

GWAS Power and Study Design

Sample Size Calculations

Suppose you are conducting a GWAS for quantitative trait *YFT* (your favorite quantitative trait), and you want to collect $N = 100,000$ individuals. For all of the calculations use the genome-wide threshold of $\alpha = 5 \times 10^{-8}$ when determining power.

- At a power threshold of 0.8, what is the minimal standardized effect size (β) detectable for a fully typed variant $r^2 = 1$ at an MAF of:
 - 5%
 - 1%
 - 0.1%
- Your colleague wants to see if a specific missense variant at 0.1% frequency in the population (with an imputation $r^2 = 0.8$), would be detectable in your current GWAS design?. What would be the minimal effect-size detectable for this variant?

◆◆ GWAS Discovery Rate

1. Fixing GWAS power at 0.8 and assuming fully typed variants ($r^2 = 1$), if causal variant effects are drawn from $\beta_{causal} \sim \mathcal{N}(0, \sigma^2)$, what is the *expected fraction of additional discoveries* made in going from $N_1 = 10^4$ to $N_2 = 10^5$ when $\sigma^2 = 2$? (Assume causal allele frequencies are drawn from the Uniform distribution).
2. If $\beta|p \sim N(0, \sigma^2)$, where $\sigma^2 = (p(1-p))^\alpha$ for causal variants (e.g. the effect size is linked to allele frequency), what is the expected fraction of additional discoveries when $\alpha = 0.75$? (assume causal allele frequencies are drawn from the Uniform distribution).

Provide either an analytical solution or a plot reflecting the numerical solution for both scenarios.

◆◆◆ Effect of Tagging Variant LD

The r^2 measure of LD is critical when you do not have direct access to a causal variant and only have a tagging variant. If we assume that $p_{tag} \geq p_{causal}$, the expression is:

$$r_{max}^2(tag, causal) = \frac{(1 - p_{tag})(1 - p_{causal})}{p_{tag}p_{causal}}$$

Using the expressions for GWAS power for a quantitative trait, and $r_{max}^2(p_{tag}, p_{causal})$, show that:

$$Power_{tag} \geq Power_{causal} \quad \forall \quad p_{tag} \geq p_{causal}$$

◆◆ Comparing GWAS

Your colleague has an interesting case where *YFT* is highly prevalent in a different population (lets say population “B”) and wants to understand if the same variant is driving this increase in prevalence. Your collaborator has access to $N_B = 50000$ samples, but doesn’t have a good sense of whether this would be well-suited to address the idea.

If the effect-size of the causal variant is the same (e.g. $\beta_A = \beta_B$), what would be the difference in frequency of the causal variant required to maintain a power of 80% if the variant in population *A* is at 0.1% frequency? (Assume $N_A = 100,000$)

GWAS Practical

For a GWAS practical, we will use publicly available summary statistics from the Pan-UKBB project. Specifically we will use data for a dataset on total bilirubin (a key liver enzyme) where GWAS was performed separately across six different ancestries in the UK Biobank. The ancestral groupings are:

- EUR = European ancestry ($N = 399286$)
- CSA = Central/South Asian ancestry ($N = 8395$)
- AFR = African ancestry ($N = 6176$)
- EAS = East Asian ancestry ($N = 2549$)
- MID = Middle Eastern ancestry ($N = 1491$)
- AMR = Admixed American ancestry ($N = 933$)

To obtain the data for this exercise run:

```
wget https://pan-ukb-us-east-1.s3.amazonaws.com/sumstats_flat_files/
      biomarkers-30840-both-sexes-irnt.tsv.bgz
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Genomic Inflation Factor

While many covariates have been accounted for when evaluating genetic effects - it is possible that there are still unobserved confounders present. One way to evaluate the extent of possible confounding has been using the genomic-inflation factor, which is defined as:

$$\hat{\lambda}_{GC} = \text{median}(\hat{\chi}^2) / F_{\chi_1^2}^{-1}(0.5)$$

where $F_{\chi_1^2}^{-1}(0.5) \approx 0.455$ is the expected median of the chi-squared distribution with 1 degree of freedom under the null hypothesis of no association.

1. Estimate $\hat{\lambda}_{GC}$ for each individual population separately using the relationship that $\hat{\chi}^2 = \left(\frac{\hat{\beta}}{s_{\beta}}\right)^2$.
2. Are the estimates of λ_{GC} significantly > 1 for each population? (Hint: use bootstrapping to re-sample the effect-sizes to construct empirical 95% confidence intervals)
3. ♦ Re-estimate λ using only every 10000th variant to avoid the effect of linkage disequilibrium and evaluate the differences relative the non LD-pruned version. Comment on how LD may violate some of the assumptions of λ_{GC} .

Power & Shared Signals

One of the useful things about the Pan-UKBB project is that it can illustrate how to compare the *power* of GWAS across different study designs and sample-populations.

1. For a start, let us compare the intersection of signals found at a genome-wide threshold $\alpha = 5 \times 10^{-8}$ in the EUR and CSA sample subsets? Plot the fraction of signals that overlap as a function of $\alpha \in \{10^{-4}, 10^{-20}\}$
2. Since we have the allele-frequency of the variants in each ancestry subset, for all shared marginal signals at the detection threshold α , estimate the power to detect each of the shared signals? What is the mean detection power threshold for shared signals at different values of α ? (NOTE: assume that $\hat{\beta} \approx \beta_{causal}$ and $r^2 = 1$ for simplicity, though consider how violations of these assumptions might alter results)