How to GWAS - ConGen 2022

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What is GWAS?

Genome Wide Association Study

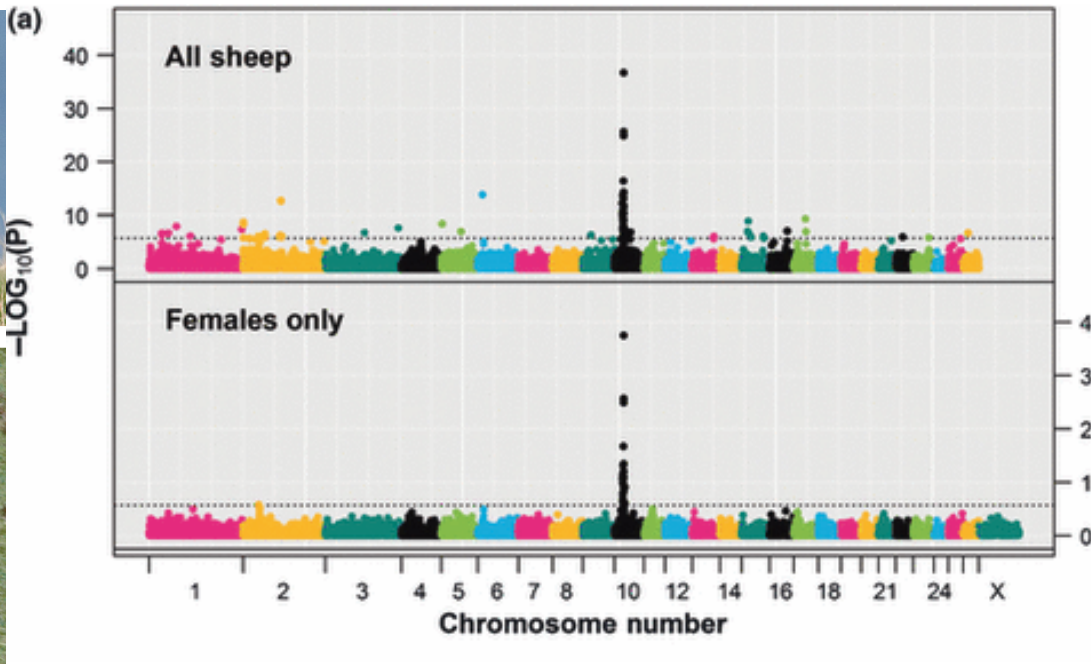
- $y = a + bx + g + e$
- y: phenotype
- b: fixed effect
- x: the SNP predictor coded as 0, 1, 2
- g: the polygenic random effect (e.g. Kinship matrix)
- e: the error term

Why do GWAS?

- Understand the genetic architecture of phenotypic traits
- link genotype to phenotype of individuals, extending quantitative genetics
- be able to measure selection directly on genomic regions, using fitness data

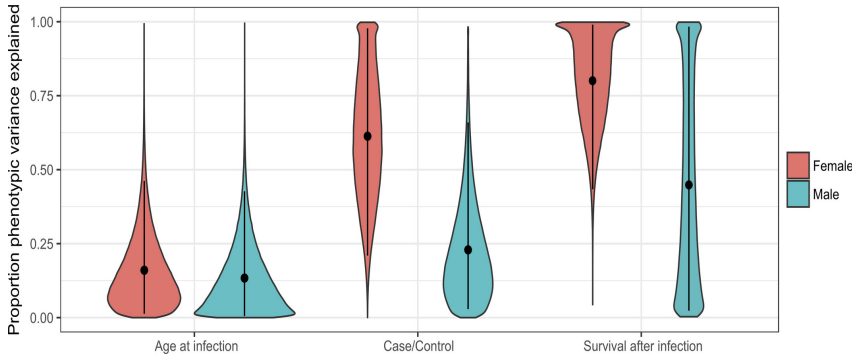
Soay Sheep Horns RXFP2 genotype

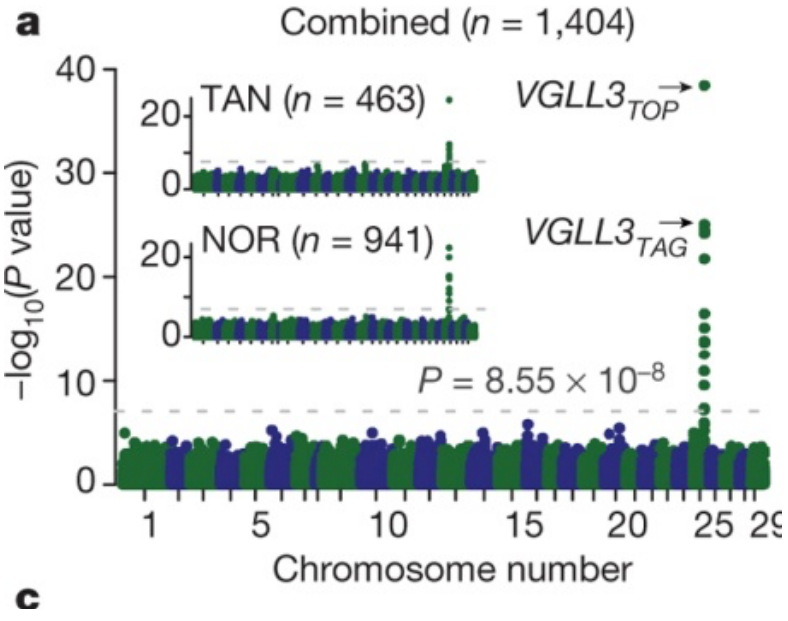
Johnson et al. 2011 Mol Ecol, Johnson et al. 2013 Nature



- 486 sheep
- 35 831 SNPs
- one huge effect locus, explains 76% of the variation in horn size

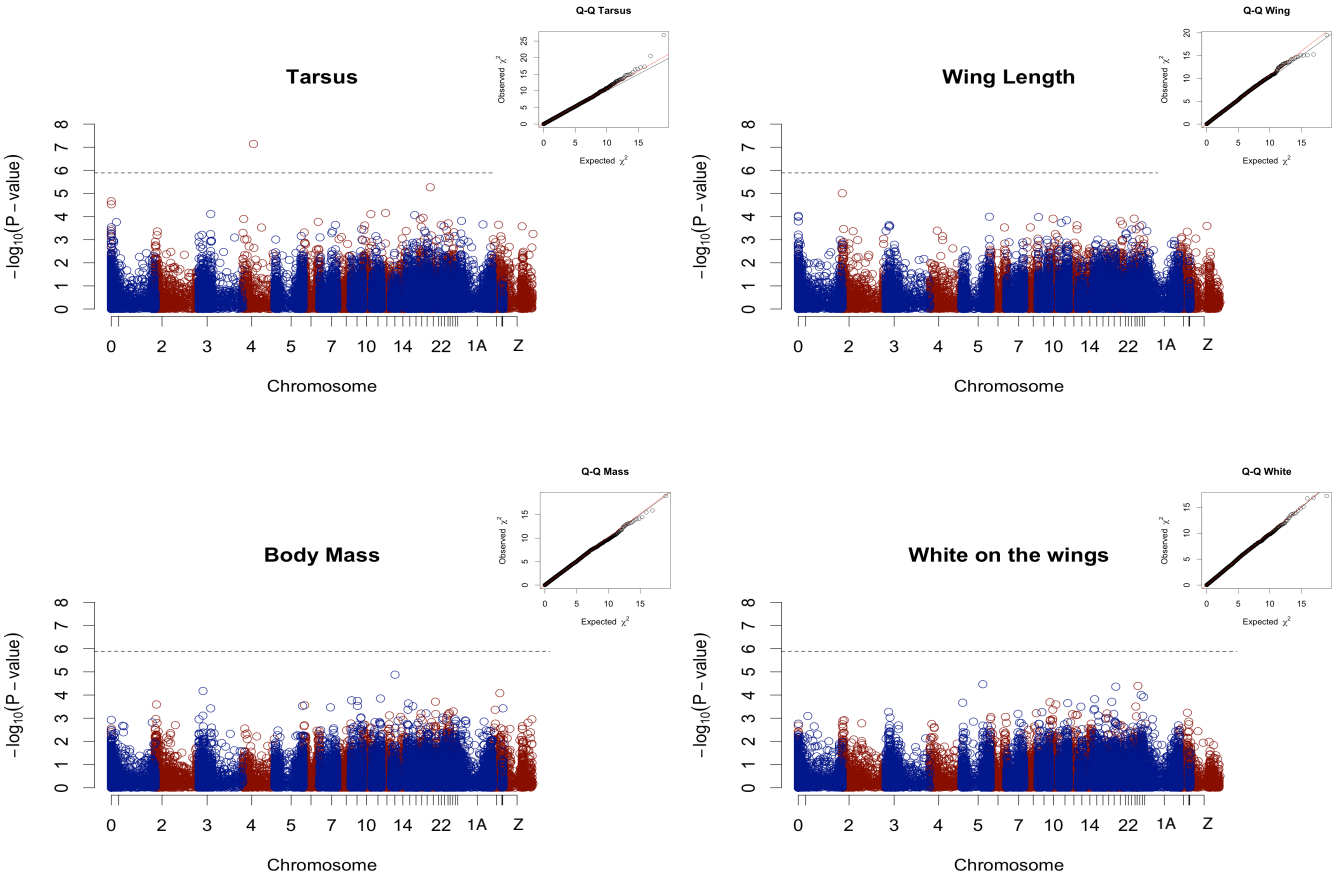
How often do people find huge effect loci using GWAS?





- Tasmanian devils face cancer 5 SNPs explain ~61% of variation in female survival (Margres et al. 2018 Mol Ecol)
- atlantic salmon - VGLL3 locus for delaying age of maturation (Barson et al. 2015 Nature)

What are the expectations for a GWAS?



- No significant SNPs for morphological traits
- 3 SNPs explaining ~3% of the variation in clutch size

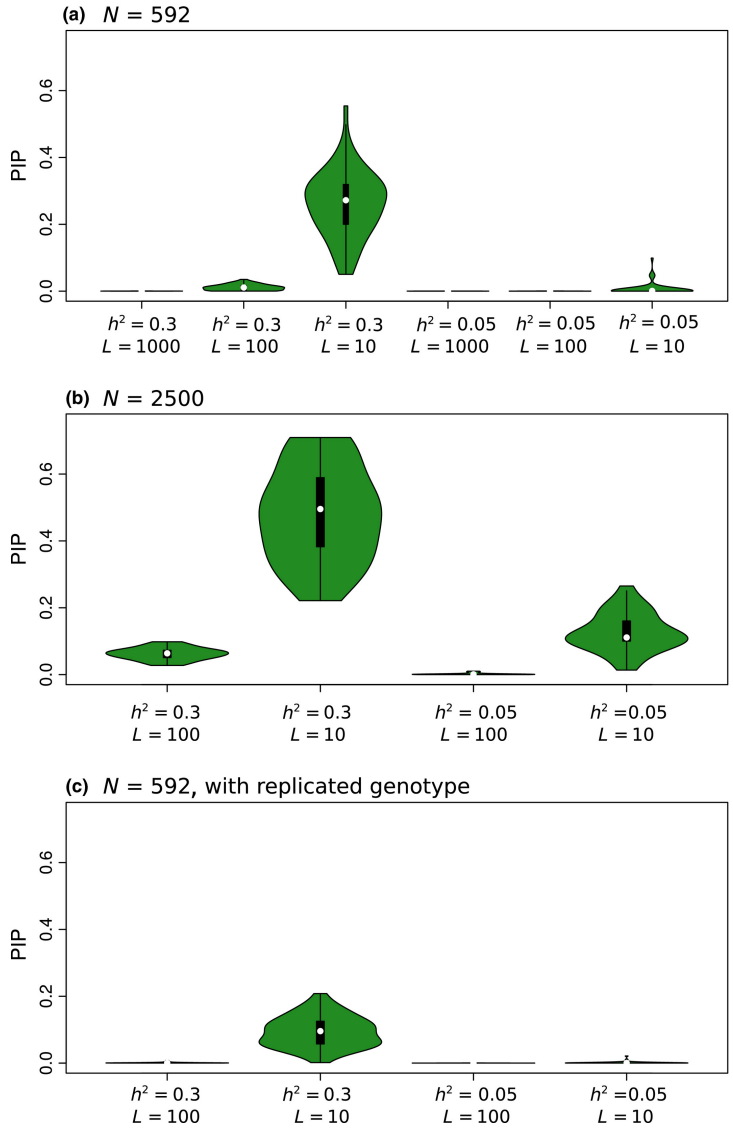
Silva et al. 2017 Heredity, Husby et al. 2014 Proc B

What are the expectations for a GWAS?

- Even if statistically significant loci are identified, they often explain a small proportion of the variation.
- 'Missing Heritability'
- not great for prediction of the trait

Some considerations for GWAS

- heritability of the trait
- genetic architecture of the trait (often unknown!)
- Linkage Disequilibrium
- number of individuals sampled
- allele frequency of causal loci (also unknown!)



Kardos 2015 MER, Gompert 2017 Mol Ecol

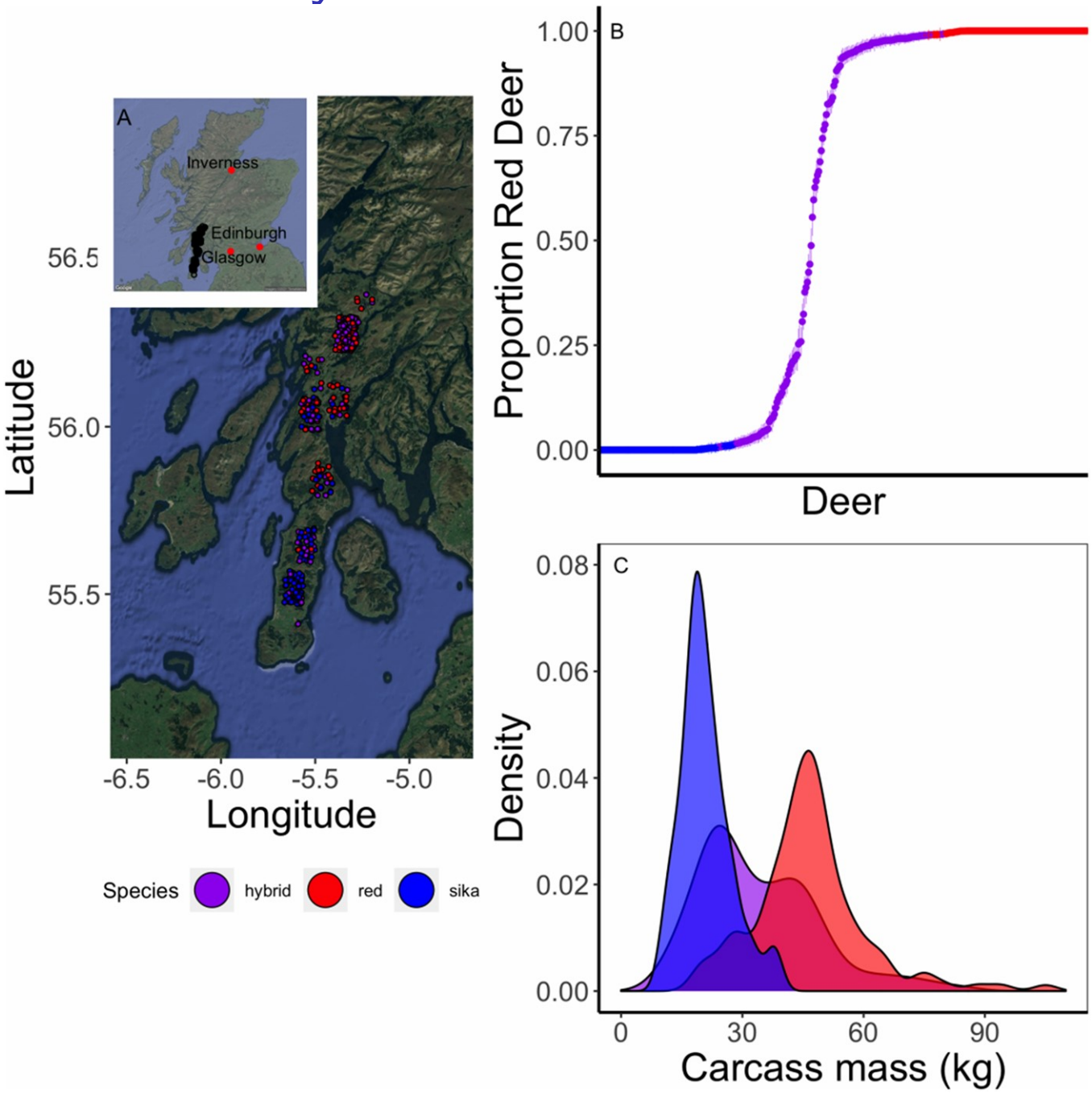
Some solutions

- Sample more individuals!
- replicated samples of individuals (RepeatABEL, RIP)
- Admixture mapping instead of within population GWAS
- sample in closed populations (but know this limits generalizability)

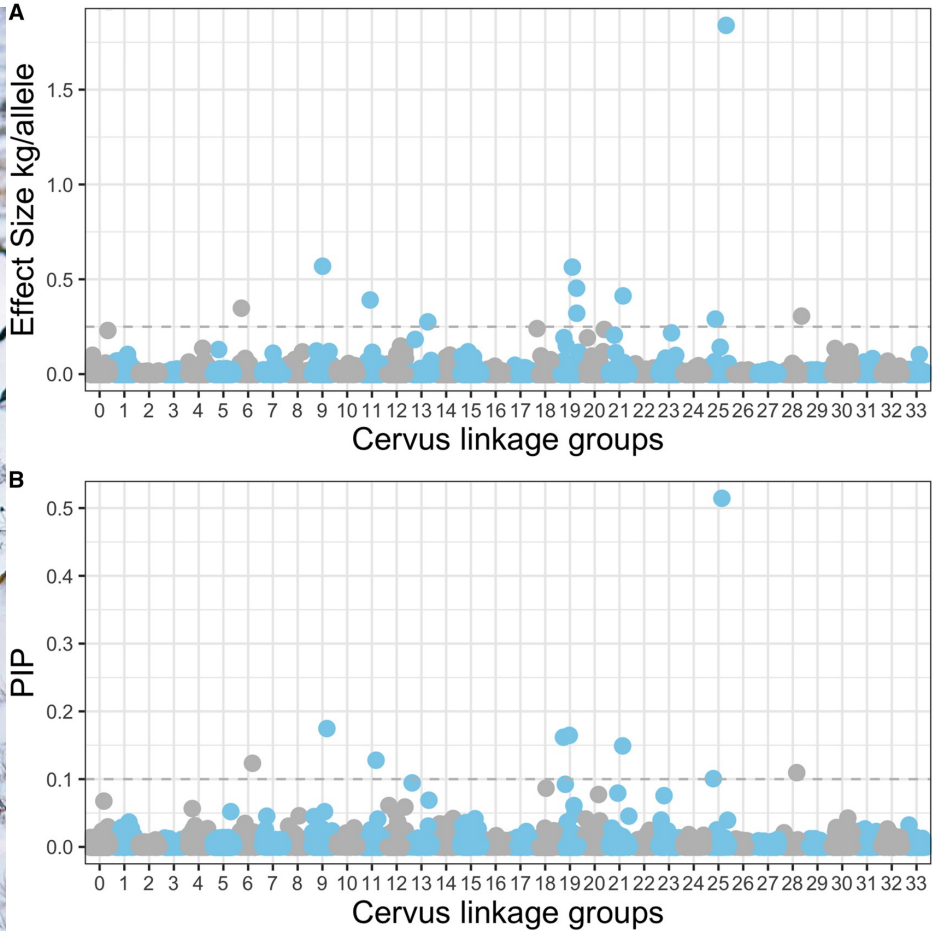
What is Admixture mapping?

- special case of GWAS
- GWAS on individuals with recombinate genotypes (from diverged species/populations interbreeding)
- Allows for QTL mapping with fewer individuals and fewer markers because of long tracts of LD

Deer Case study



Deer Case study



- McFarlane & Pemberton 2021 G3

So what are we doing today?

- Simulated GWAS, using GEMMA
- BSLMM in GEMMA (GEMMA can do LMM as well)
- Simulated 10,000 SNPs, 2000 individuals
- ' Choose your own adventure'

What is BSLMM, and how does it work?

-Bayesian Sparse Linear Mixed Model

- Models two distributions for the genetic effects:
  - polygenic distribution where we estimate the overall genetic variation -sparse (or beta) distribution where we estimate the effect sizes for specific SNPs
  - assumings a negligible effect size for all the other SNPs
- This sparse framework allows us to estimate effect sizes for only a few parameters, which helps with the p»N problem that we have.
  - ask me about sparsity in general, it's a current research avenue of mine!
- Gives n.gamma, or number of expected SNPs explaining the trait.