

# 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

- Pre-reqs: [Unix Shell module](#) and [R module](#).
- 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/stat\\_gen](https://github.com/UofT-DSI/stat_gen)

- Schedule
- These slides (HTML & PDF)
- Our database for live coding
- 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](#)

# Assignments

- Three assignments (TBA), released on Monday of each week.
- Broken into three sections:
  - Section 1 focuses on review of molecular genetics and basic genetic models
  - Section 2 focuses on population genetics & consequences on genetic association studies
  - Section 3 focuses on genome-wide association studies
- Review questions/answers in Office Hours course support

# Grading

- Pass/Fail. Do the work, pass the course :)
- Assignment 1: Navigating Genetic Dataset to Understand Genotype – Phenotype Data Structure
- Assignment 2: TBA
- Assignment 3: TBA
- Review rubrics for full details
- Class Attendance: *not graded this cohort, come anyway!*
  - Let me or course support know if you are unable to attend a lesson

**What questions do you have about the course?**

# What You'll Learn Today

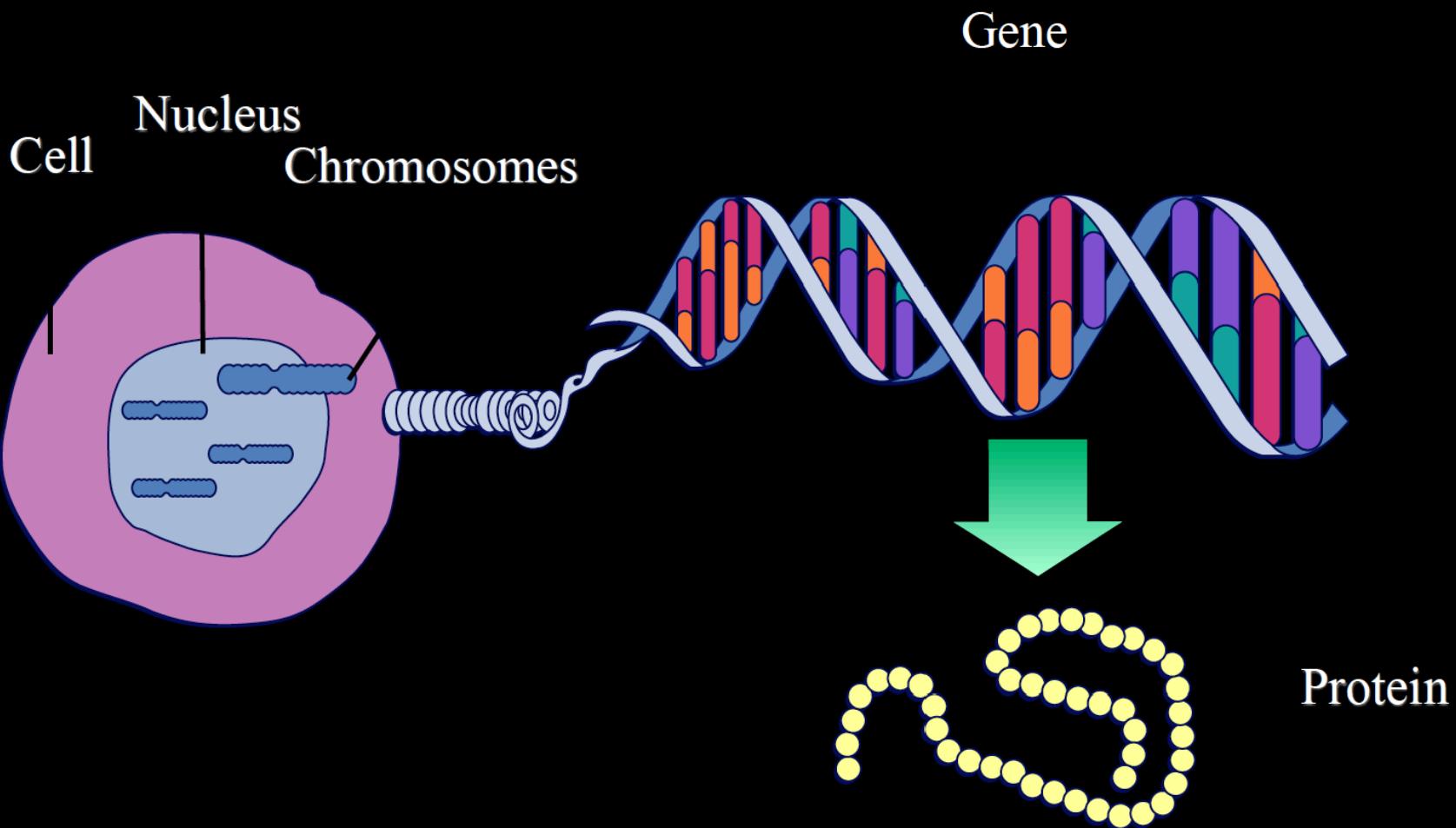
- Foundations of genetic variation
  - DNA → chromosomes → genes
  - Common variant types (e.g., SNPs)
- From variants to traits
  - Mendelian vs. complex disease
  - Inheritance models: dominant / recessive / additive (genotype coding 0/1/2)

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?

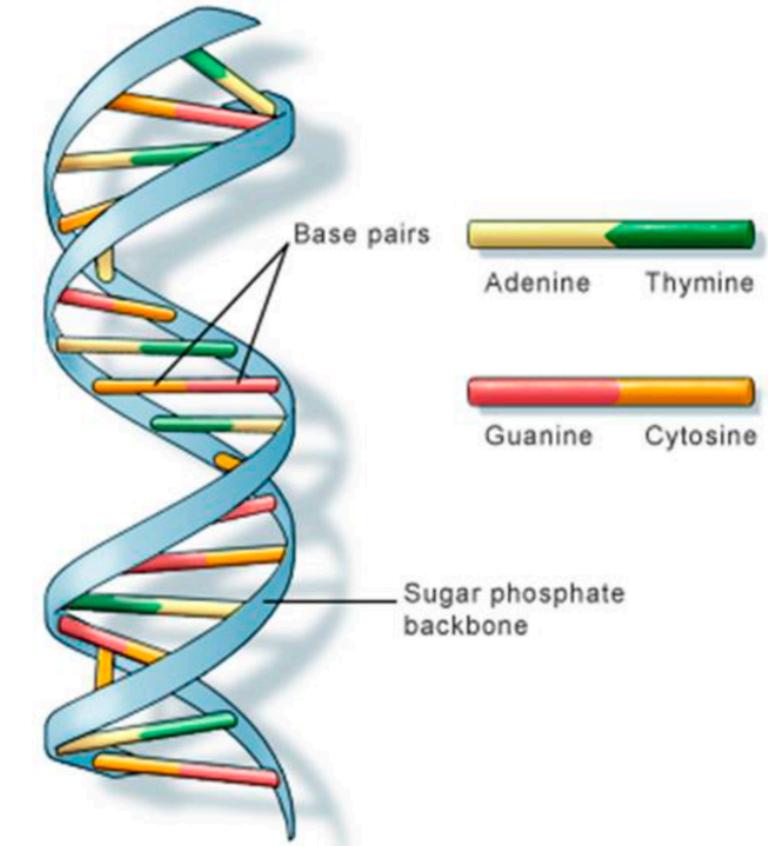
- Statistical genetics is an interdisciplinary field at the interface between statistics and genetics and is concerned with the development of statistical methods for problems in genetics.
- Genetics is a subfield of biology concerned with the study of heredity (transmission of genetic material from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

# Chromosomes, DNA and Genes



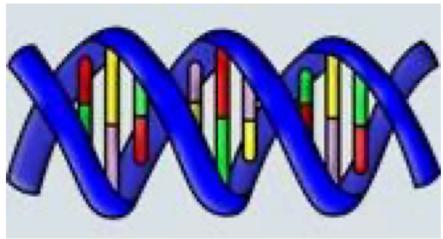
# Deoxyribonucleic Acid (DNA)

- 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

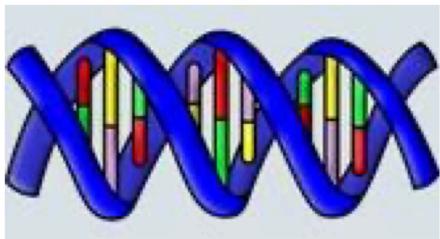


S. National Library of Medicine

# Deoxyribonucleic Acid (DNA)



CTCGTCACCTTCAC  
GAGCAGTG?????

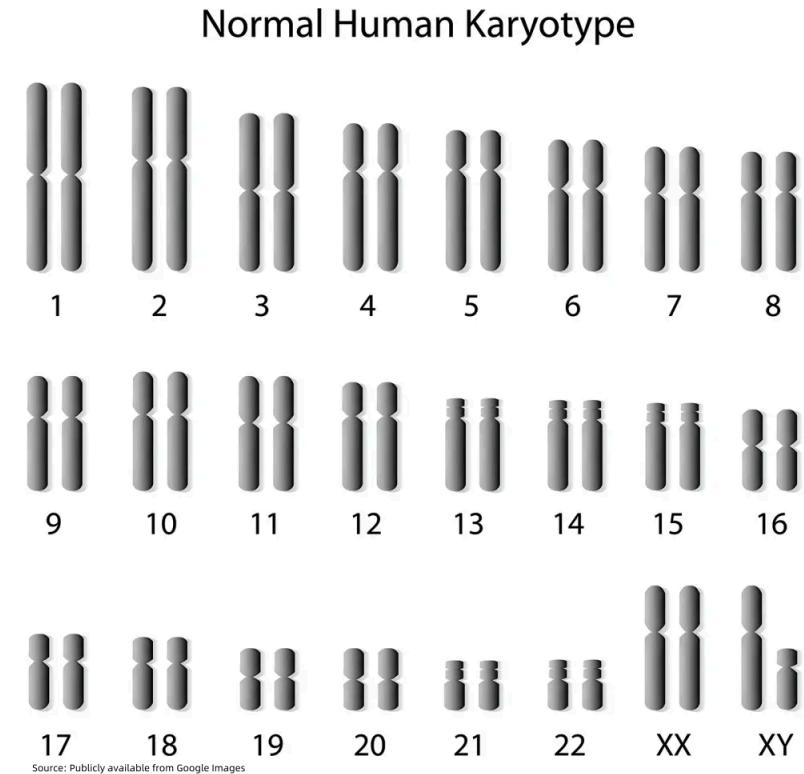


CTCGTCACCTTCAC

Source: Created by Fan Wang

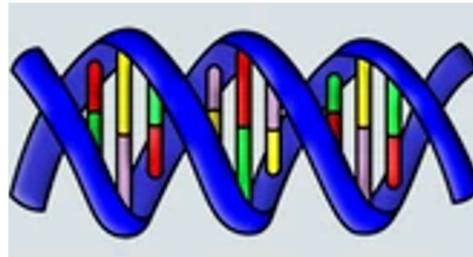
# Chromosomes

- 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.

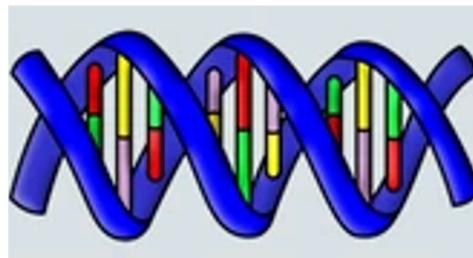


# Double Helix Structure

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



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

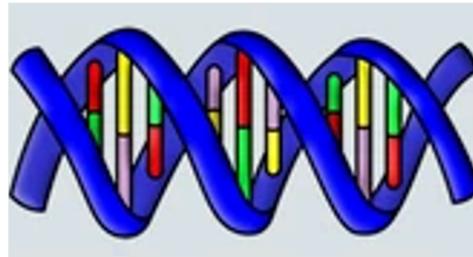


CTCCTCACCTTCAC  
| | | | | | | | | |  
GAGGAGTGAAGTG

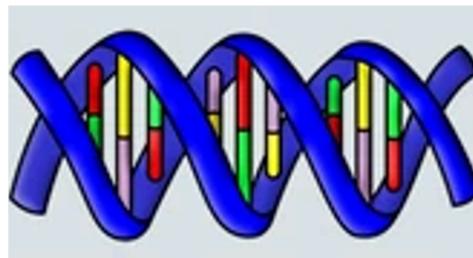
Source: Created by Fan Wang

# 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

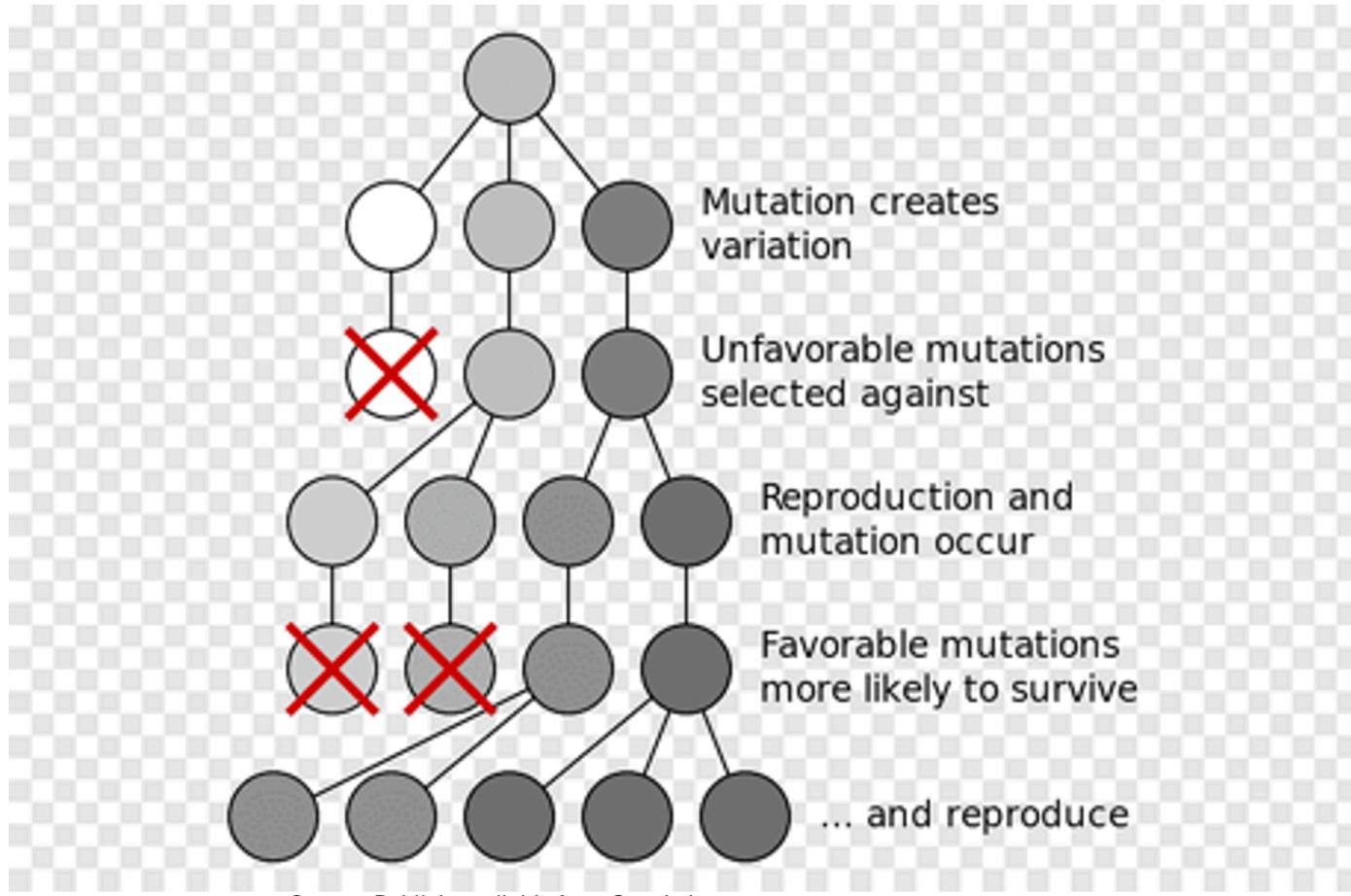
↑  
**Translocation** (segment from another region)

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

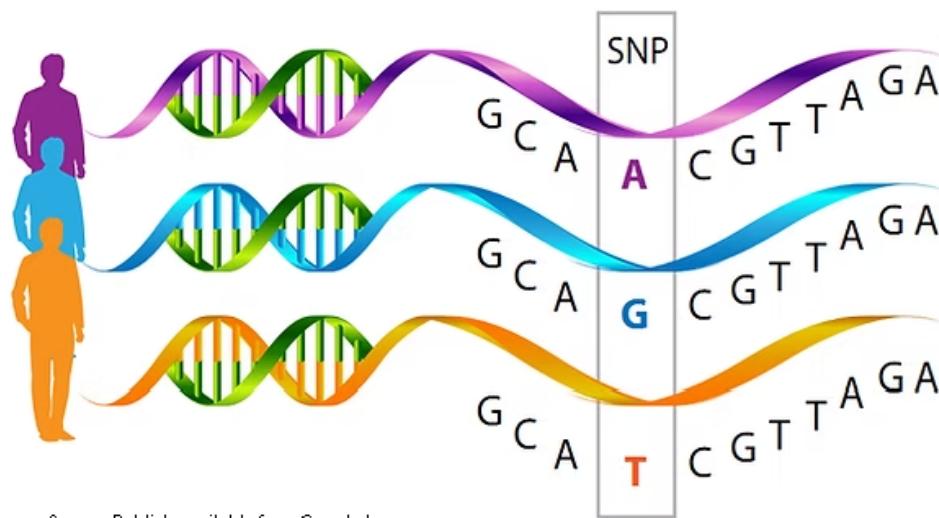


# Genetic Variants/Polymorphism

- 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

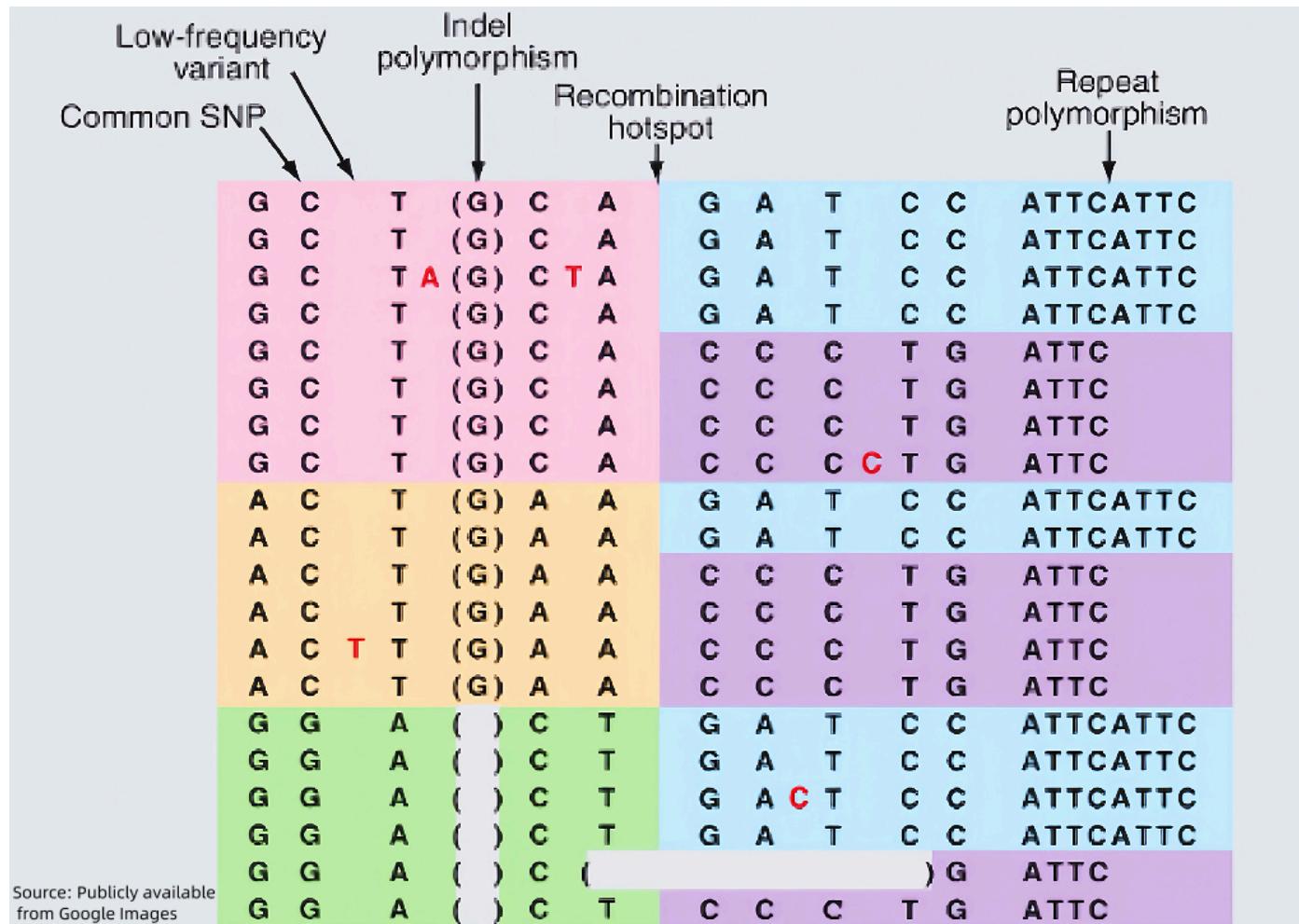
- A **single nucleotide polymorphism (SNP)** is a type of genetic variation where a single nucleotide (A, C, G, or T) differs between individuals.
  - An **allele** at a SNP refers to one of the possible nucleotide bases — A, C, G, or T.
  - Appear about every 300 base pairs →  $\approx 10$  million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



# Types of Genetic Variants

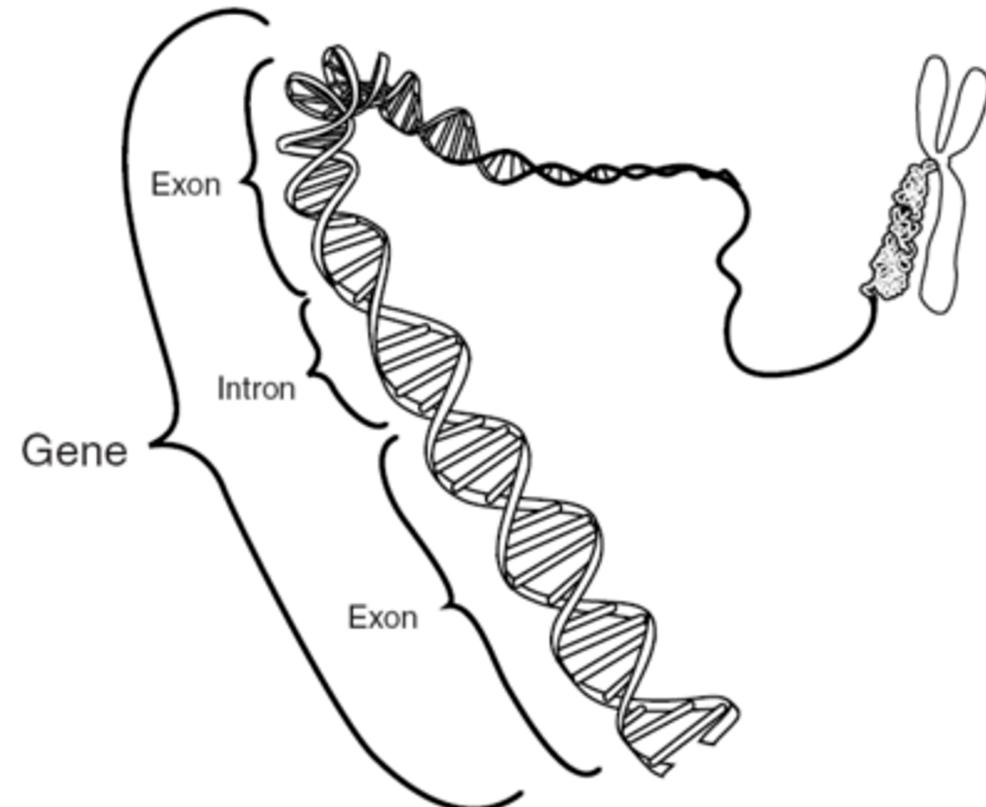
- **Variable number of tandem repeats (VNTR)**: Specific DNA sequences that are repeated immediately adjacent to each other for a variable number of times.
  - e.g. 16, 14 and 11 repeats of CA.
  - **Microsatellites** consist of small sequences (1-6) that are repeated.
  - The number of repeats can vary 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

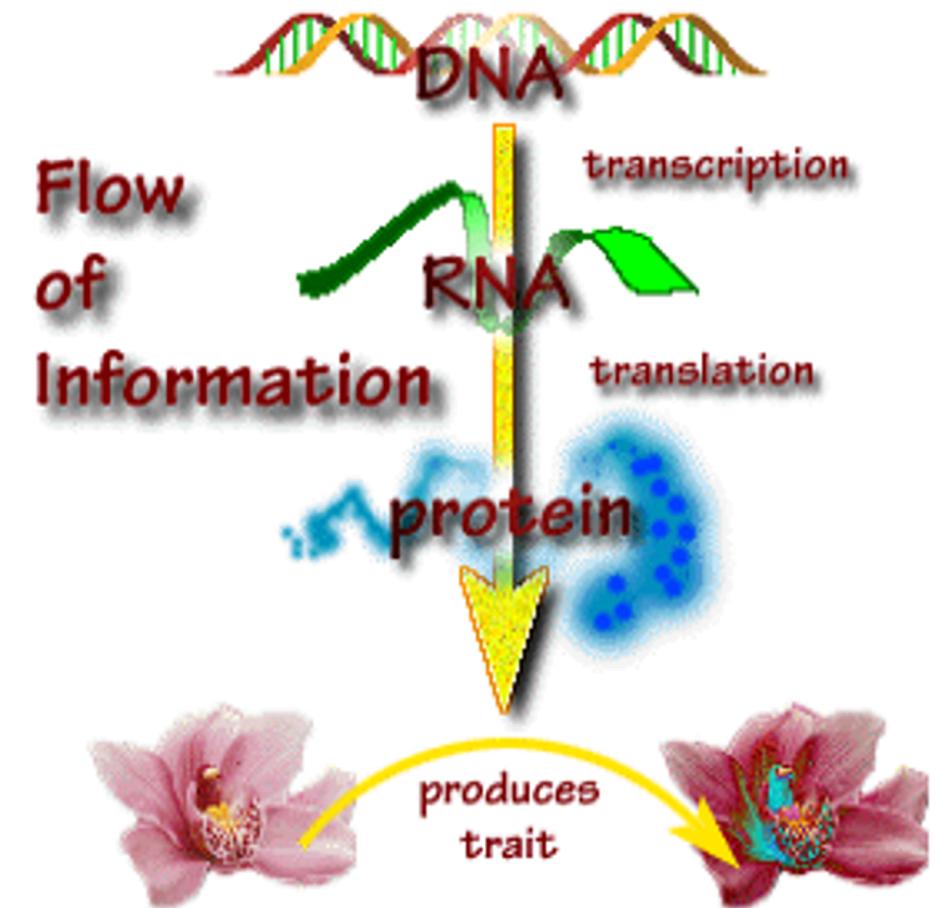
- A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that **encodes a specific functional product** (a protein or RNA molecule).
- A gene is a segment of DNA consists of several coding segments (**exons**), separated by non-coding sequences (**introns**).
- 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	

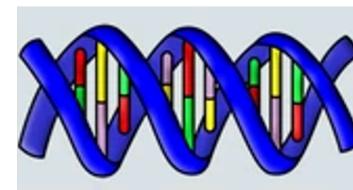
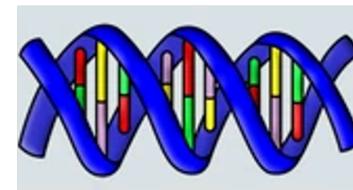
Source: Publicly available from Google Images

# 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**

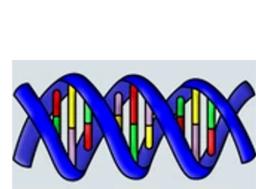
The **genotype** at this SNP: **Aa**

Source: Created by Fan Wang

# Alleles and Genotypes

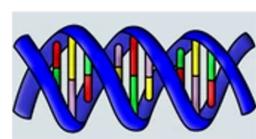
- A SNP with two alleles (A and a) has 3 possible (unordered) genotypes: AA, Aa/aA, aa.
- **Homozygous** genotype: same allelic type (AA or aa);
- **Heterozygous** genotype: different allelic type (Aa/aA).

Individual 1:



Allele A

CTCGTCACCTCAC  
GAGCAGTGAAGTG



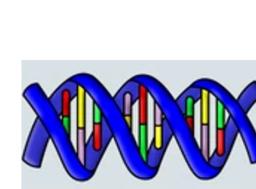
Allele a

CTCATCACCTCAC  
GAGTAGTGAAGTG

Source: Created by Fan Wang

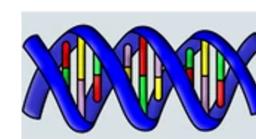
The **genotype** at this SNP: **Aa**

Individual 2:



Allele a

CTCTTCACTTCAC  
GAGAAGTGAAGTG



Allele a

CTCATCACCTCAC  
GAGTAGTGAAGTG

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

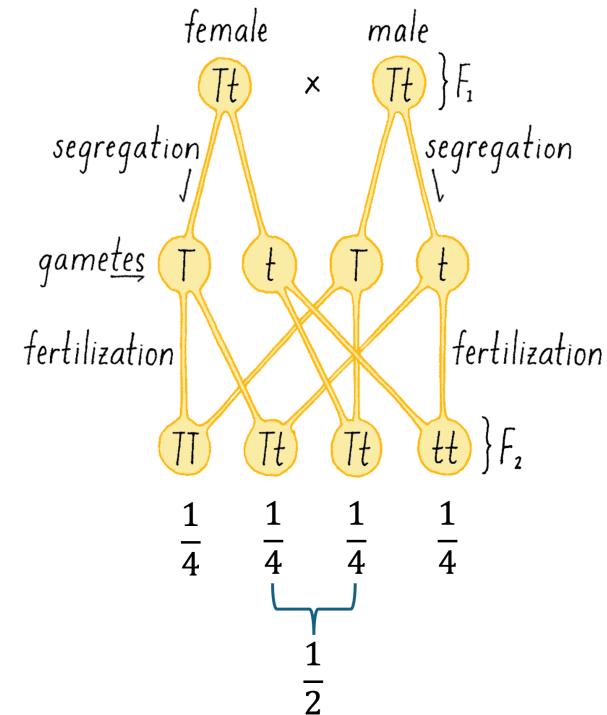
# Recap

- 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?

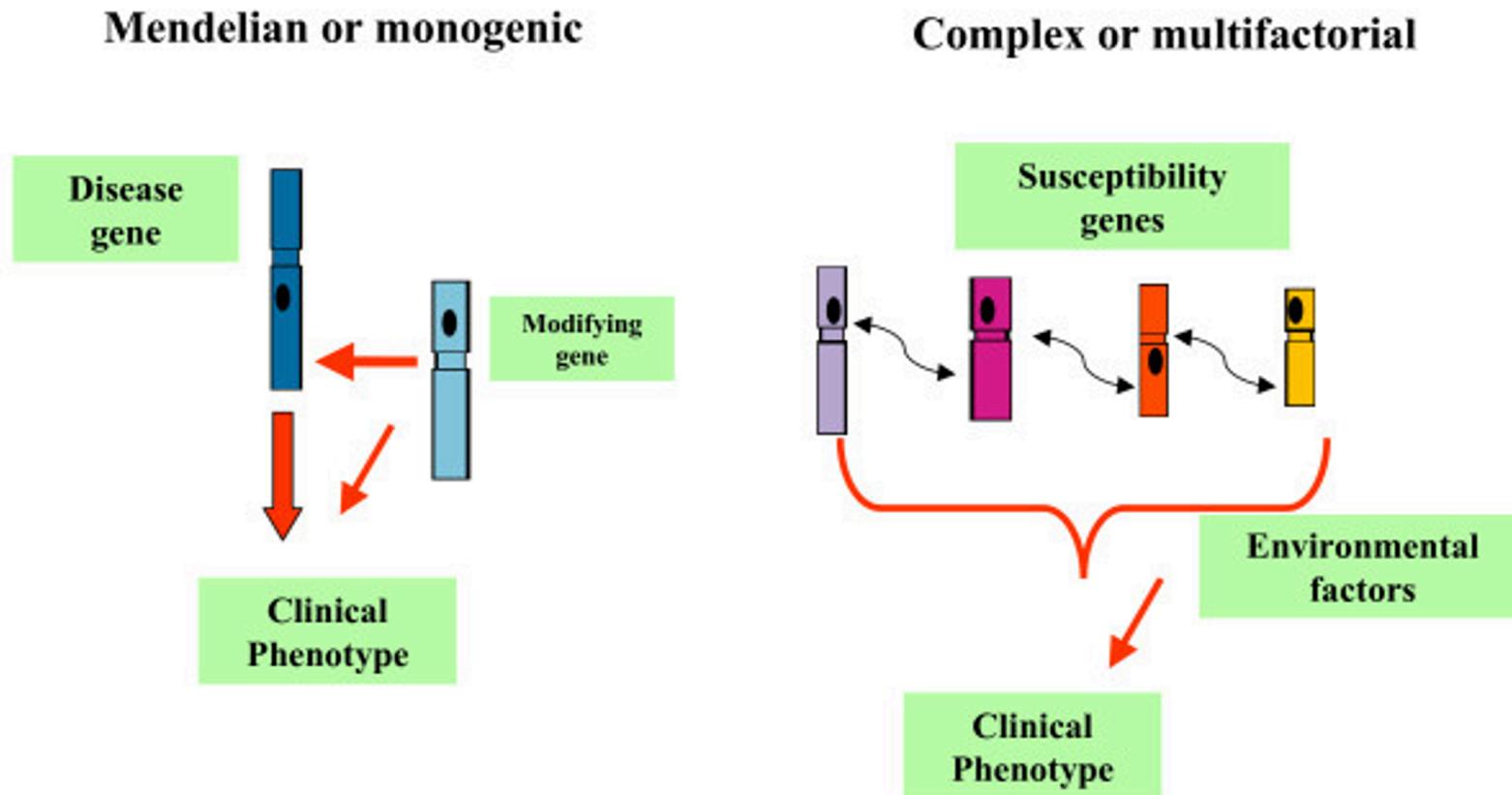
# Application of Mendel's First Law

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)).

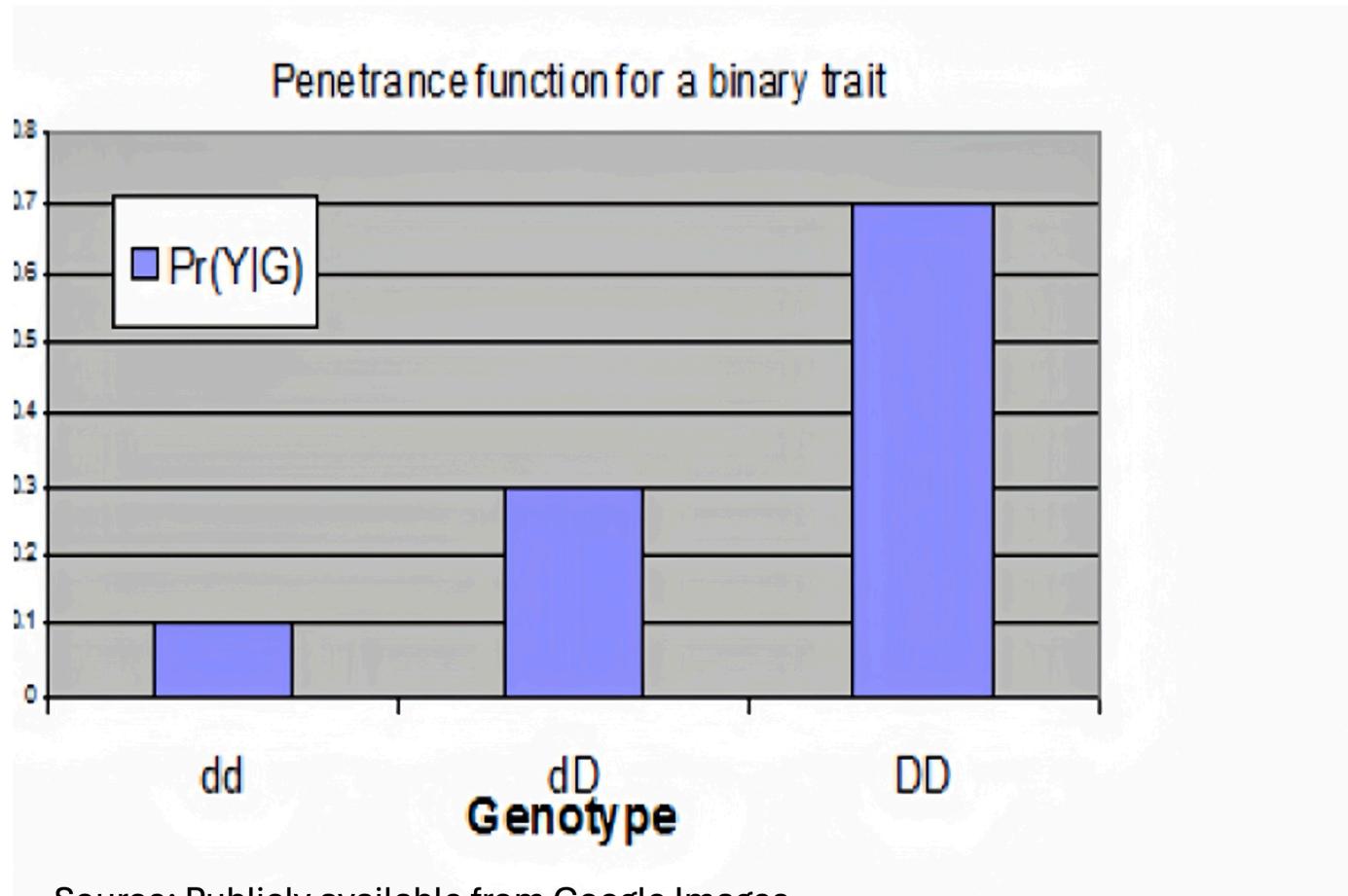
# Simple Disease Models - Binary Traits

- $A, a$ : 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

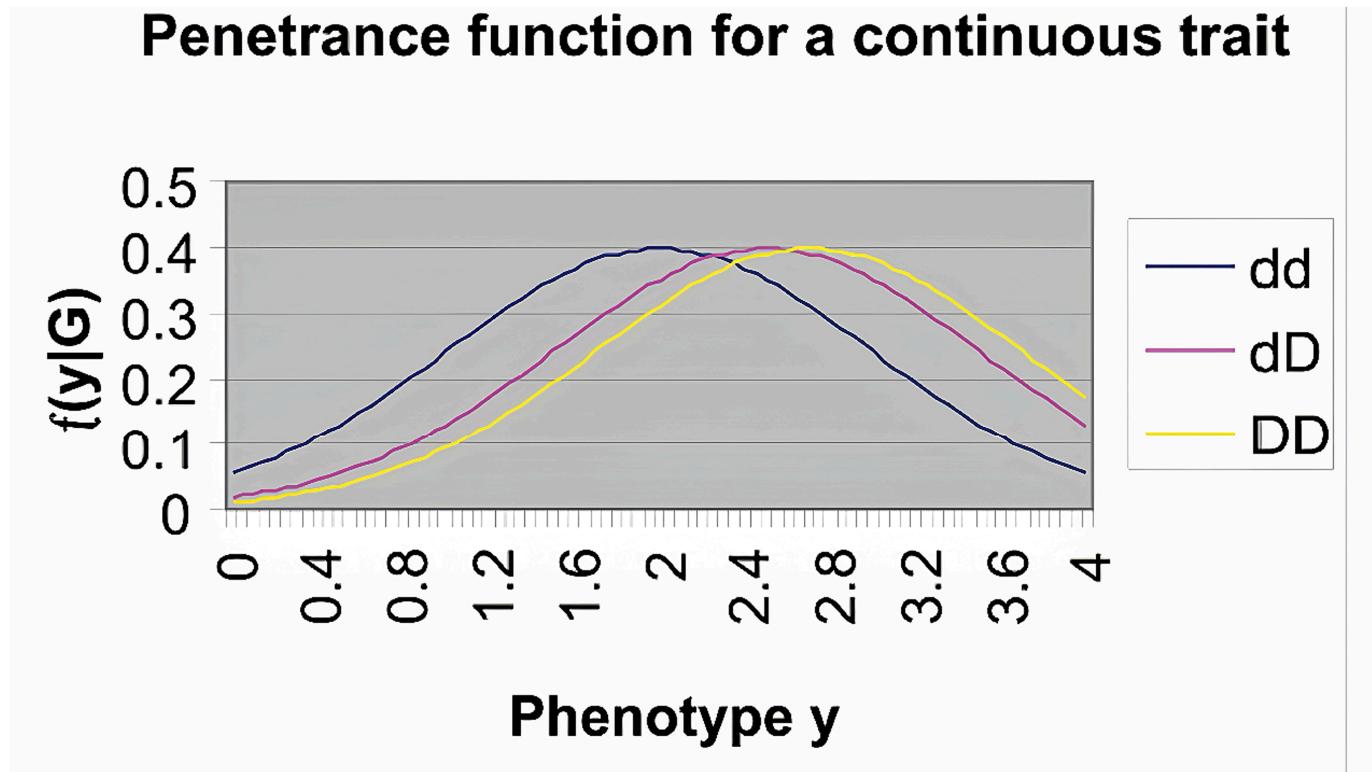
# Quantitative Traits

- 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?**