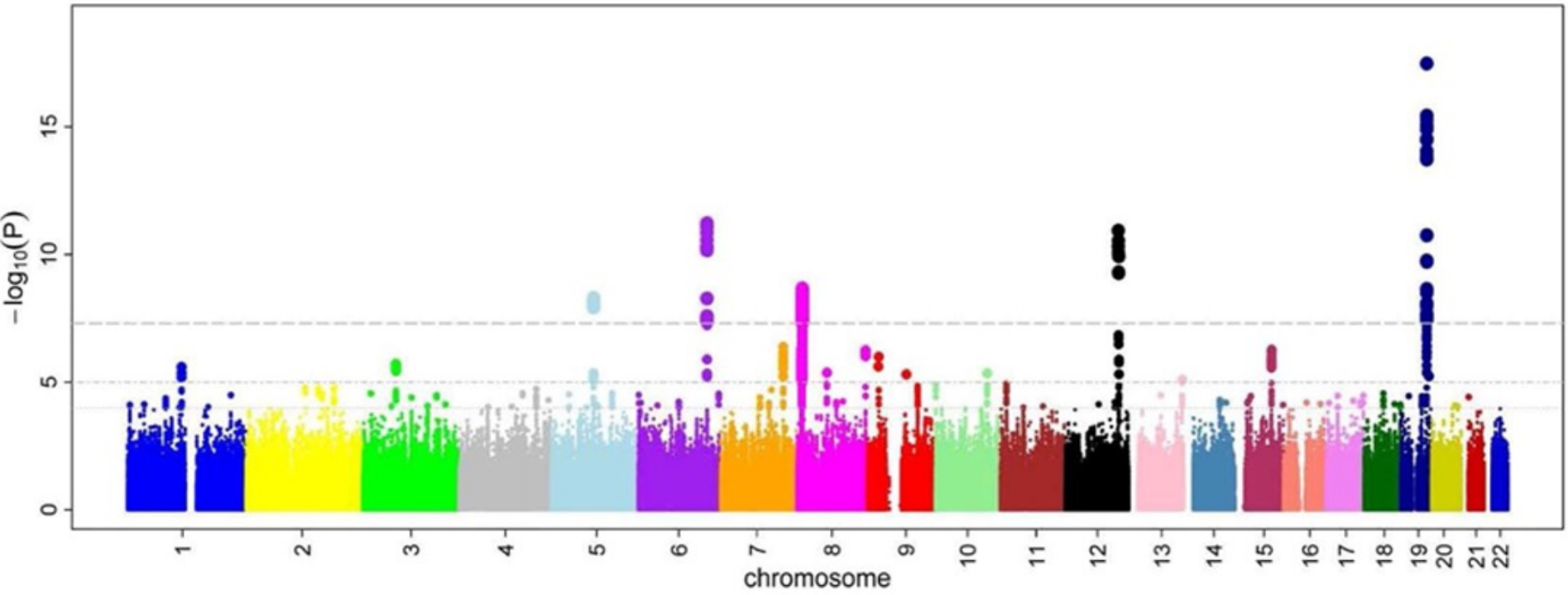
Useful software

- **PLINK (Standard tool for QC and association analysis)**
- http://pngu.mgh.harvard.edu/~purcell/plink

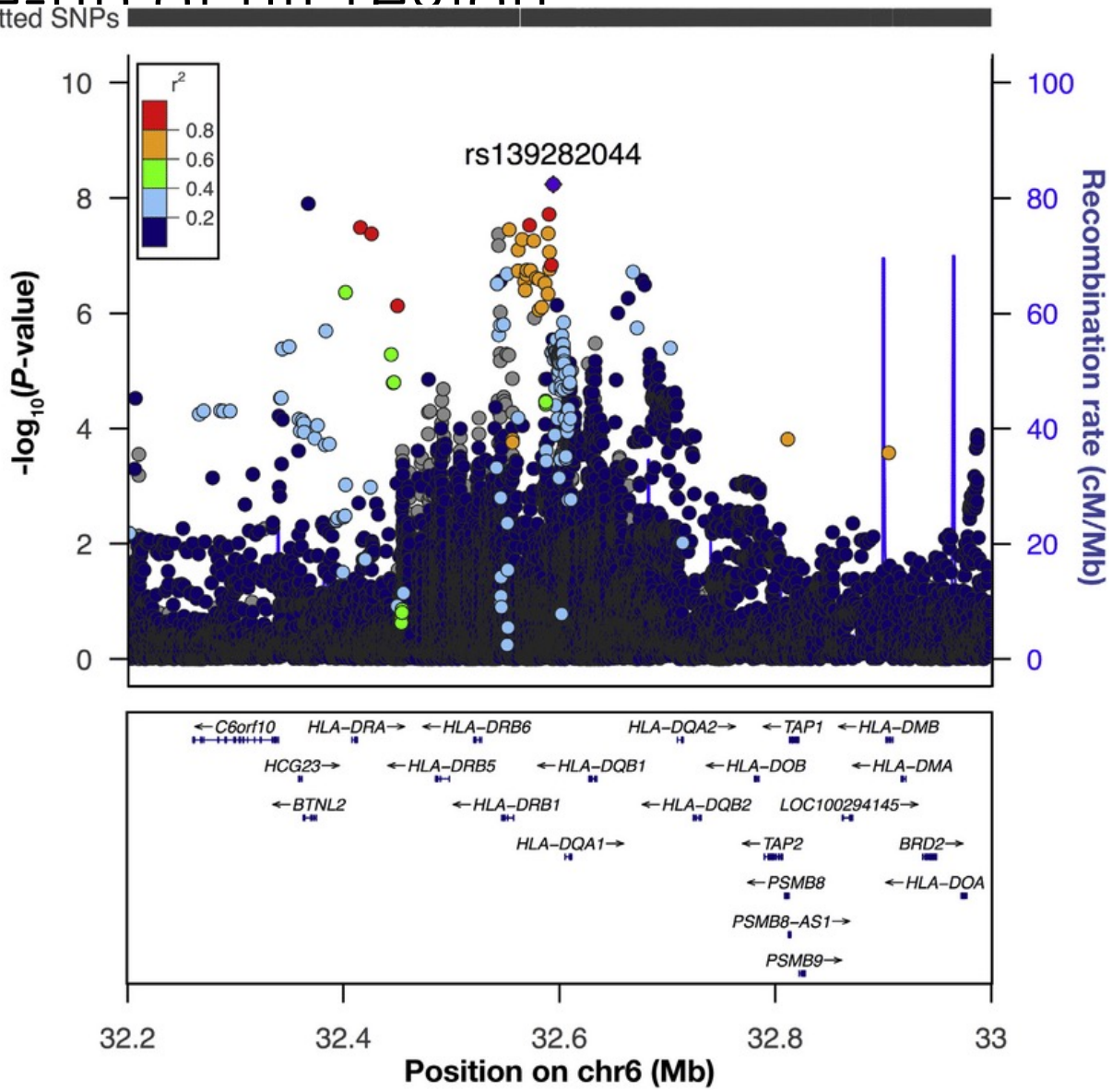
- **GEMMA (Association) – Implemented Mixed Model**
- http://home.uchicago.edu/xz7/software

- **SNPTEST (Association)**
- https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html

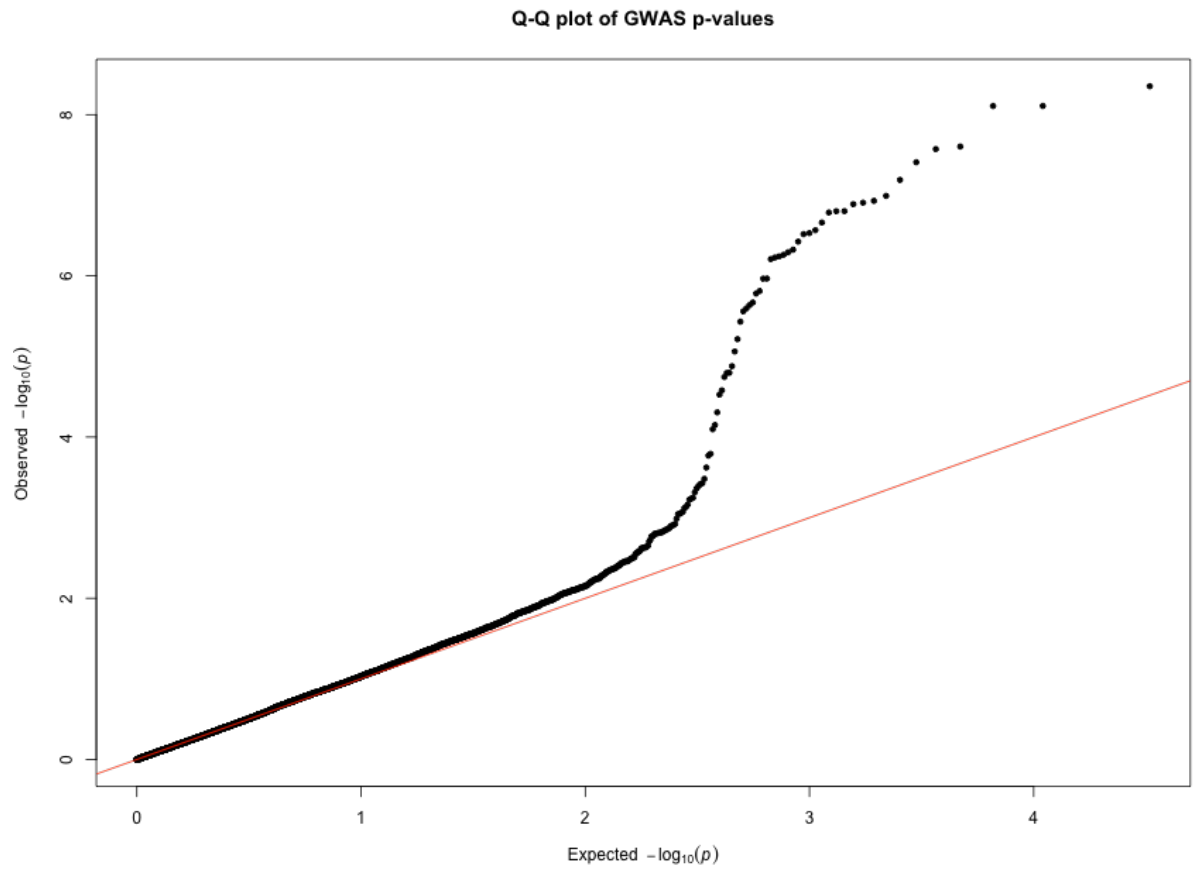
Manhattan Plot



Close-up of hit region



Quantile-Quantile (QQ) Plot



Conclusions

- **In designing GWAS, the selection of the appropriate association test depends on a number of factors:**
  - type of phenotype,
  - control for covariates eg population structure.
  - etc

- **Visualisation of GWAS output is key**
  - Manhattan
  - QQ Plot
  - Regional plot

Further Reading

Pearson, T.A. and Manolio, T.A., 2008. How to interpret a genome-wide association study. *Jama*, *299*(11), pp.1335-1344.
http://www.biostat.jhsph.edu/~iruczins/teaching/misc/gwas/papers/pearson2008.pdf

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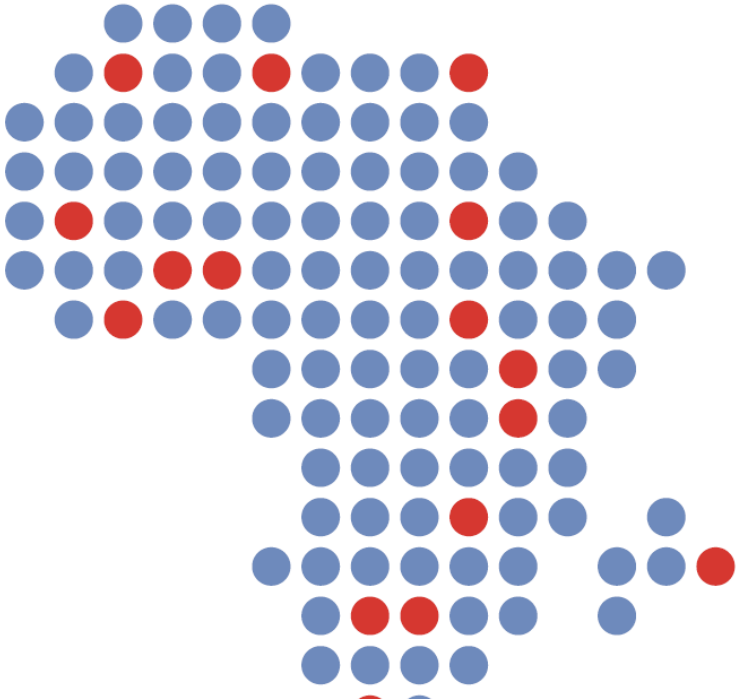

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