BIOL3120 –Human Genetics and Evolutionary Medicine

Genome Wide Association Studies

6	Genetic Testing Techniques GWAS	Problem Set 4	~~Problem Set 4 (5%)~~	Explain the importance of new techniques in human genetics for understanding human disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources
Recess				
Recess		Pracs for External Students only		
7	Treatment for Genetic Conditions Epigenetics and Imprinting	Problem Set 5	Problem Set 4 (5%) & Problem Set 5 (5%)	Explain the importance of new techniques in human genetics for understanding human disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources

DNA sequence variation

- In humans, approximately 0.1–0.4% of nucleotides differ between any given pair of unrelated genomes
- The vast majority of sequence variation is comprised of single nucleotide polymorphisms (SNPs), which occur every 100–300 bases, and are mostly located within noncoding sequence
- A large number of inherited human diseases are caused by sequence variation in single genes
- Many complex diseases, including cancer, diabetes, and heart disease, are mediated, at least in part, by genetic factors
- The majority of rare diseases, such as those affecting only a small percentage of the population, result from hereditary or *de novo* genetic mutations
- Technological advances in high-throughput genotyping methods over the past two decades revolutionized the field of human genetics

Candidate Gene Approach

- Focuses on associations between genetic variation within pre-specified genes of interest, and disease

- Candidate genes are most often selected for study based on prior knowledge of the gene's biological functional impact on the trait or disease in question

- In contrast to genome-wide association studies (GWAS), which scan the entire genome for common genetic variation.

BIOL3120 –GWAS

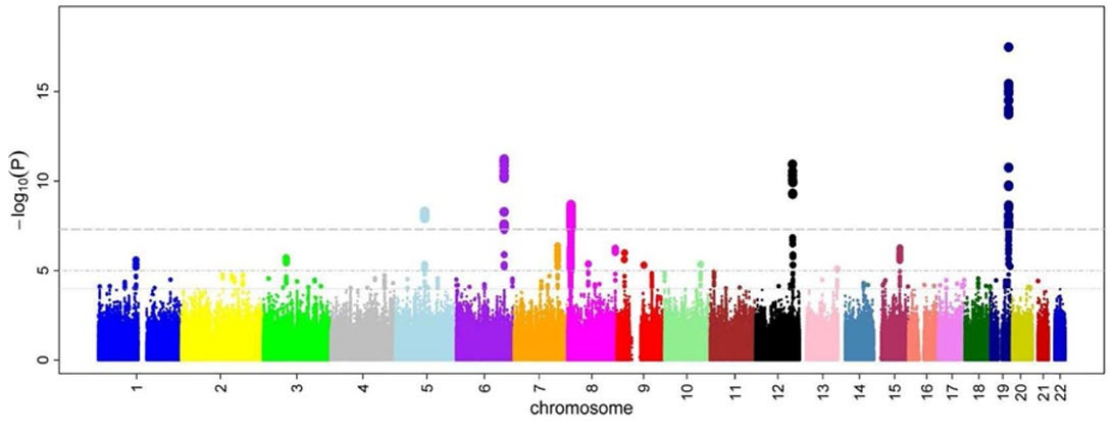
LEARNING OBJECTIVES

On successful completion of this lecture, you will be able to:

- Understand the difference between a candidate gene approach and GWAS
- Describe genome wide association studies
- Understand the limitations of GWAS

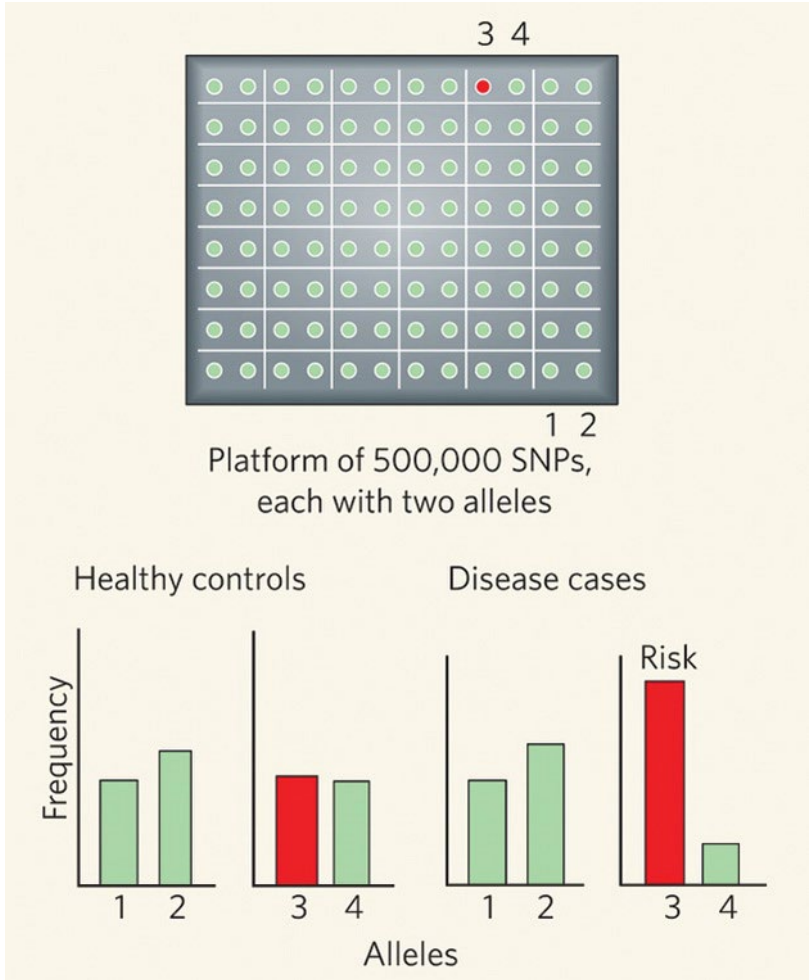
Genome Wide Association Studies

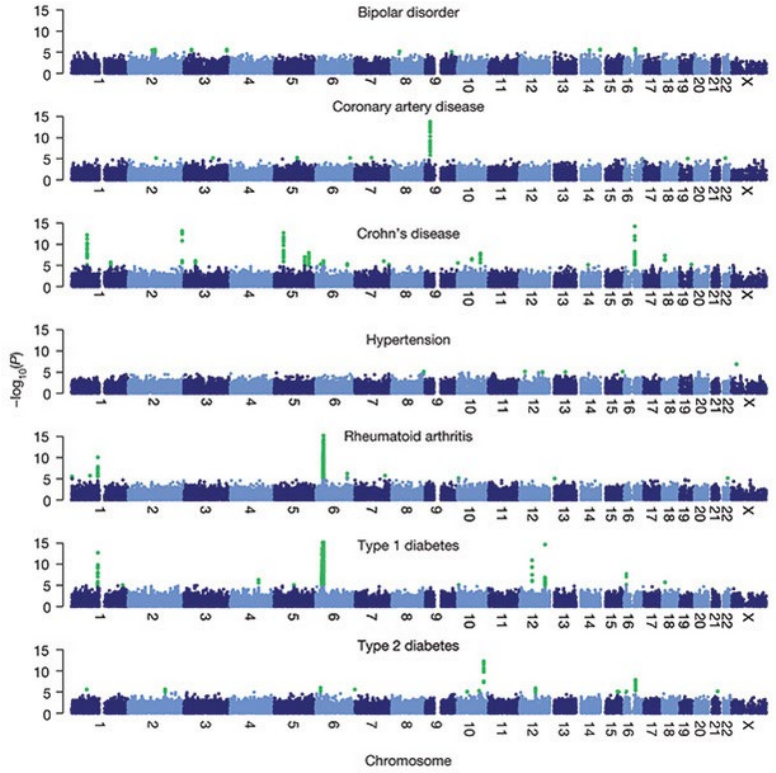
Genome-wide association studies (GWAS)

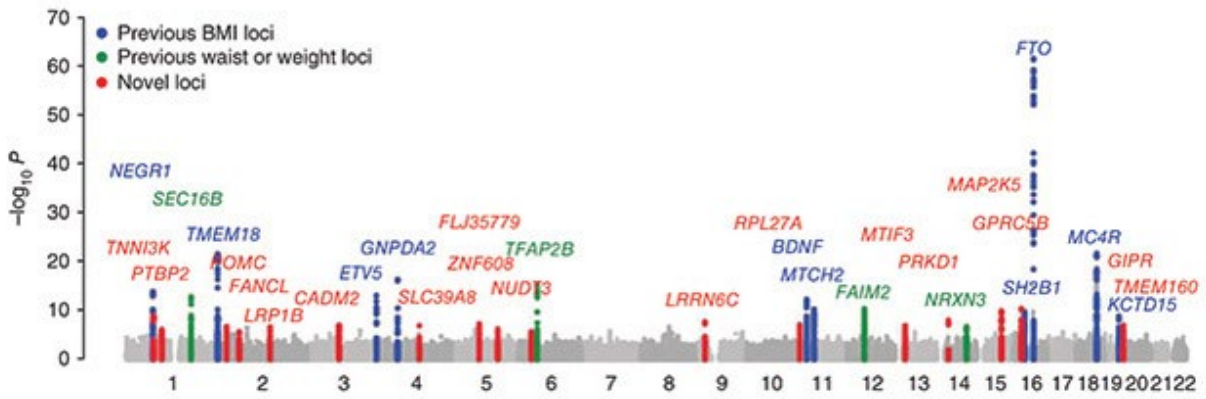


- A genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait (disease)
- GWAS studies compare the DNA of participants having varying phenotypes for a particular trait or disease
- Each person gives a sample of DNA, from which millions of genetic variants are read using SNP arrays
- If one type of allele is more frequent in people with the disease, the variant is said to be *associated* with the disease
- The associated SNPs are then considered to mark a region of the human genome that may influence the risk of disease

Genome-wide association studies (GWAS)

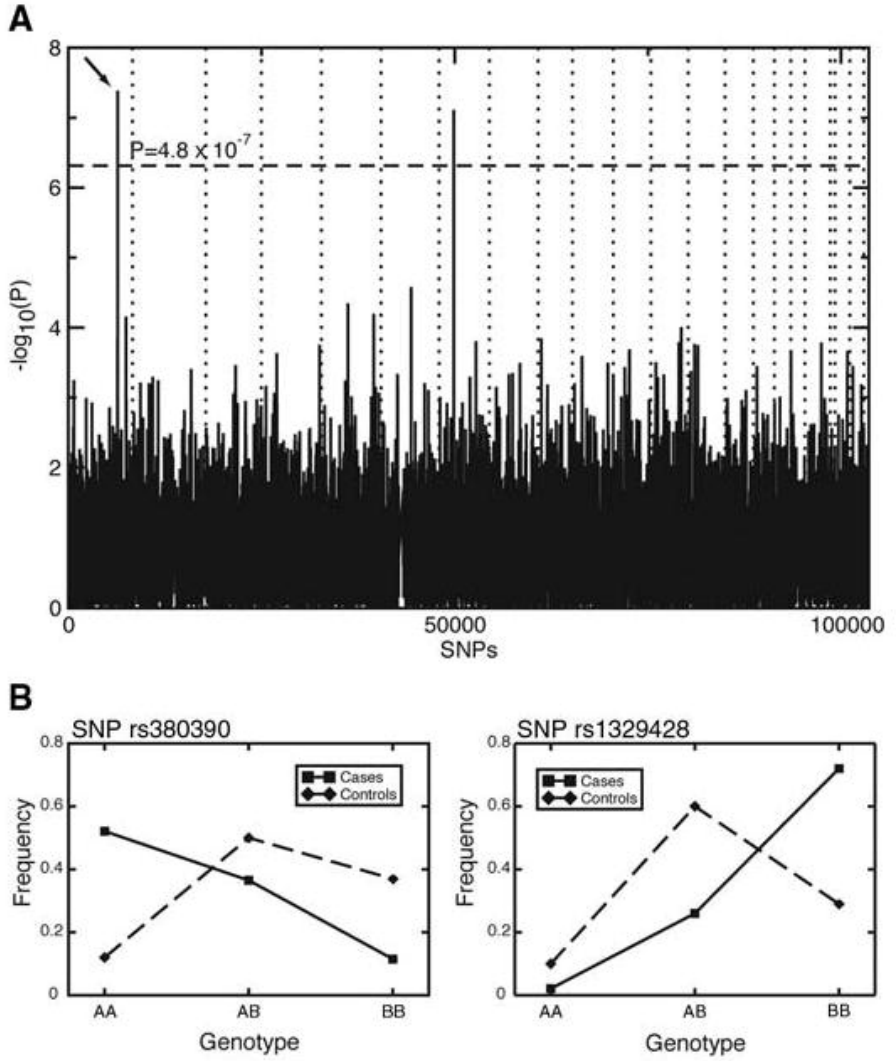






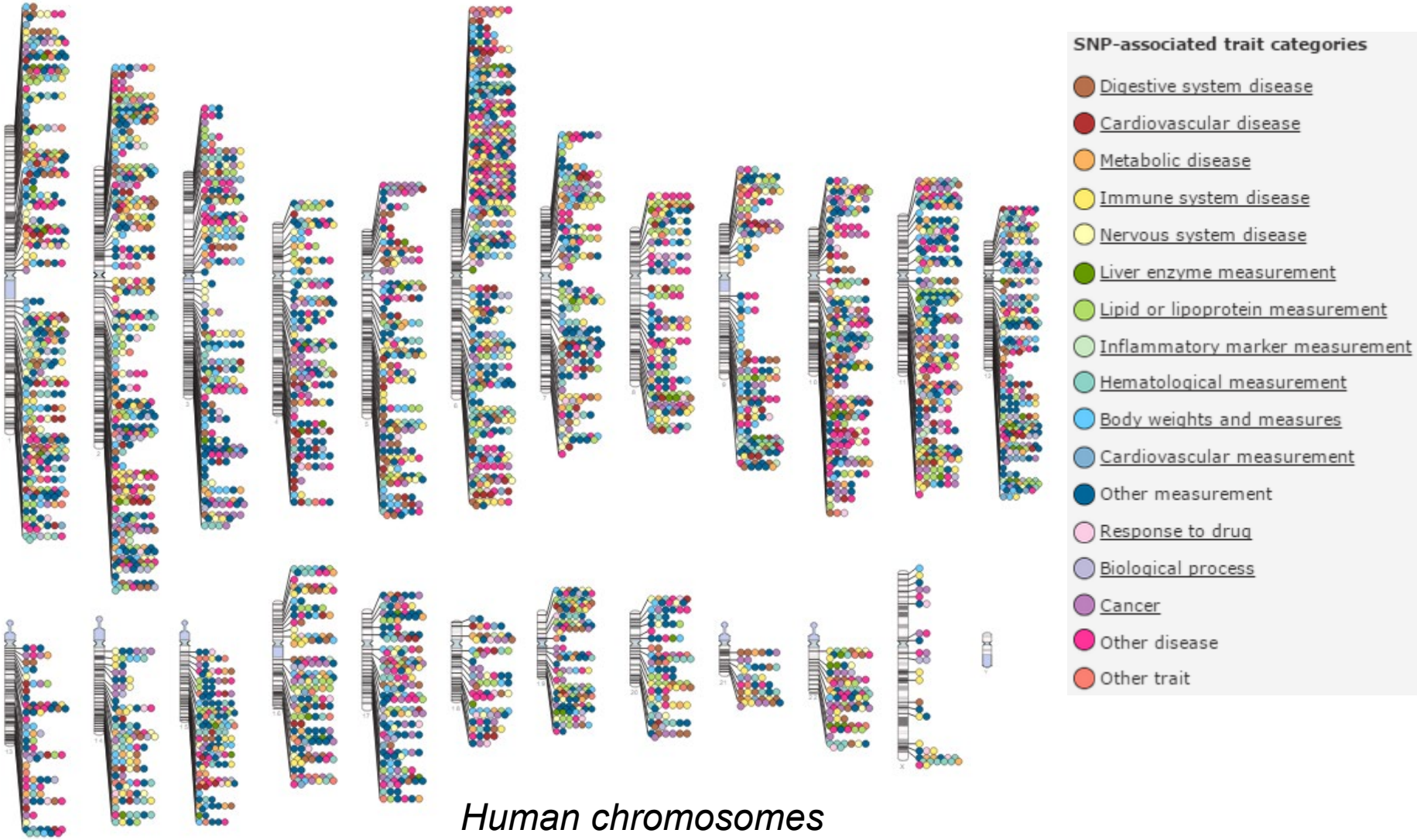
Genome-wide association studies (GWAS)

- The first successful GWAS was published in 2005
- It investigated patients with age-related macular degeneration and found two SNPs with significantly altered allele frequency compared to healthy controls
- Hundreds or thousands of individuals are tested in a typical GWA study, over 3,000 human GWA studies have examined over 1,800 diseases and traits, and thousands of SNP associations have been found



Klein et al., 2005. Complement Factor H Polymorphism in Age-Related Macular Degeneration. Science 308(5720).

Examples of GWAS Discoveries



Human chromosomes

Success and Limitations of GWAS

Here at Macquarie

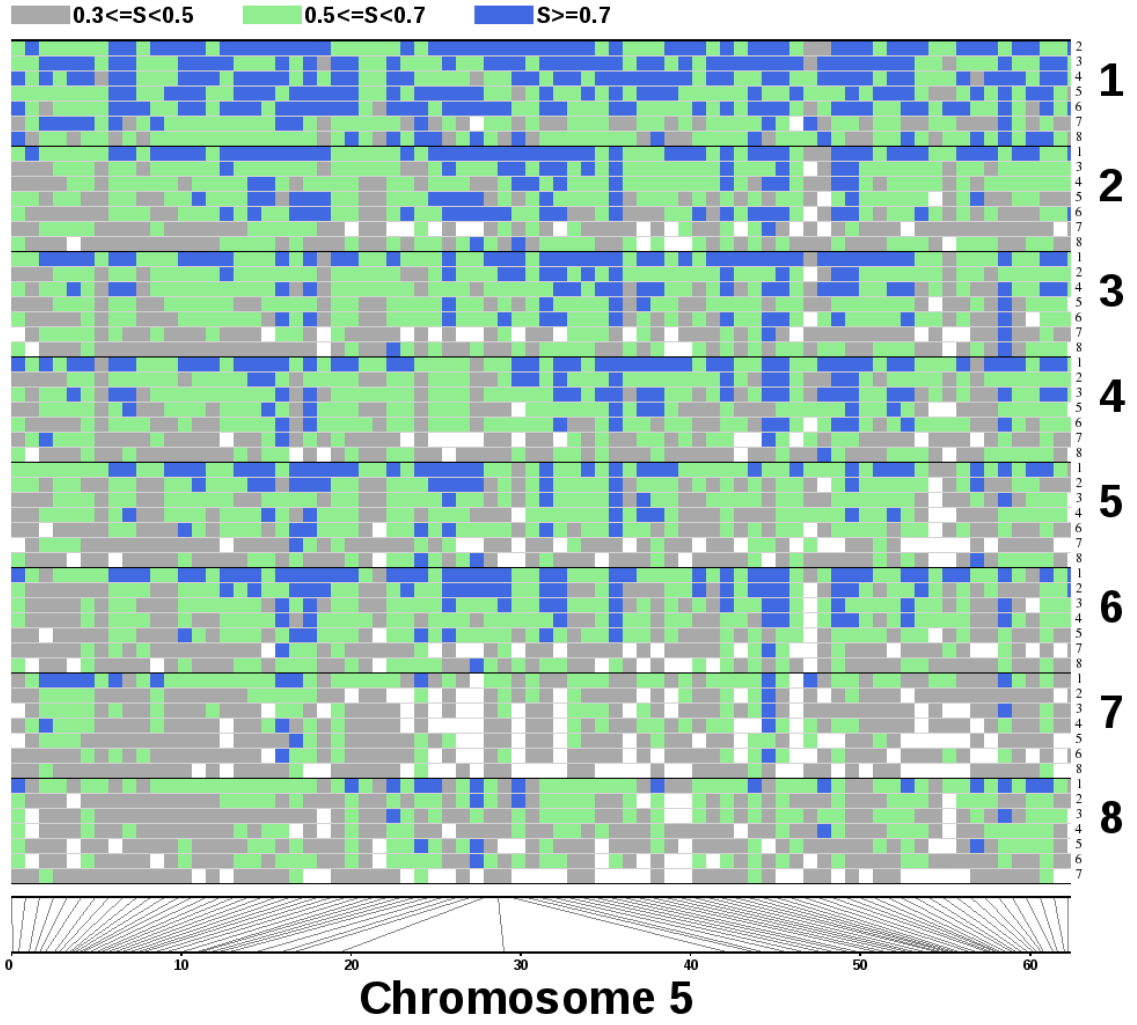
- Project MinE

- We plan to map the full DNA profiles of at least 15,000 people with ALS and 7,500 control subjects, and to perform comparative analyses on the resulting data.

- https://www.projectmine.com/about/

High-throughput genotyping

- Genome-wide association approaches have identified statistically significant evidence supporting relationships between complex human diseases and hundreds of common genetic variants in the human population
- However, finding disease-associated alleles is only the first step on the path to identifying those variants that directly contribute to disease risk
- A major challenge inherent in these studies is moving from identification of a genetic variant via association studies to determination of actual causal variants through functional genomics experimentation

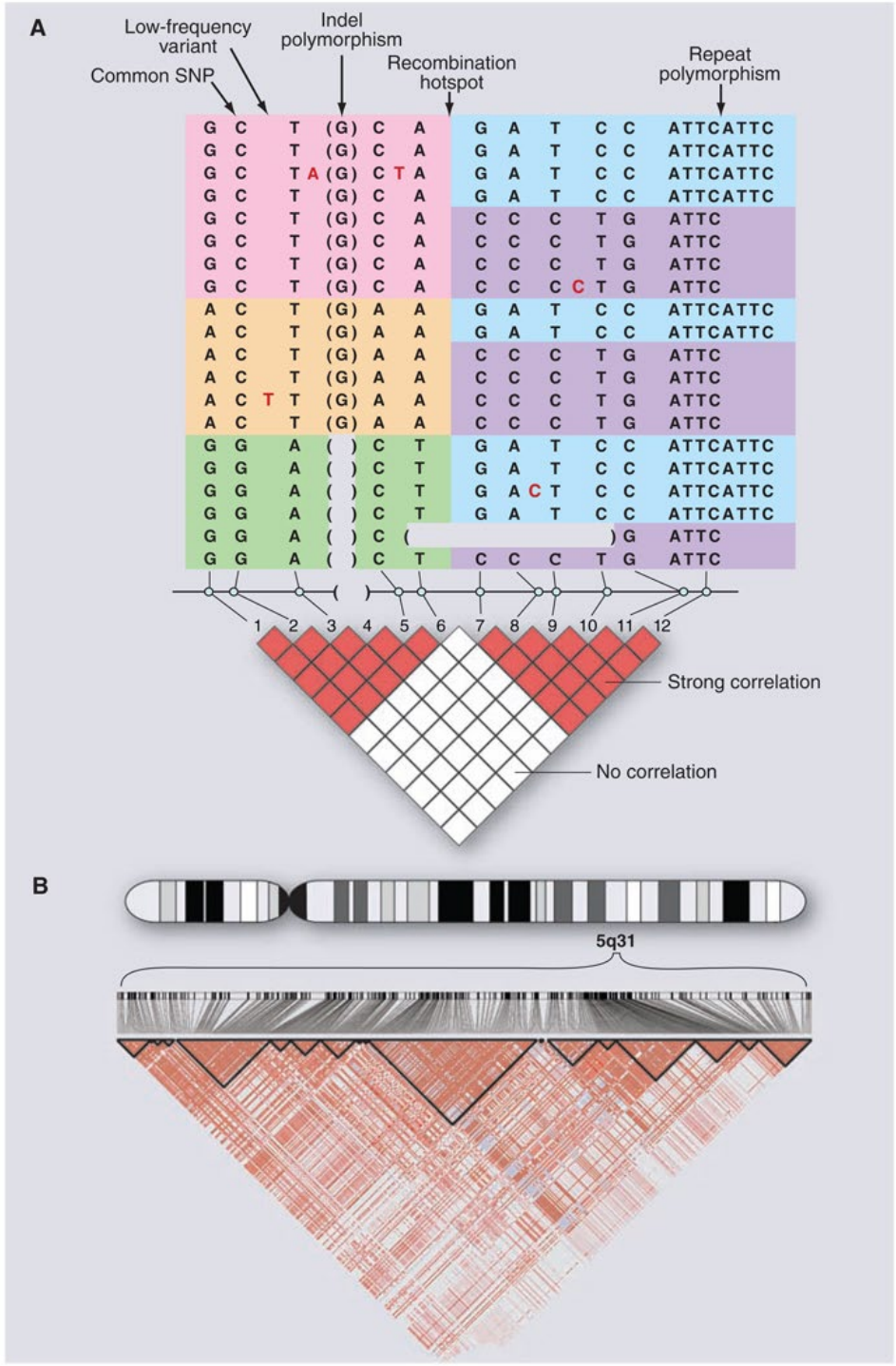


Limitations of GWAS

As the SNP catalog grows, a critical question looms:

Would GWASs require directly testing each of the ~10 million common variants for association to disease? That is, if only 5% of variants were tested, would 95% of associations be missed?

Or could a subset serve as reliable proxies for their neighbors?



Limitations of GWAS

- Despite the success of GWAS in enhancing understanding of disease mechanisms, the variants identified by this approach represent only a fraction of the overall genetic contribution to common disease risk
- While many disease-associated variants have been identified through GWAS, they have mostly been common variants with moderate to high (i.e., >0.1) allele frequencies
- Assumption that common genetic variation plays a large role in explaining the heritable variation of common disease
- The question of whether common or rare variants underlie the majority of risk for common diseases continues to remain an open one

BIOL3120 –GWAS

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