

Introduction to Statistical Genetics

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$ echo "Data Sciences Institute"
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Learning Objectives

- This course provides an INTRODUCTION to concepts and fundamentals in statistical genetics.
- At the end of the course, I hope you will:
 - Understand foundational principles of population genetics.
 - Learn statistical methods commonly used in genetic data analysis.
 - Understand and apply computational and statistical methods used in the design and analysis of genome-wide studies.

Course Content

- Background in molecular genetics and basic genetic models
- Concepts from population genetics
- Principles of inheritance
- Aggregation, heritability and segregation analysis
- Genome-wide association studies (GWAS)
 - Quality control
 - Genotype imputation
 - Multiple testing
 - Meta-analyses
 - Population stratification adjustment

Background Needed

- Assume no formal training in genetics.
 - Basic concepts in molecular genetics will be introduced in the class.
- Familiarity with key concepts in statistical inference, including:
 - Elementary probability and statistical methods
 - Distributions of basic random variables (e.g., binomial, normal)
 - Likelihood-based methods: estimation and hypothesis testing
 - Basic regression techniques (e.g., linear, logistic)

GitHub Repo

https://github.com/UofT-DSI/gen_data/

- Schedule
- These slides (PDF)
- All in-class code
- Assignment details and rubrics
- Policies, due dates, etc

Online Resources

- **Textbook:** *The Fundamentals of Modern Statistical Genetics* (Nan Laird & Christoph Lange).
- **Introductory Genomics Videos:** [BigBio YouTube Channel – Genomics Playlists](#)
- Other useful resources beyond the scope of this course:
 - **Biomedical Data Resource Guide:** [StatsUpAI – Curated Biomedical Datasets](#)

What questions do you have about the course?

What You'll Learn Today

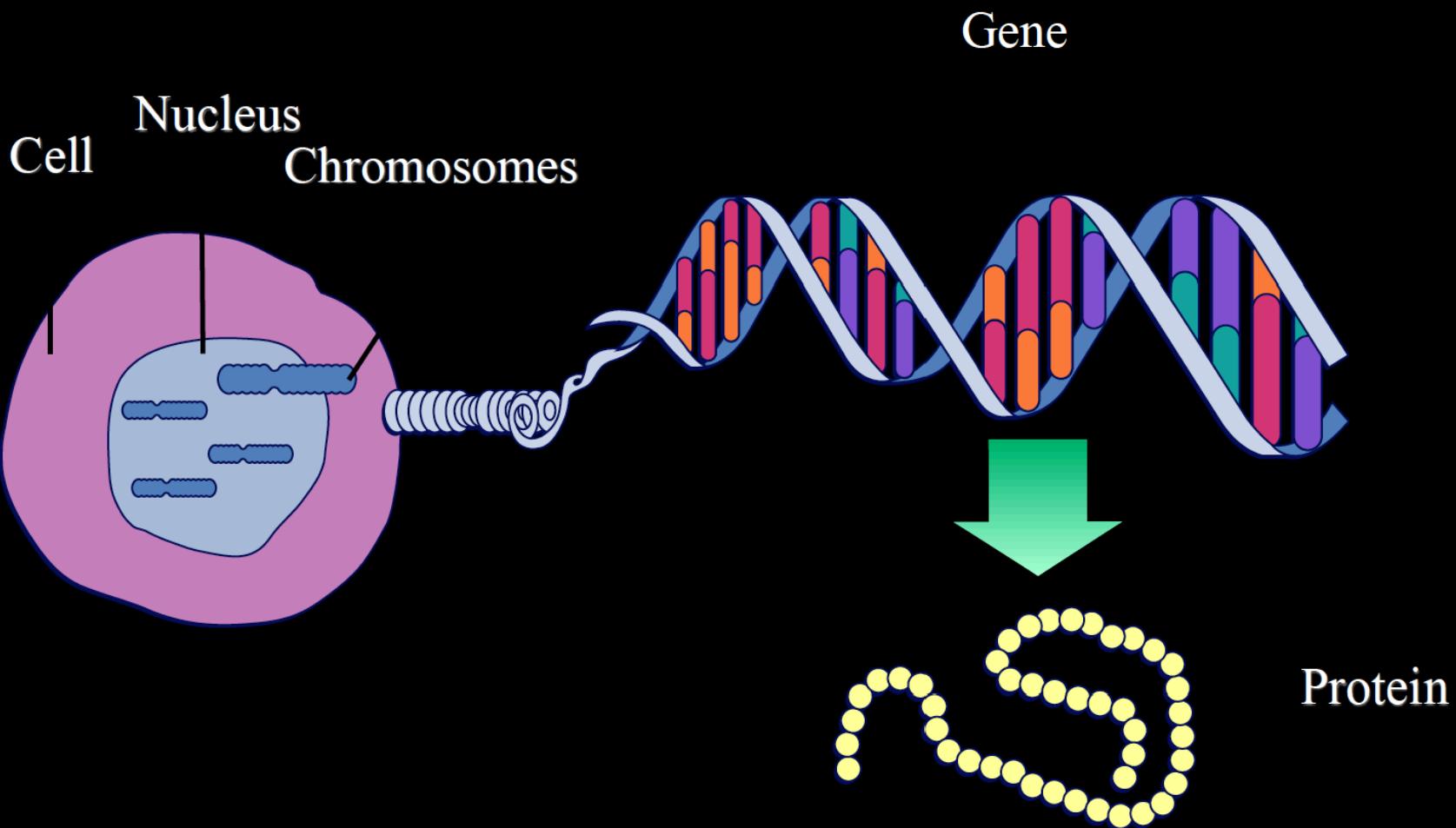
- Foundations of genetic variation
 - DNA → chromosomes → genes
 - Common variant types (e.g., SNPs)
- From variants to traits
 - Mendelian vs. complex disease
 - Inheritance models: dominant / recessive / additive (genotype coding 0/1/2)

By the end of this lecture, you should be able to define alleles/genotypes, recognize common variant classes, explain penetrance, and map a coded genotype into a simple regression model.

What is Statistical Genetics?

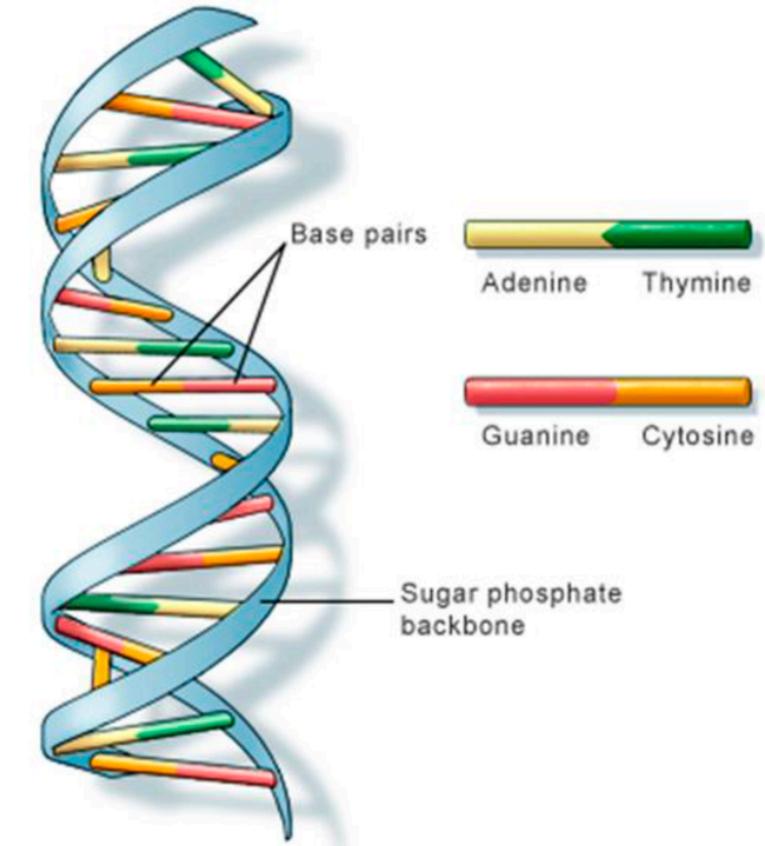
- Statistical genetics is an interdisciplinary field at the interface between statistics and genetics and is concerned with the development of statistical methods for problems in genetics.
- Genetics is a subfield of biology concerned with the study of heredity (transmission of genetic material from parents to offspring) and genetic variation.

Chromosomes, DNA and Genes



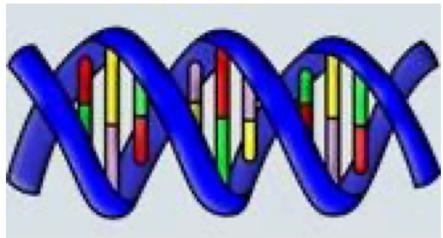
Deoxyribonucleic Acid (DNA)

- DNA is the basic biological material of inheritance; it determines how proteins are manufactured in the body
- Each strand of DNA is a long molecule made up of a linear sequence of subunits/base pairs: A,T,G,C.
- A-T and G-C matching: information on one strand is sufficient.
- 'Size' of the genome: \approx 3 billion of DNA base pairs

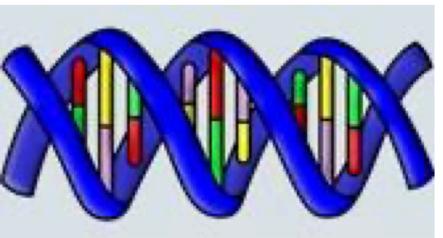


S. National Library of Medicine

Deoxyribonucleic Acid (DNA)



CTCGTCACCTTCAC
GAGCAGTG?????

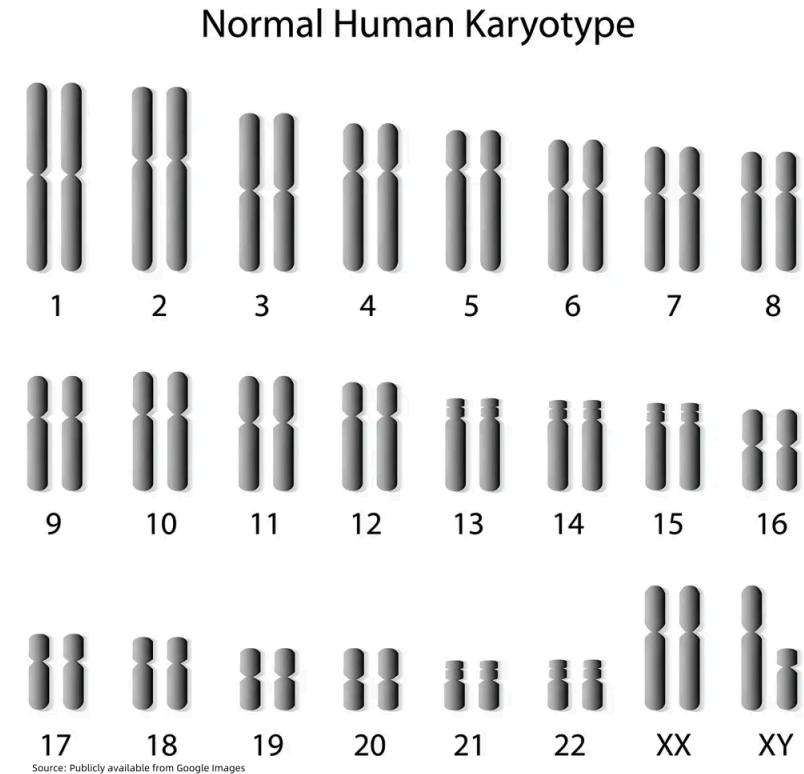


CTCGTCACCTTCAC

Source: Created by Fan Wang

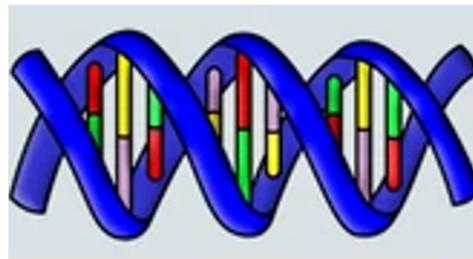
Chromosomes

- Each chromosome has a double helix structure: two long strands of DNA, bound to each other lengthwise.
- 23 pairs of chromosomes: 22 homologous pairs (Autosomes) and 1 pair of sex chromosomes (XX female, XY male).
- In each pair, one copy is inherited from the mother and one from the father.
- Where genetic material is stored and in the nucleus of every cell.

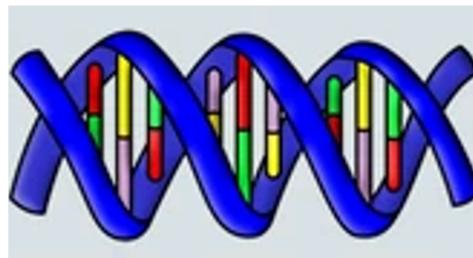


Double Helix Structure

- Each chromosome has two long strands of DNA.
- Homologous chromosome pair:



CTCGTCACCTTCAC
| | | | | | | | | |
GAGCAGTGAAGTG

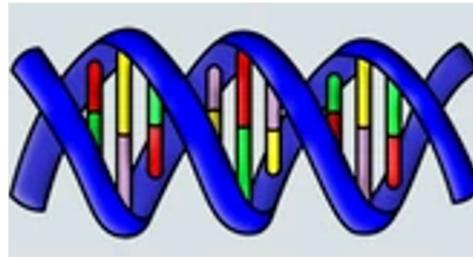


CTCCTCACCTTCAC
| | | | | | | | | |
GAGGAGTGAAGTG

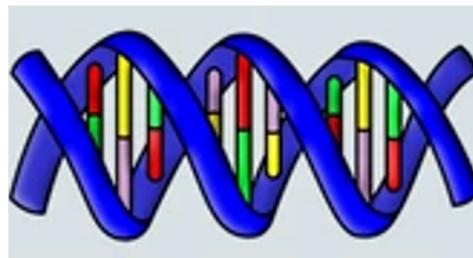
Source: Created by Fan Wang

Double Helix Structure

- Each chromosome has two long strands of DNA.
- Homologous chromosome pair:



CTCGTCACCTCAC
| | | | | | | | |
GAGCAGTGAAGTG



CTCCCTCACCTCAC
| | | | | | | | |
GAGGGAGTGAAGTG

Source: Created by Fan Wang

Human Genome

- 3 billion nucleotides (A,C,G,T) in the whole human genome.s
 - Paired, double helix
- About 3 million of them differ between people (0.1% difference) - Genetic Variations.
- Most of these variations are in 'junk DNA'.
 - Not directly code for proteins.
 - May have regulatory or unknown functions.
- Minority of these variations change how products of genes (proteins) behave.
- Scientists study which variations are linked to specific traits or diseases.

Mutations

- Mutations are **changes** in DNA.

Reference Sequence:

ATG TCT GGA TAC CCG AAT GTC

ATG TCA GGA TAC CCG AAT GTC

↑
Substitution

ATG TCT TAC CCG AAT GTC

↑
Deletion

ATG TCT GTT AGC GGA TAC CCG AAT GTC

↑
Insertion

TGA CTA ATG TCT GGA TAC CCG AAT GTC

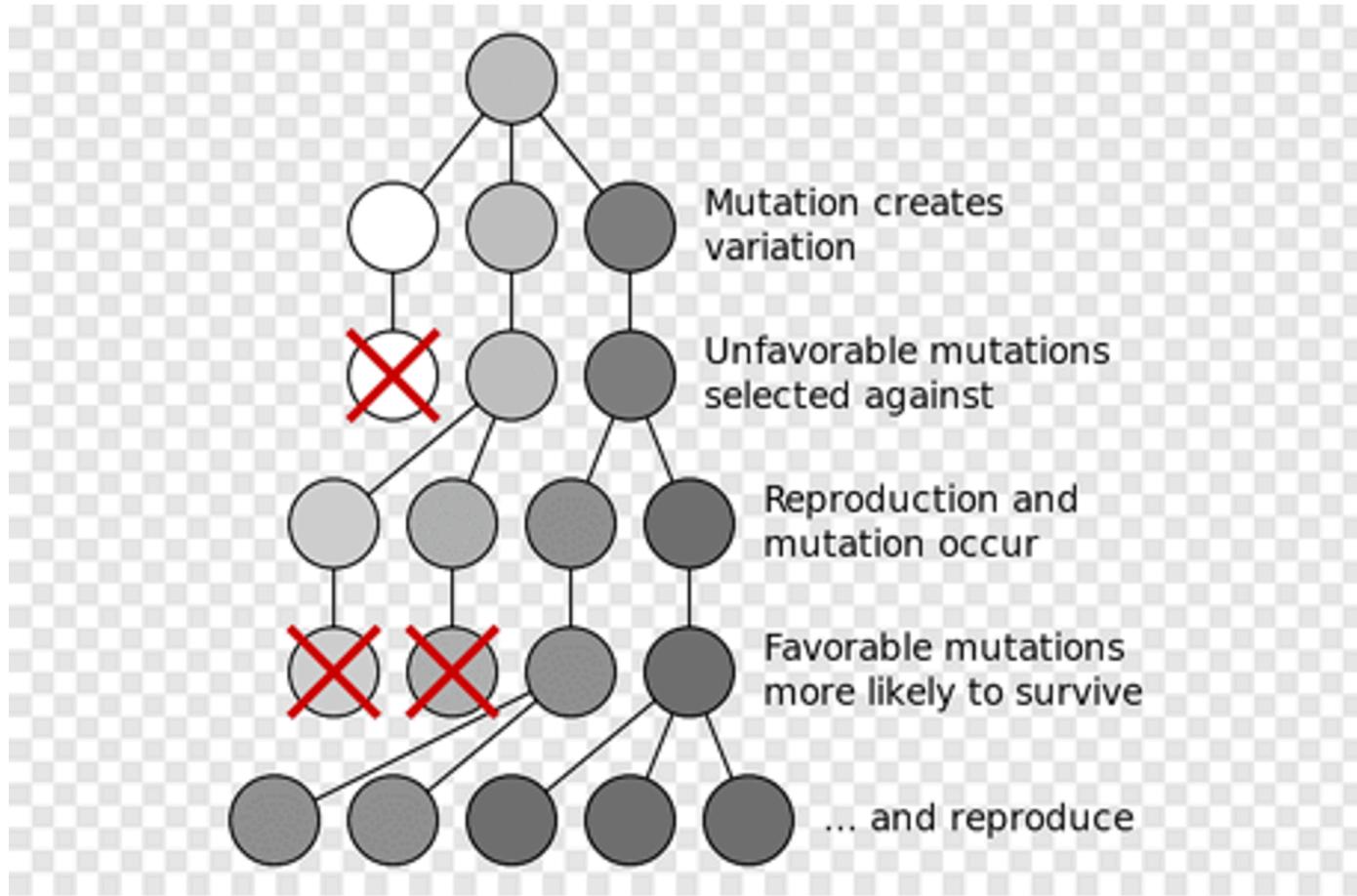
↑
Translocation (segment from another region)

Source: Created by Fan Wang

Effects of Mutations

- Mutations can be very detrimental to an organism.
 - May cause proteins to malfunction.
 - cells that rely on the proteins may not function properly.
- Most of these deleterious mutations remain rare in the population, because they are rarely transmitted to the next generation.
- Many of the mutations have no effect.
 - e.g., TCT and TCA both code for the same amino acid (protein building block), so changing one to the other has no impact.

Mutations Give Rise to Genetic Variants

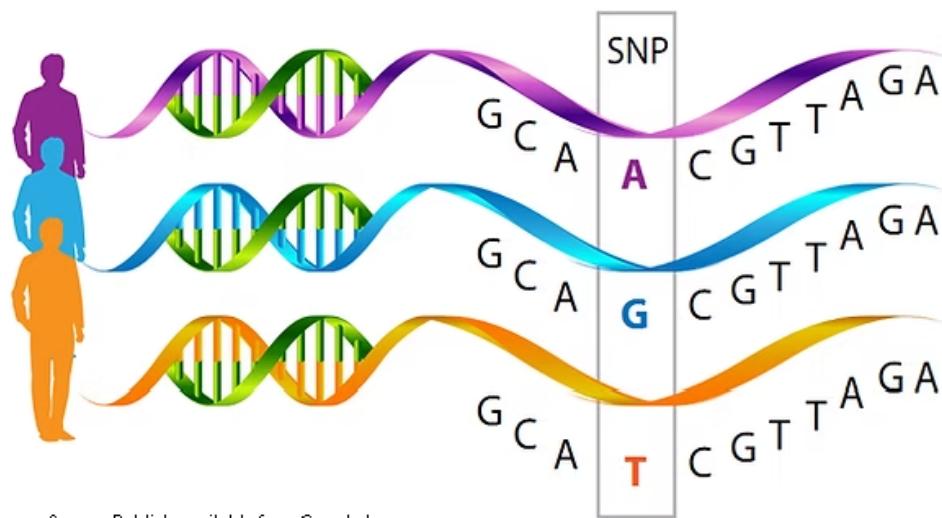


Genetic Variants/Polymorphism

- A **polymorphism** is a part of DNA that can differ between individuals.
- These variations come from mutations that happened over long periods of human history.
- The different versions (or "states") of a polymorphism are called **alleles**.
- In statistical terms: a polymorphism is a random variable and an allele is one of the outcomes in the sample space.

Types of Genetic Variants

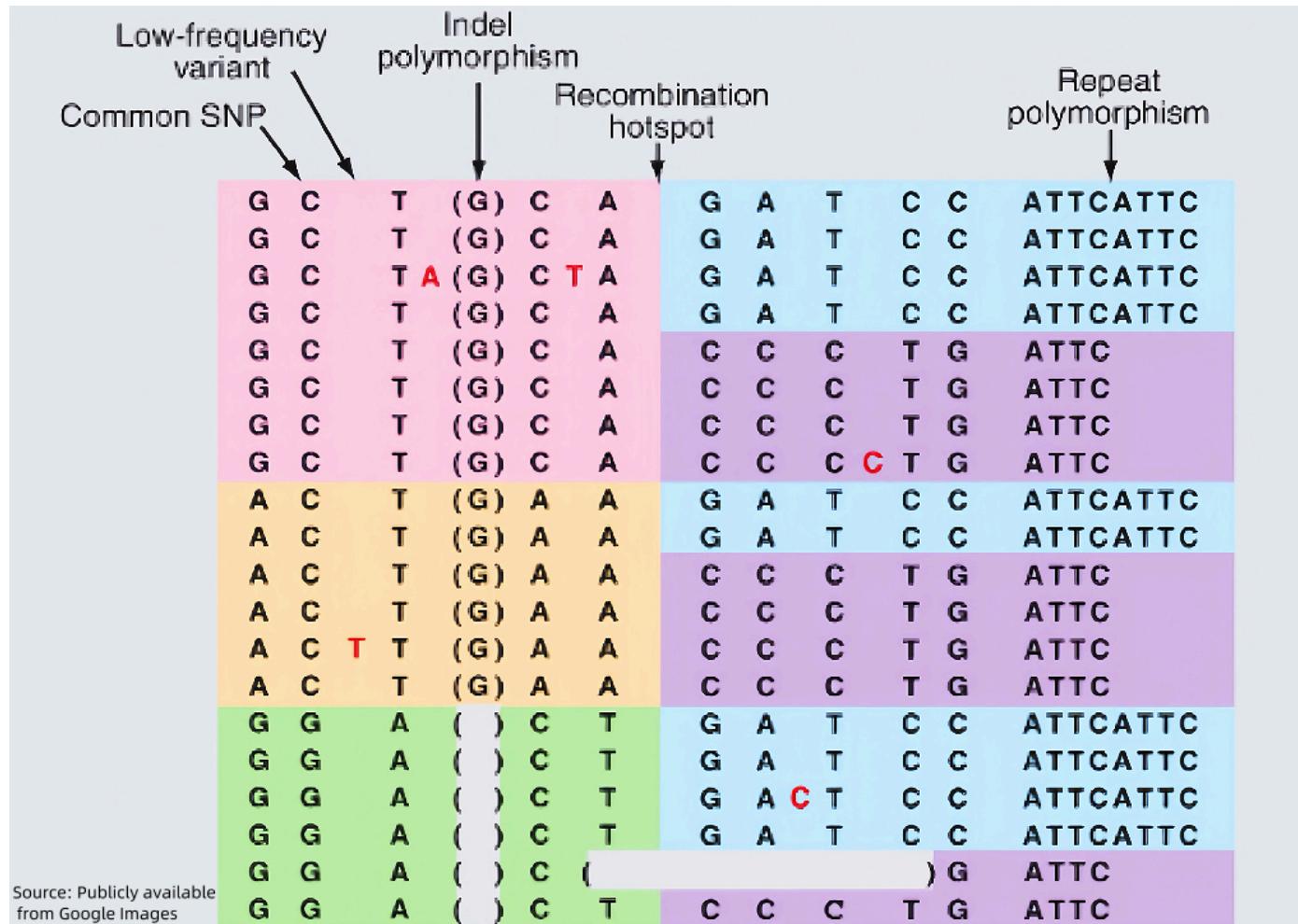
- A **single nucleotide polymorphism (SNP)** is a type of genetic variation where a single nucleotide (A, C, G, or T) differs between individuals.
 - An **allele** at a SNP refers to one of the possible nucleotide bases — A, C, G, or T.
 - Appear about every 300 base pairs → ≈ 10 million SNPs.



Types of Genetic Variants

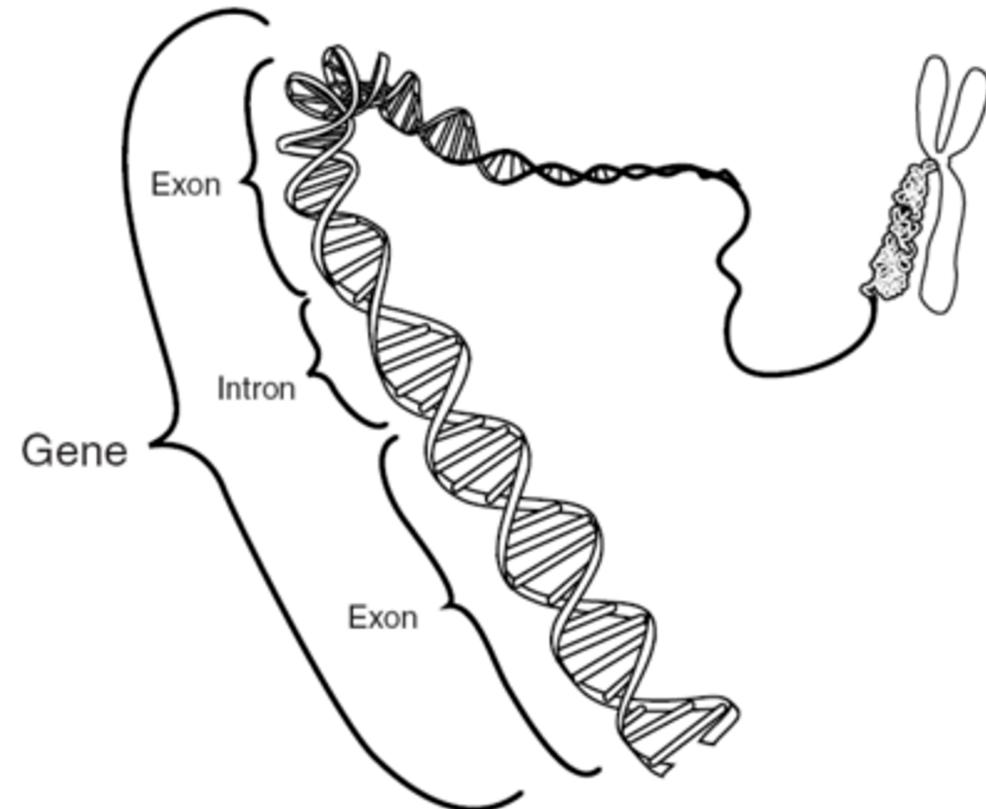
- **Variable number of tandem repeats (VNTR)**: Specific DNA sequences that are repeated immediately adjacent to each other for a variable number of times.
 - e.g. 16, 14 and 11 repeats of CA.
 - **Microsatellites** consist of small sequences (1-6) that are repeated.
 - The number of repeats can vary widely from one person to the next, therefore they are used often in forensic DNA and paternity testing, and in linkage mapping.
- **Indels**: extra base pairs (between 1 and 1000) can be inserted/deleted between two specific base pairs.
- **Structural variants**: duplications, deletions, inversions, translocations
- **CNV (copy number variants)**: large insertions/ deletions

Types of Genetic Variants



Genes

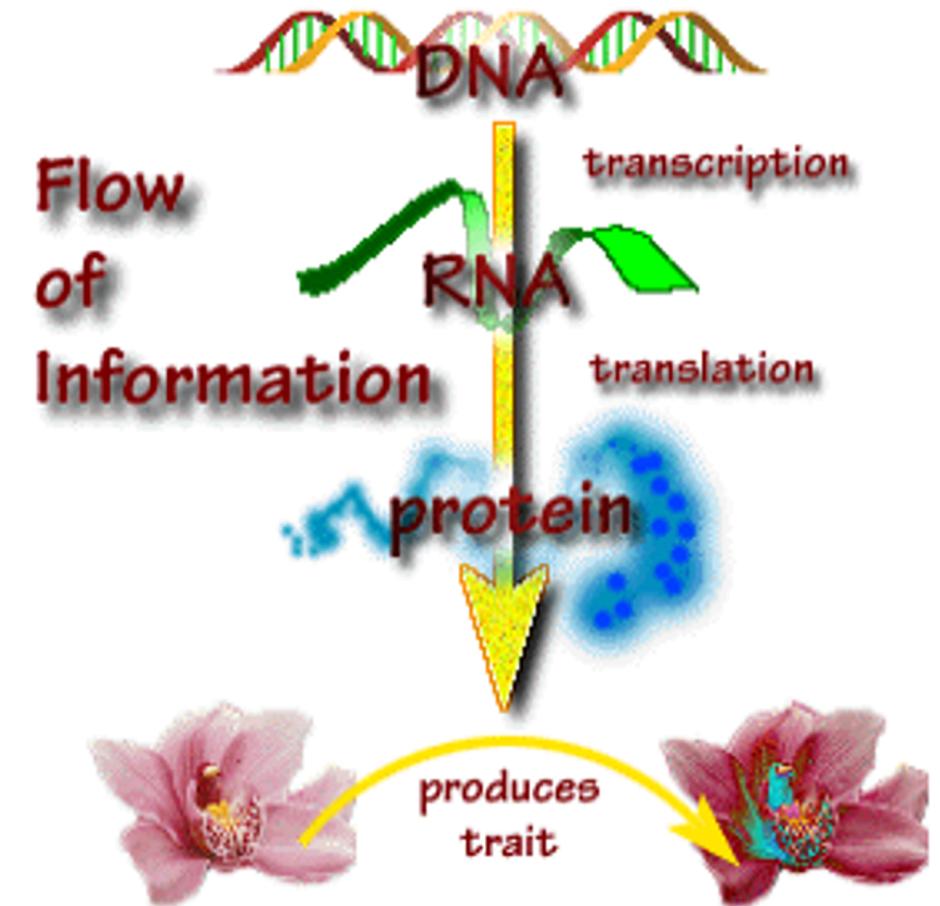
- A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that **encodes a specific functional product** (a protein or RNA molecule).
- A gene is a segment of DNA consists of several coding segments (**exons**), separated by non-coding sequences (**introns**).
- Introns do not code for specific proteins, but they are not junk and may regulate exons.



Source: Publicly available from Google Images

Genes

- Gene sizes vary from about 1K DNA base pairs to more than 1 million bp.
- About 20,000 - 30,000 genes throughout the genome.
- Genes themselves do not directly affect traits.
- Proteins - the coded product of genes - are the ones influencing traits.
- Through the processes of **transcription** and **translation**, information from genes is used to make proteins.



Source: Publicly available from Google Images

Proteins

- Proteins are strings of amino acids.
- There are **20 different amino acids** that are coded by codons.
- A **codon** is a sequence of **3 letters** (nucleotides) in DNA or RNA.
- There are 64 possible codons (4 bases: A, T, C, G — and combinations of 3)
- Multiple codons can code for the same amino acid.
 - For example: TCT and TCA both code for Serine.
 - This redundancy helps protect against mutations.

Codon Change Causes Sickle Cell Trait

- A Variant in the Hemoglobin Gene Causing Sickle Cell Anemia

HBB Sequence in Normal Adult Hemoglobin (Hb A):

Nucleotide	CTG	ACT	CCT	GAG	GAG	AAG	TCT
Amino Acid	Leu	Thr	Pro	Glu	Glu	Lys	Ser
	3			6		9	

HBB Sequence in Mutant Adult Hemoglobin (Hb S):

Nucleotide	CTG	ACT	CCT	GTG	GAG	AAG	TCT
Amino Acid	Leu	Thr	Pro	Val	Glu	Lys	Ser
	3			6		9	

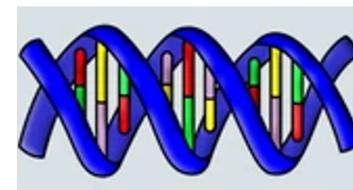
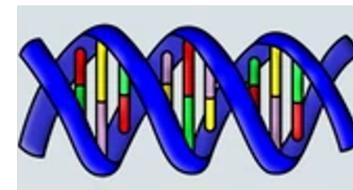
Source: Publicly available from Google Images

Alleles and Genotypes

Genotype: the two alleles at each chromosomal location (a pair of chromosomes) for a given individual.

- Most SNPs are bi-allelic; two alleles can be either G-C or A-T (matching).
- Could code them A (say for G-C) and a (for A-T).

Individual 1:



Allele A

CTCGTCACCTCAC
| | || | | | | | |
GAGCAGTGAAGTG

CTCATCACCTCAC
| | || | | | | | |
GAGTAGTGAAGTG

Allele a

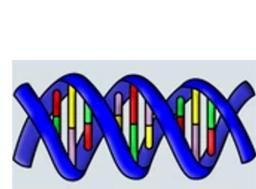
The **genotype** at this SNP: **Aa**

Source: Created by Fan Wang

Alleles and Genotypes

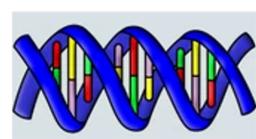
- A SNP with two alleles (A and a) has 3 possible (unordered) genotypes: AA, Aa/aA, aa.
- **Homozygous** genotype: same allelic type (AA or aa);
- **Heterozygous** genotype: different allelic type (Aa/aA).

Individual 1:



Allele A

CTCGTCACCTCAC
GAGCAGTGAAGTG



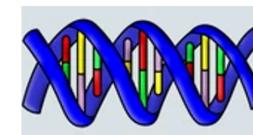
Allele a

CTCATCACCTCAC
GAGTAGTGAAGTG

Source: Created by Fan Wang

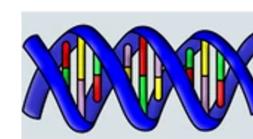
The **genotype** at this SNP: **Aa**

Individual 2:



Allele a

CTCTTCACTTCAC
GAGAAGTGAAGTG



Allele a

CTCATCACCTCAC
GAGTAGTGAAGTG

The **genotype** at this SNP: **aa**

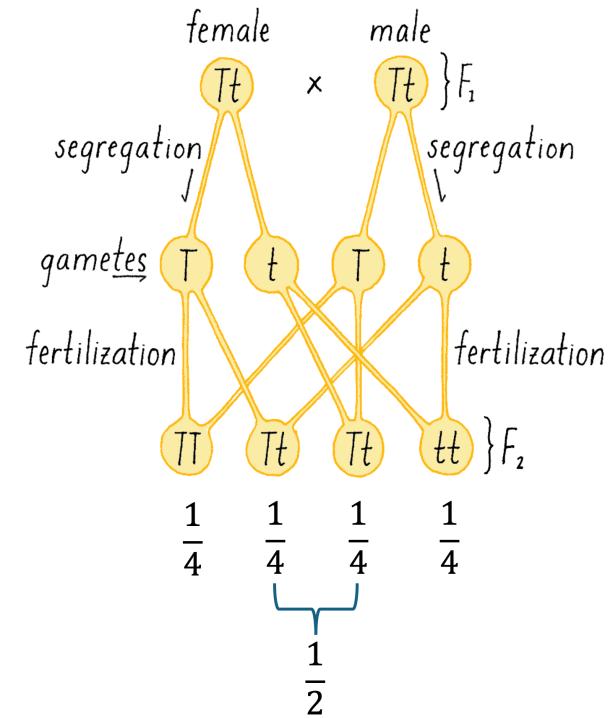
Recap

- Human genomes and **paired** chromosomes
- DNA has double helix structure: a 4-letter (A-T, G-C) system.
- Variations/Mutations
 - polymorphisms/genetic variants \equiv discrete random variables
 - alleles \equiv outcomes of a random variable
 - **SNP** \equiv a r.v. with two outcomes
 - Microsatellite \equiv a random variable with typically 3-30 outcomes
- **Genotype** data of a polymorphism/genetic variant: paired alleles (from the paired chromosomes).

Mendel's Inheritance Laws

- **Law of Segregation (The "First Law"):** every individual has two alleles and each parent passes a randomly selected copy to each of its offspring.
- **Law of Independent Assortment (The "Second Law"):** alleles/genes for different traits are passed independently (only true if the genes are not linked).

SEGREGATION OF TRAITS IN MALE & FEMALE GAMETES



Source: Adapted from a publicly available image (via Google Images); modified by Dr. Fan Wang.

Exercise

If the father's genotype is **dD** and the mother's genotype is **dd**, what is the probability that an offspring's genotype is dd, dD, or DD?

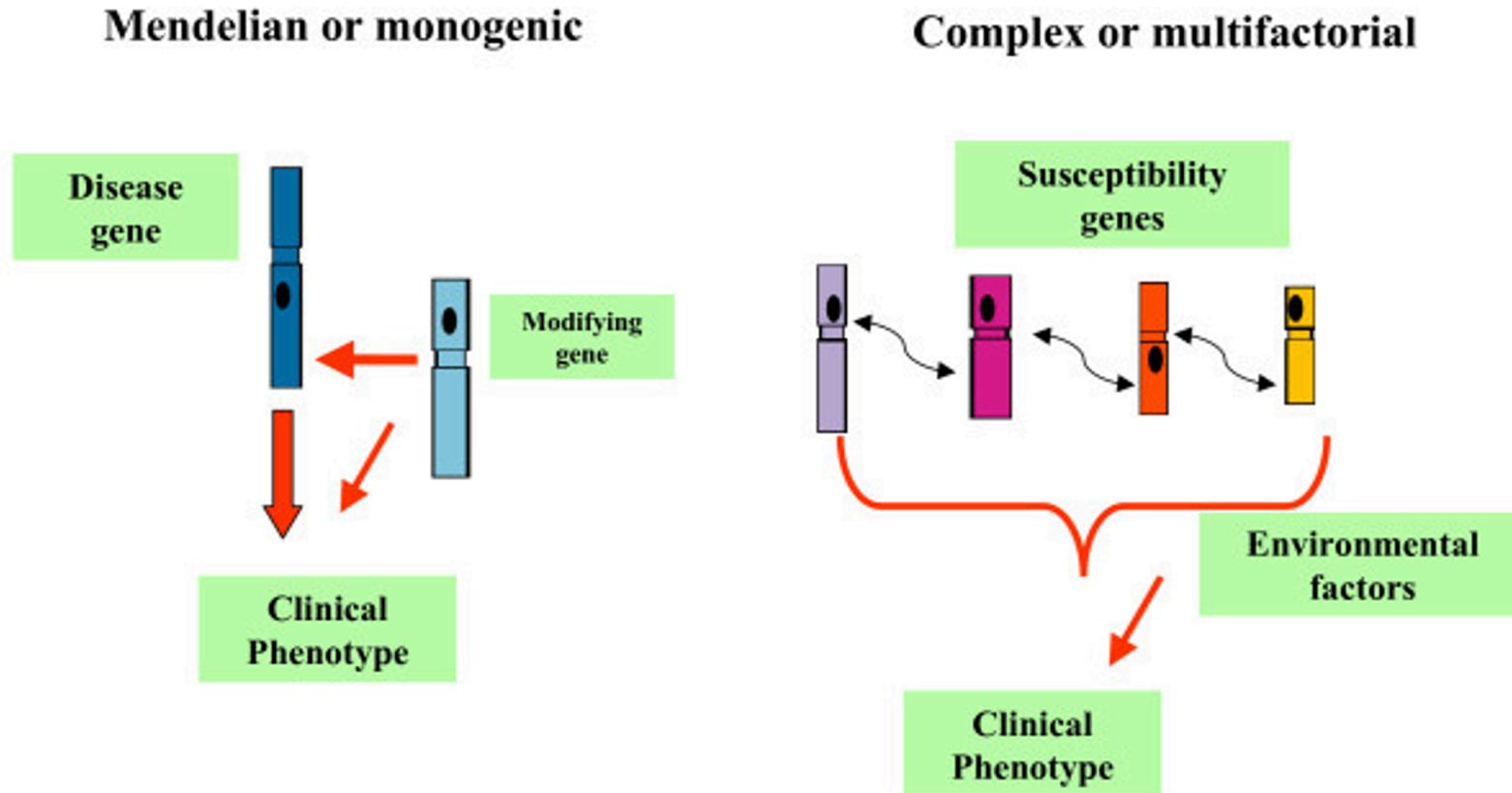
Application of Mendel's First Law

Father's Genotype	Mother's Genotype	Offspring's Genotype		
		dd	dD	DD
dd	dd	1	0	0
dd	dD	$\frac{1}{2}$	$\frac{1}{2}$	0
dd	DD	0	1	0
dD	dd	$\frac{1}{2}$	$\frac{1}{2}$	0
dD	dD	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$
dD	DD	0	$\frac{1}{2}$	$\frac{1}{2}$
DD	dd	0	1	0
DD	dD	0	$\frac{1}{2}$	$\frac{1}{2}$
DD	DD	0	0	1

Table 2.1: Distribution of offspring's genotype conditional upon parental genotypes

Source: Publicly available from Google Images

Mendelian vs. Complex Diseases



Source: Publicly available from Google Images

Example of a Mendelian (rare) Disease

- Sickle cell anemia: Mendelian disease that affects red blood cells, i.e. red blood cells have a sickle (rather than round) shape which results in an abnormal blood flow, blocked blood vessels and severe anemia.
- Widely recognized as inherited disorder for centuries in sub-Saharan Africa because of the way it appeared in families.
- Laboratory studies showed that the sickle shape was due to a genetic variant that changed the molecular structure of hemoglobin.
- Interestingly, the variant that causes sickle cell anemia protects against malaria. This explains the high prevalence of this variant in the population despite its deleterious effect: balancing selection.

Example of a Complex (common) Disease

- Alzheimer's disease (AD) is a complex disorder with a strong genetic component, first described in 1906.
- Brain disorder with progressive destruction of brain cells leading to loss of memory and other cognitive impairment.
- Late onset (>65), but a small fraction of cases develop AD very early (late 30's or 40s).
- Early onset AD is more likely to have a family history (familial AD).
- Over 200 rare variants in three genes have been reported in familial AD.
- Late onset AD is far more common: genetic causes (over 75 loci from GWAS), but also environmental risk factors such as head injury, high blood pressure, diabetes.

Genetic Models

- A genetic model describes the relationship (usually probabilistic) between an individual's genotype and their phenotype (or trait).
- Binary trait Y : affection status ($Y=1$ vs. $Y=0$).
- Continuous trait Y : quantitative phenotype (BMI, height, cholesterol).
- The genetic model can be deterministic (i.e. the genotype determines the phenotype exactly in Mendelian diseases).
- Most often the model is probabilistic (i.e. the genotype influences the probability of disease: $P(Y|G)$ (aka penetrance function in genetics)).

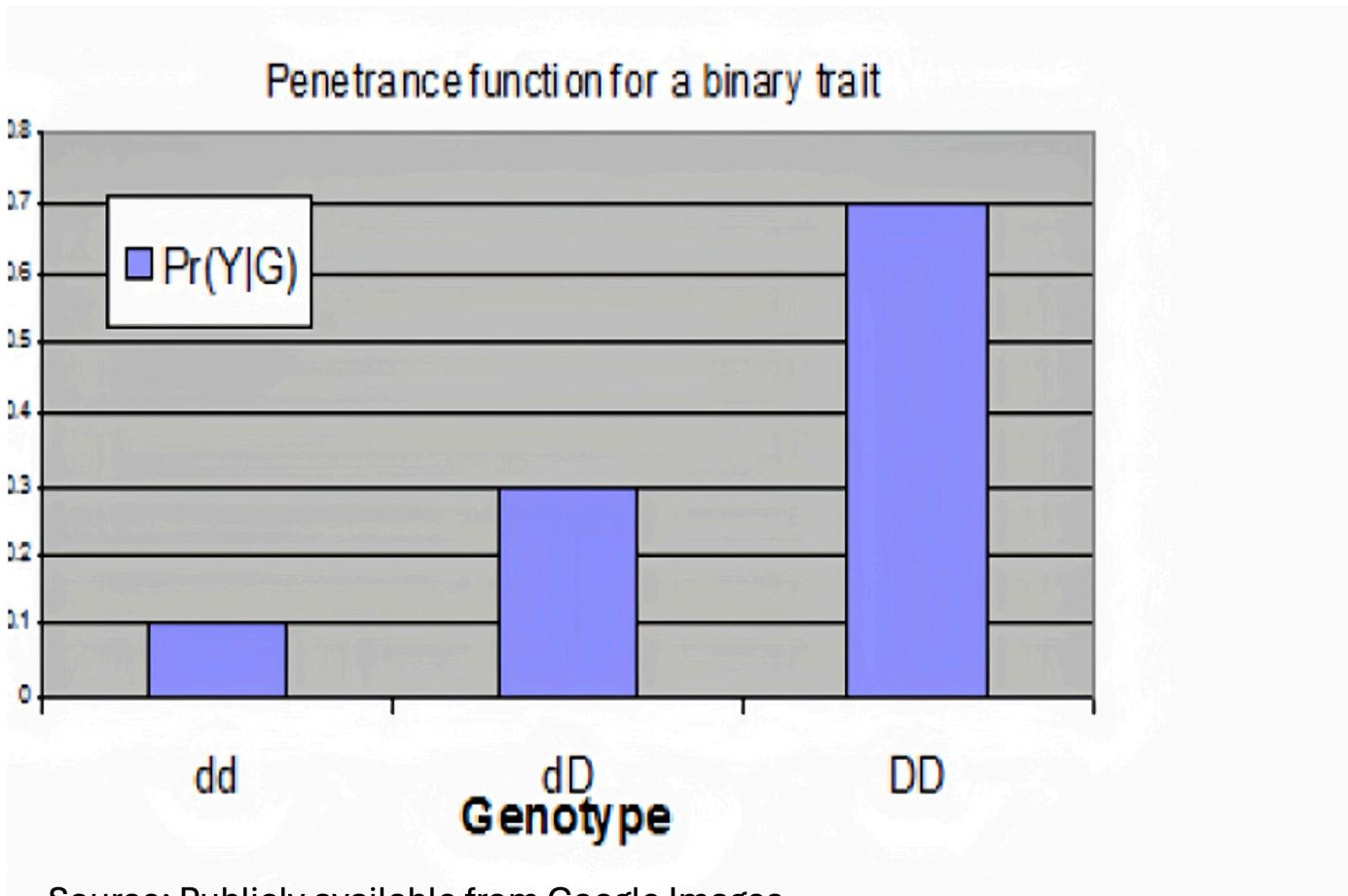
Simple Disease Models - Binary Traits

- A, a : the two alleles at a disease locus; A is the risk allele.
- If the genetic locus has no effect on disease then
$$P(Y = 1 \mid aa) = P(Y = 1 \mid Aa) = P(Y = 1 \mid AA).$$
- **Dominant:** $P(Y = 1 \mid AA) = P(Y = 1 \mid Aa) = 1, P(Y = 1 \mid aa) = 0.$
- **Recessive:** $P(Y = 1 \mid AA) = 1, P(Y = 1 \mid Aa) = P(Y = 1 \mid aa) = 0.$
- These deterministic models **hold only rarely for simple Mendelian diseases.**
- More realistic are stochastic models with reduced penetrance and phenocopies.

Simple Disease Models - Binary Traits

- Reduced penetrance: the probabilities above are less than 1.
 - e.g. in the recessive model $P(Y = 1 | DD) < 1$.
- Phenocopy means probability $P(Y = 1 | dd) > 0$
 - Disease can be caused by a different genetic locus than the one under consideration.
- **Additive** if the penetrance of the heterozygous genotype is midway between the two homozygous genotypes.

Penetrance Function for a Binary Trait



Source: Publicly available from Google Images

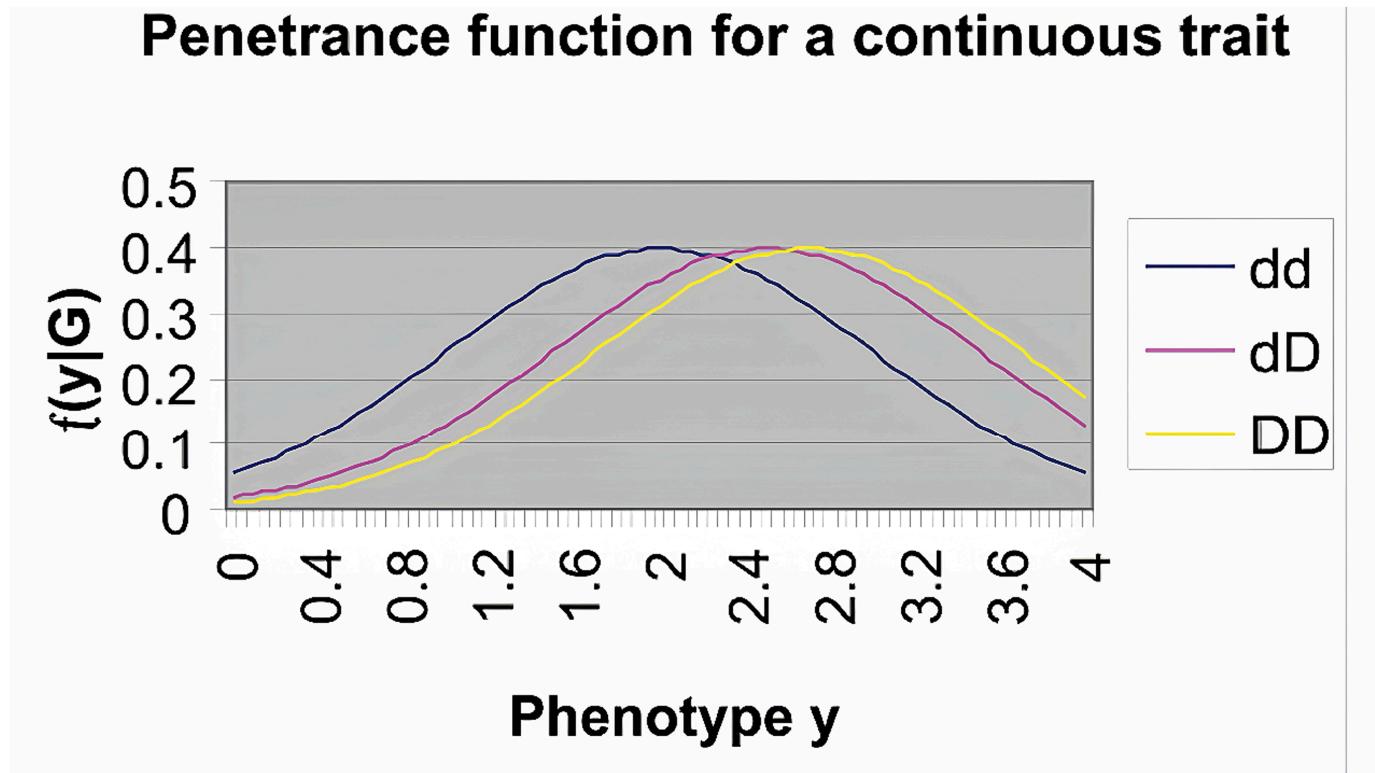
Quantitative Traits

- For **quantitative traits**: a natural choice for the penetrance function is a normal density with a mean depending on the genotype.
- A more general approach uses a generalized linear model (GLM):

$$g(E(Y | X)) = b_0 + X'b_1, \text{ where } g \text{ is the link function.}$$

- Logistic function for binary traits: $\log \frac{E(Y|X)}{1-E(Y|X)} = b_0 + X'b_1,$
- Identity function for continuous traits: $E(Y | X) = b_0 + X'b_1$
- X (the coded genotype) reflects the mode of inheritance.
- Test for genetic effect: $H_0 : b_1 = 0$ (b_1 = effect size).

Penetrance Function for a Continuous Trait



Source: Publicly available from Google Images

Genotype Coding

Recessive	
X	G
1	AA
0	Aa or aa

Dominant	
X	G
1	AA or Aa
0	aa

Additive	
X	G
2	AA
1	Aa
0	aa

Source: Created by Fan Wang

What's Next

- Fundamental principles of population genetics
- Estimation of allele frequency
- Population substructure
- Hardy–Weinberg equilibrium
- Mode of inheritance
- Association testing

What questions do you have about anything from today?