Introduction to GWAS and Polygenic Risk Score

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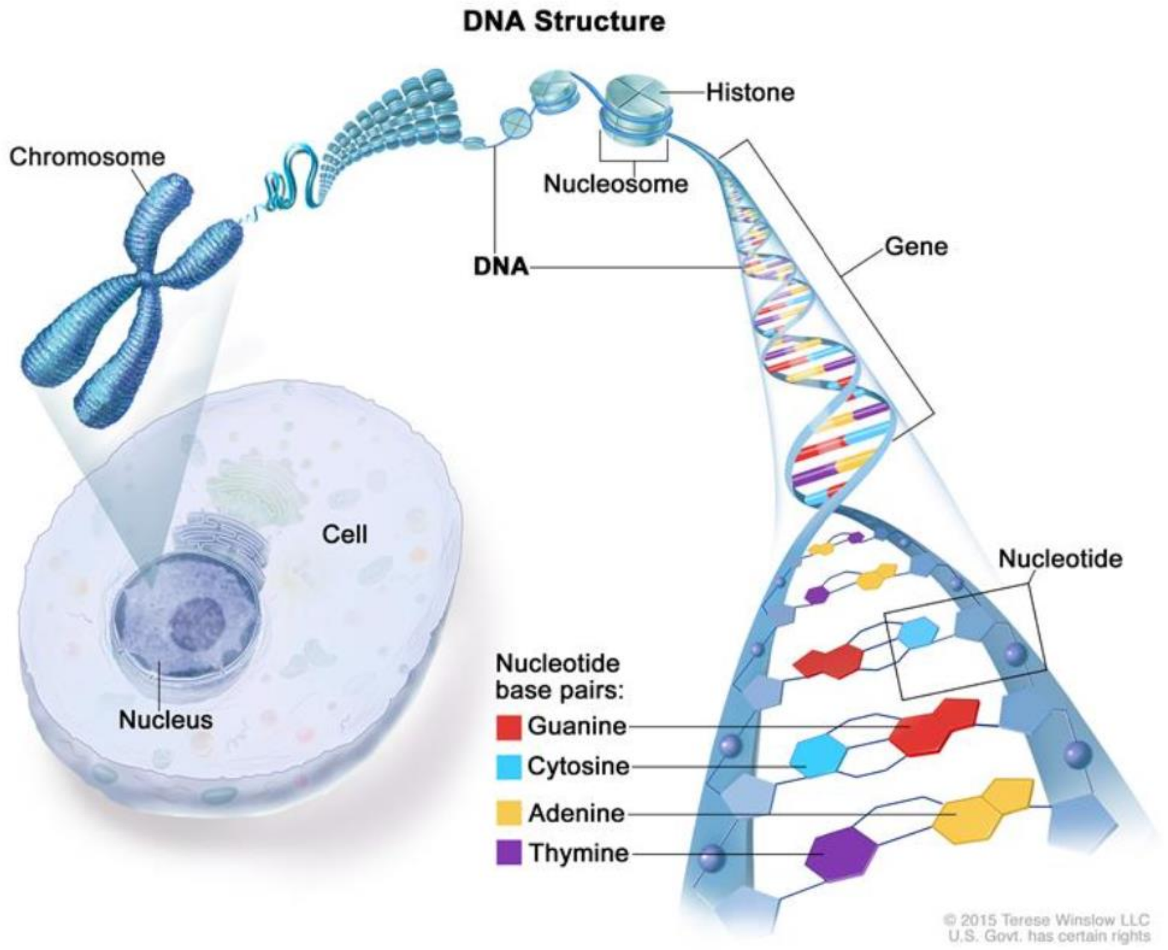
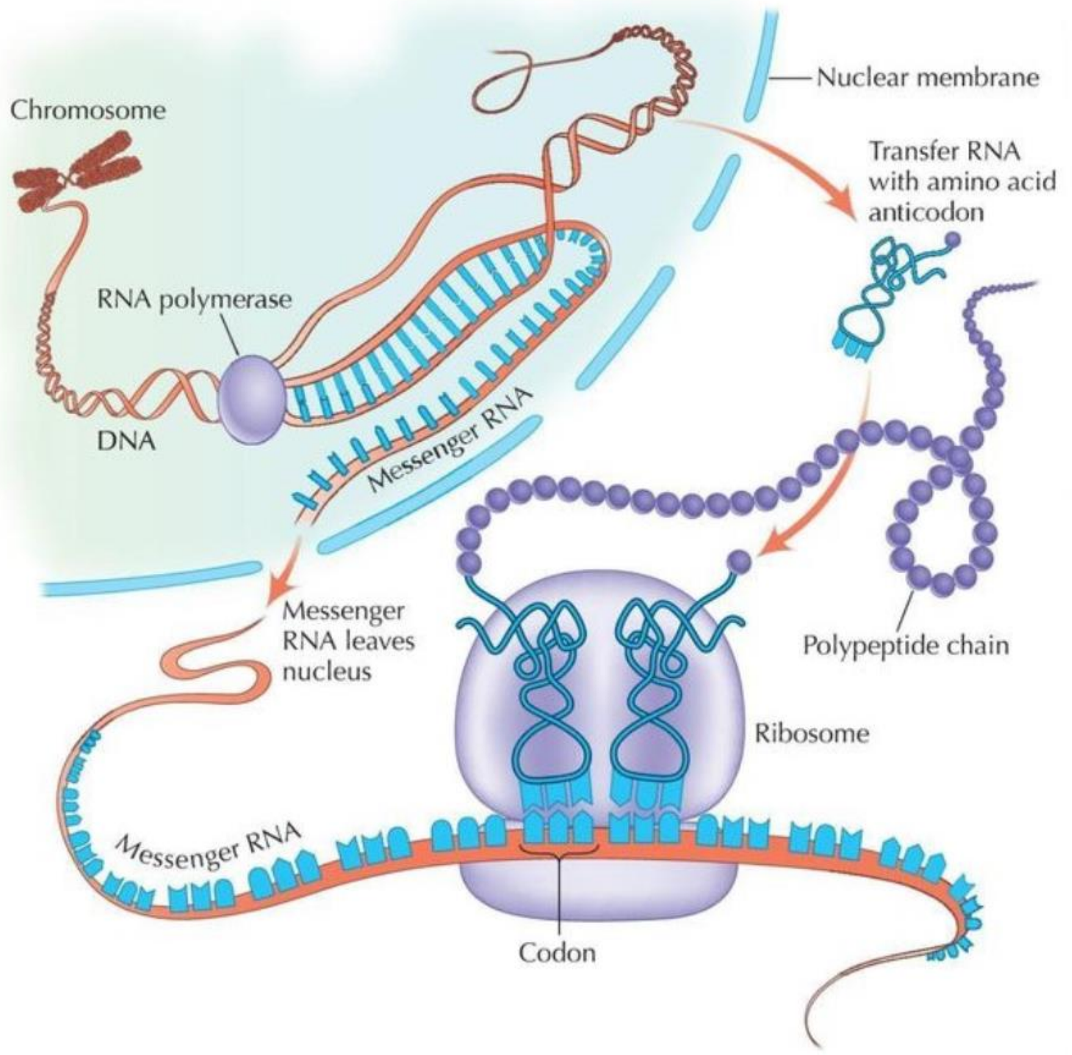
January 2026

DNA…?

- Cell → Nucleus → Chromosome → DNA



The central dogma of molecular biology



DNA

↓ Transcription

RNA

↓ Translation

PROTEIN

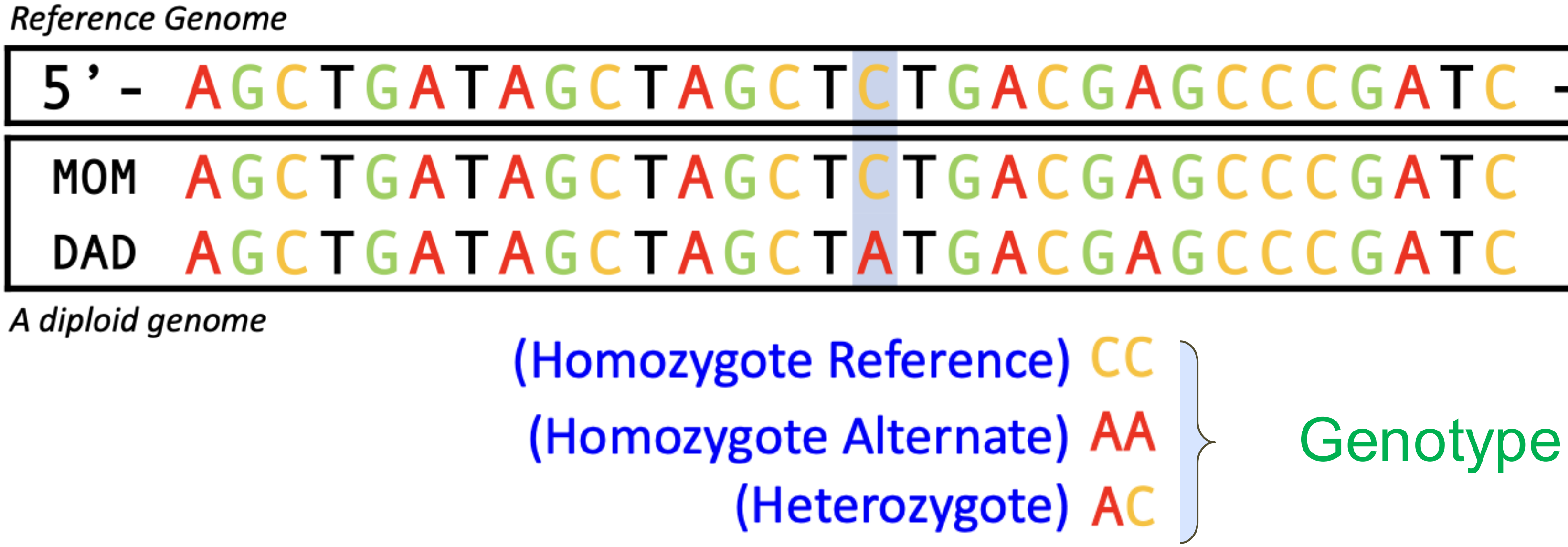
(Phenotype)

Human Genome Overview

- Total Genome Length $\approx$ 3 billion base pairs
- Inter-individual Genomic Similarity $\approx$ 99.9%
  Genomic Differences $\approx$ 0.1% (3 million base pairs)
- These differences are called "Single Nucleotide Polymorphisms (SNPs)"

Sigle Nucleotide Polymorphism (SNP)

- Human Genome Project
  - Collected allele data across nearly the entire human genome.



Reference Genome

5'- AGCTGATAGCTAGCTCTGACGAGCCCGATC -3'

MOM AGCTGATAGCTAGCTCTGACGAGCCCGATC

DAD AGCTGATAGCTAGCTATGACGAGCCCGATC

A diploid genome

(Homozygote Reference) CC

(Homozygote Alternate) AA

(Heterozygote) AC

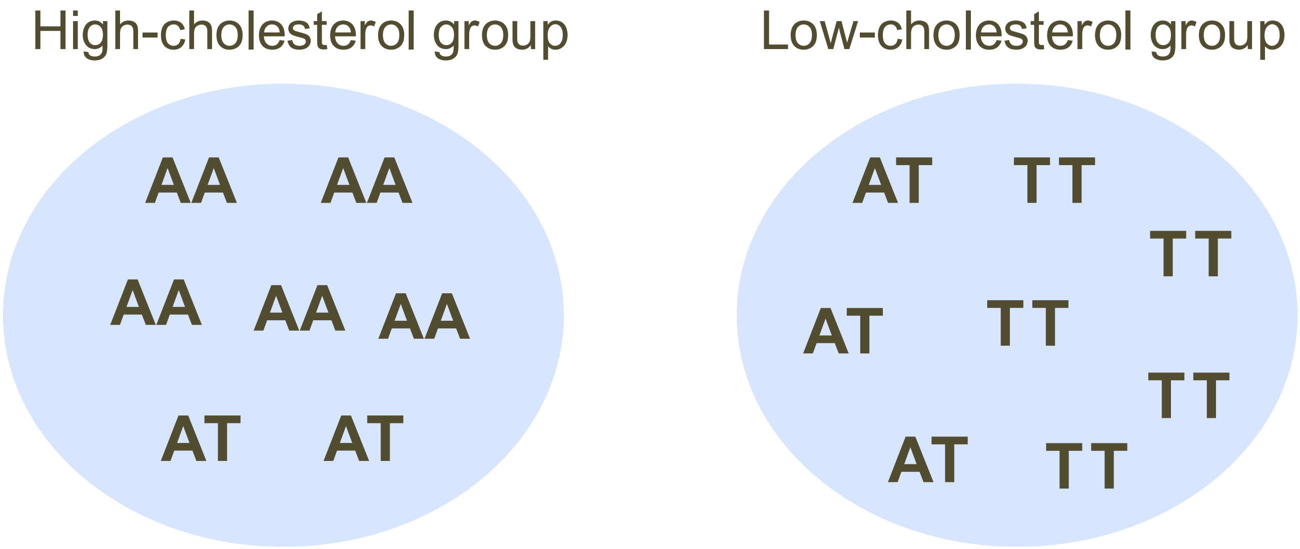
Genotype

- SNP genotyping
  - At each SNP location, we observe genotype information that reflects the combination of alleles inherited from both parents.

Genome-Wide Association Study (GWAS)

- Identify genetic variants (e.g., SNPs) associated with specific traits or diseases of interest.
  - e.g. cholesterol levels or well-being outcomes

- e.g., at a certain SNP, we observed the following genotypes



High-cholesterol group

AA AA

AA AA AA

AT AT

Low-cholesterol group

AT TT

TT

AT TT

TT

AT TT

Statistical Testing in SNP Analysis

- Testing methods
  - Continuous traits:
    - Two-sample comparison: t-test
    - Multiple group comparison: ANOVA
    - Simple linear regression
  - Categorical traits:
    - Chi-squared test, Fisher's exact test
    - Logistic / Multinomial regression
  - etc. (more details on this later.)

- We can prioritize SNPs through statistical significance based on their p-values.

SNP data structure

Sample ID	SNPs					
	1	2	3	4	5	…
1	AA	GC	CC	TT	GC	
2	AG	GC	CC	TT	GC	
3	GG	CC	TT	AT	CC	
4	AG	CC	TC	TT	CC	
5	AG	CC	TT	AT	CC	…
6	GG	GC	TC	AT	CC	
7	GG	CC	TC	TT	CC	
8	AG	CC	CC	TT	CC	
9	GG	CC	CC	TT	CC	
10	GG	GG	CC	AT	CC	
…						

GG=0	CC=0		CC=0
AG=1	GC=1	…	GC=1
AA=2	GG=2		GG=2

Dependent variable

- Disease
- Phenotypes
- Psychological outcomes
- etc.

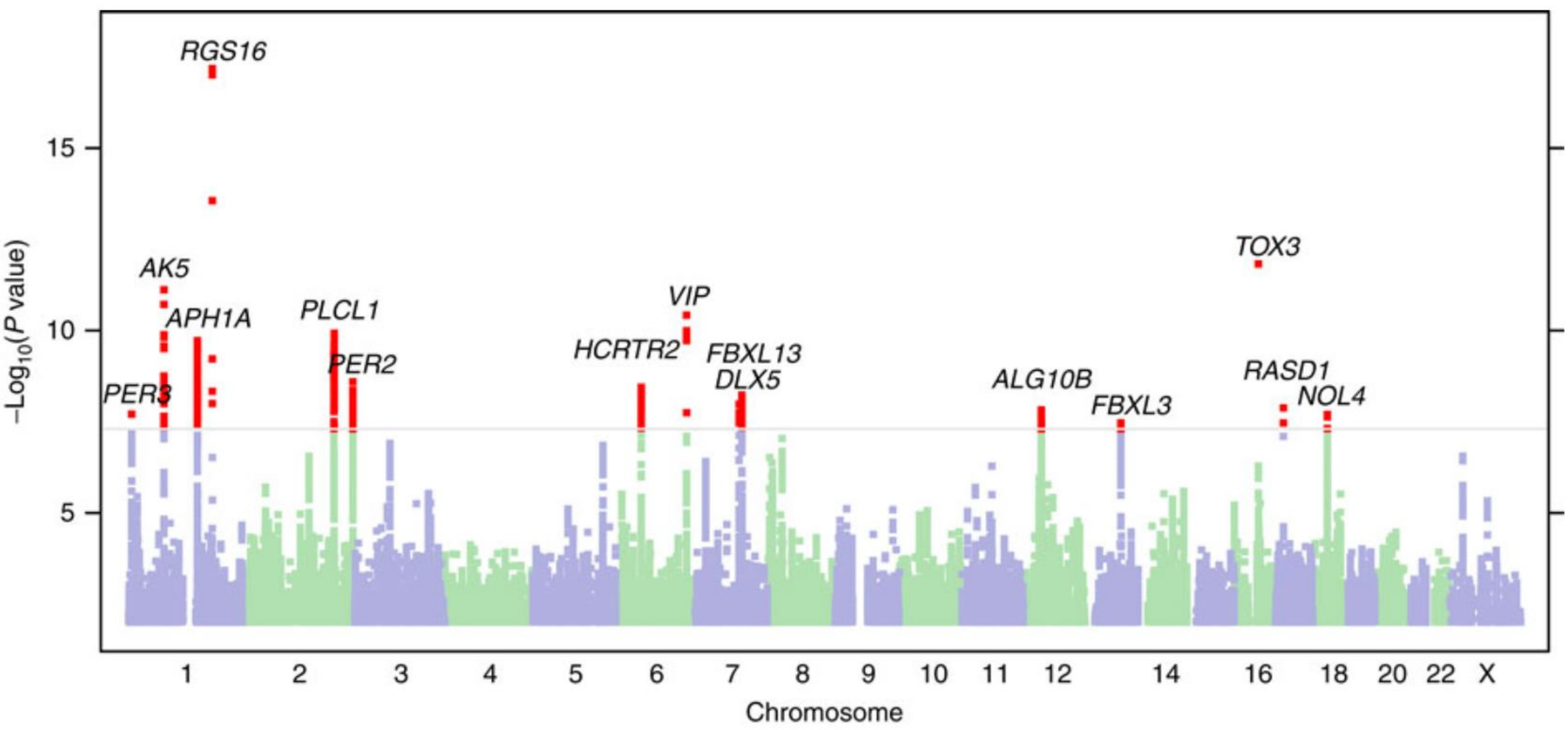
Covariates

- Age
- Gender
- Genomic PCA
- etc.

PC adjustment for GWAS

- What is PCA?
  - A simple math tool that finds the biggest patterns in genetic data.
- Goal:
  - Adjust for population stratification and confounding intrinsic to genomic data.
- Concept:
  - Extract principal components (PCs) from genomic data representing major genetic variation.
  - Each PC summarizes an individual's genetic background.
- Why It's Needed:
  - Minimizes false positives due to population structure.

Manhattan plot



- In GWAS, it is important to detect truly causal SNPs correctly from limited sample sizes.

Large sample theory in association test

- Total Bias in GWAS association test

  Total Bias = Systematic Bias + Estimation Bias

  - Systematic bias
    - Arises from the selection of testing methods and study design.
    - Choosing appropriate testing methods → systematic bias ↓
  - Estimation bias
    - Occurs when estimating the true parameter from a limited sample size.
    - The sample size ↑ → consistency of estimators → estimation bias ↓

- Total Bias ↓ ≡ Statistical Power ↑ & False Discovery ↓
  - Detects subtle effects of individual SNPs that contribute small increments to phenotypic variance.

Introduction to Polygenic Risk Scores (PRS)

- Research Question:
  - Quantify complex traits (e.g., happiness) for each individual using SNP data.
- Regression model:

$$\text{Happiness} = \beta_1 \times \text{SNP}_1 + \cdots + \beta_p \times \text{SNP}_p + \text{error}$$

  - Each β_j represents the effect of SNP_j on the trait.
- Polygenic Risk Score (PRS):
  - Quantifies the cumulative effect of many genetic variants (usually SNPs) on an individual's predisposition to a particular trait or disease.

$$\text{PRS} = \sum_{j=1}^{p} \hat{\beta}_j \times \text{SNP}_j \quad \text{for } j \in \{j\text{: p}-\text{value}_j < \alpha\}$$

※ α is a significance level.

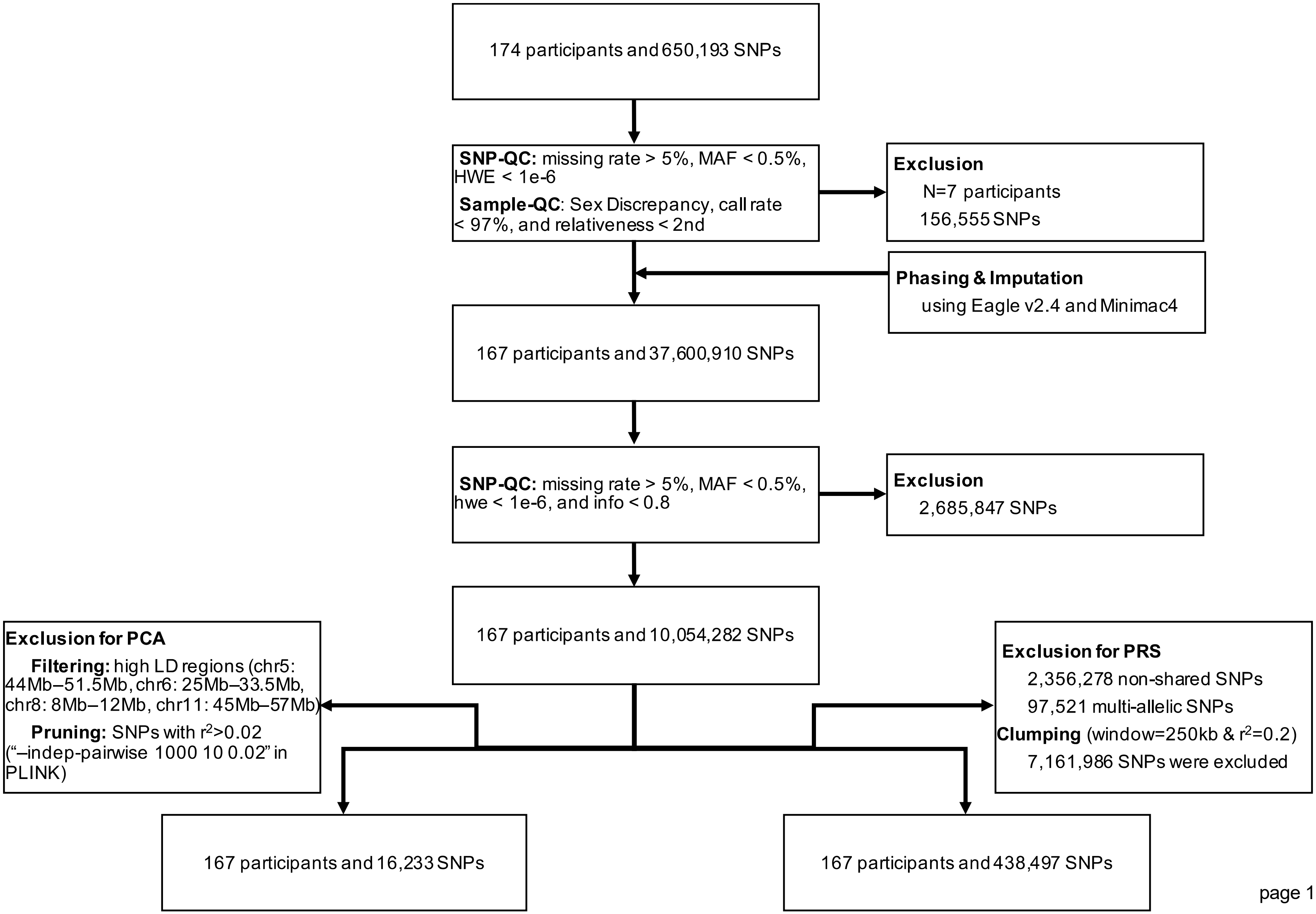
PRS calculation using large-scale dataset

- Typically,
  - Each SNP's effect size $\hat{\beta}_j$ is directly taken from the estimates derived from large-scale GWAS results (summary statistics).

- Why large-scale?
  - Higher Statistical Power: Large sample sizes enable more precise estimation of SNP effect sizes.

+ LD Clumping:
  - Prune SNPs in high Linkage Disequilibrium (LD) to avoid redundancy.

GWAS workflow



174 participants and 650,193 SNPs

SNP-QC: missing rate > 5%, MAF < 0.5%, HWE < 1e-6

Sample-QC: Sex Discrepancy, call rate < 97%, and relativeness < 2nd

Exclusion
N=7 participants
156,555 SNPs

Phasing & Imputation
using Eagle v2.4 and Minimac4

167 participants and 37,600,910 SNPs

SNP-QC: missing rate > 5%, MAF < 0.5%, hwe < 1e-6, and info < 0.8

Exclusion
2,685,847 SNPs

167 participants and 10,054,282 SNPs

Exclusion for PCA

Filtering: high LD regions (chr5: 44Mb–51.5Mb, chr6: 25Mb–33.5Mb, chr8: 8Mb–12Mb, chr11: 45Mb–57Mb)

Pruning: SNPs with r^2>0.02 ("–indep-pairwise 1000 10 0.02" in PLINK)

Exclusion for PRS
2,356,278 non-shared SNPs
97,521 multi-allelic SNPs

Clumping (window=250kb & r^2=0.2)
7,161,986 SNPs were excluded

167 participants and 16,233 SNPs

167 participants and 438,497 SNPs

GWAS workflow

1. Data preparation
   - Collect and integrate genomic and clinical data.
2. Sample QC / SNP QC
   - High missingness, gender disparity, outliers
   - High missingness, low MAF (rare variants), Hardy-Weinberg Disequilibrium
3. Phasing & Imputation → SNP QC
   - Estimate haplotype structures by leveraging SNP correlations.
   - Predict missing genotypes using reference panels.
4. GWAS & LD Clumping
   - Estimate regression coefficients for SNPs.
   - Select representative SNPs, reducing redundancy.
5. PRS calculation
   - Compute PRS by weighting SNP effects (e.g., from large-scale GWAS results).

Useful sites

- * https://2cjenn.github.io/PRS_Pipeline/
- * https://github.com/statpng/GWAS/blob/main/PRS.md
- * https://choishingwan.github.io/PRS-Tutorial/
- https://www.cog-genomics.org/plink/
- https://github.com/statpng/GWAS/blob/main/plink_tutorial.md
- https://www.bioinf.wits.ac.za/courses/sahgp/plink-tut-jul14.pdf
- https://genomicsbootcamp.github.io/book/genotype-data-quality-control.html#how-qc-works-in-plink

[PGS catalog]

- https://www.pgscatalog.org/downloads/#dl_ftp_list
- https://ftp.ebi.ac.uk/pub/databases/spot/pgs/scores/

Thank you for your attention ! ☺