Introduction to Statistical Genetics

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$ echo "Data Sciences Institute"
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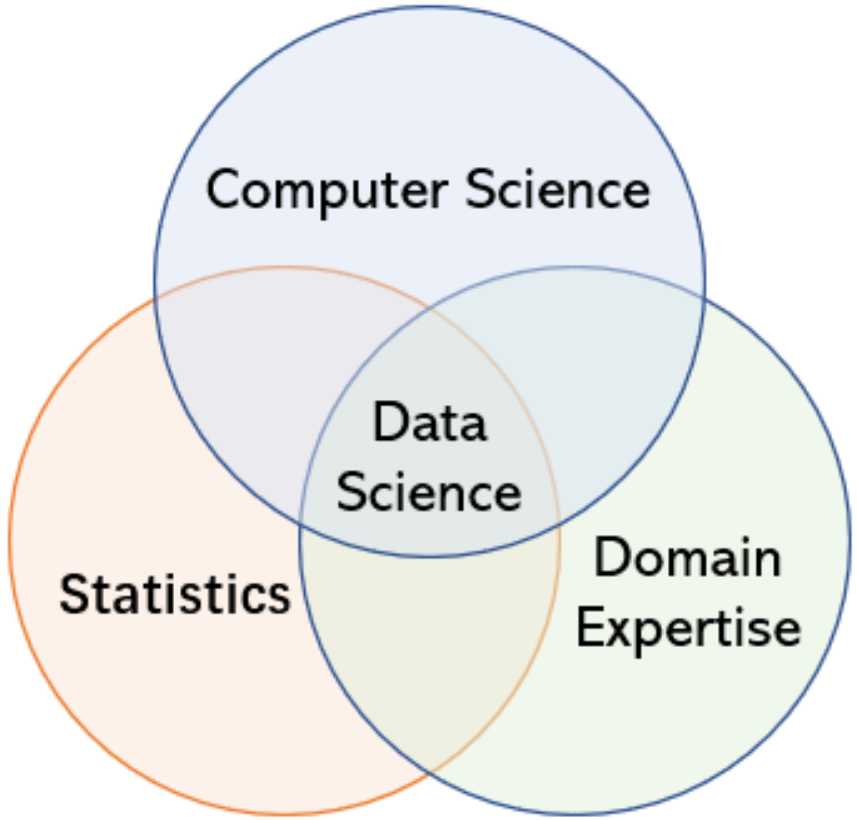
Introduction

→ What is Statistical Genetics and Genomics?

Big Data: $n > 10^3$, $p > 10^6$ (high-level processed data in GB and raw data in TB)

Complex: (e.g. multiple causal factors, interactions, pathway/network...)



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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

- 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 anyways!*
    - Let myself or course support know if you are unable to attend a lesson

What questions do you have about the course?

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

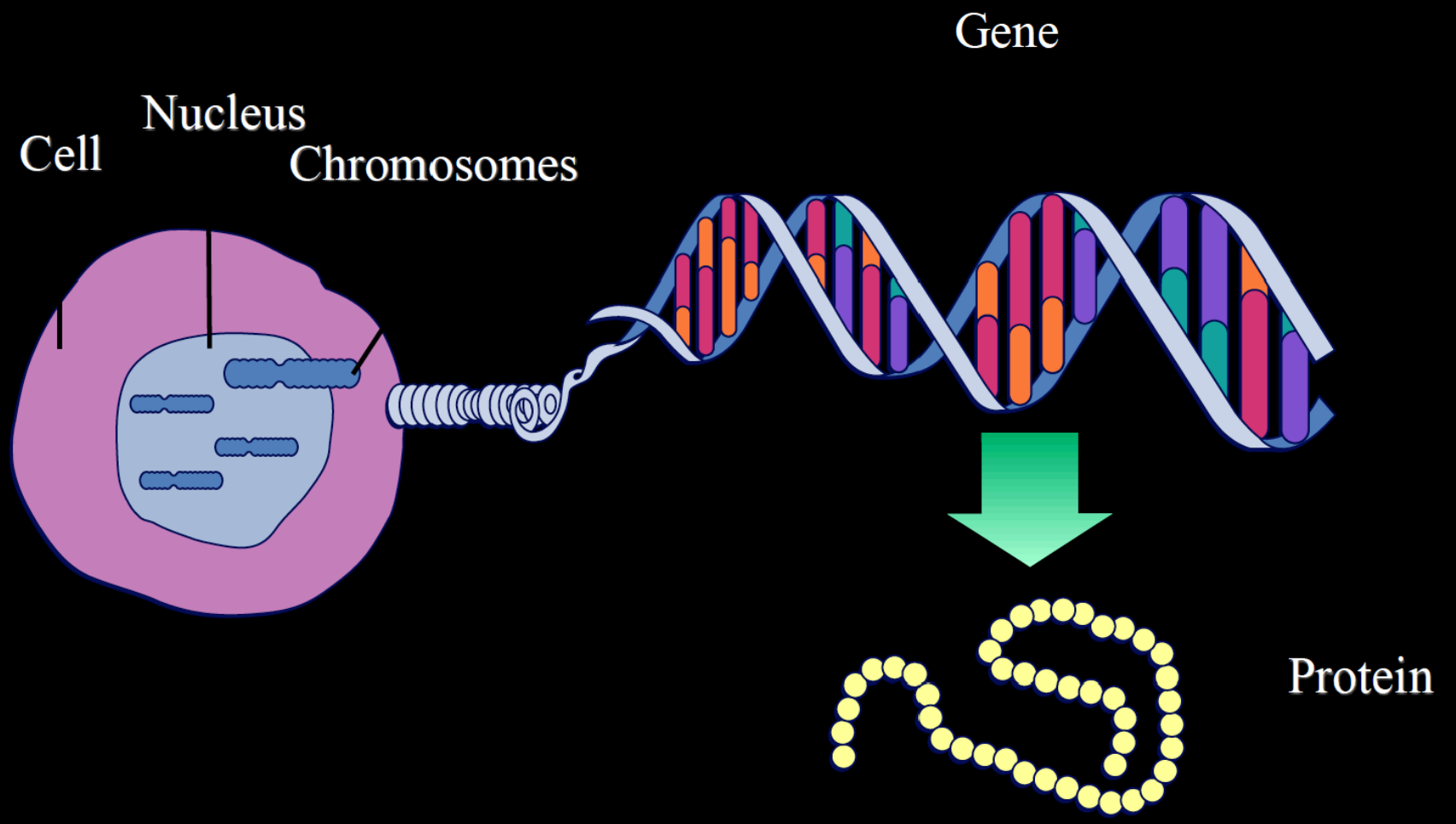
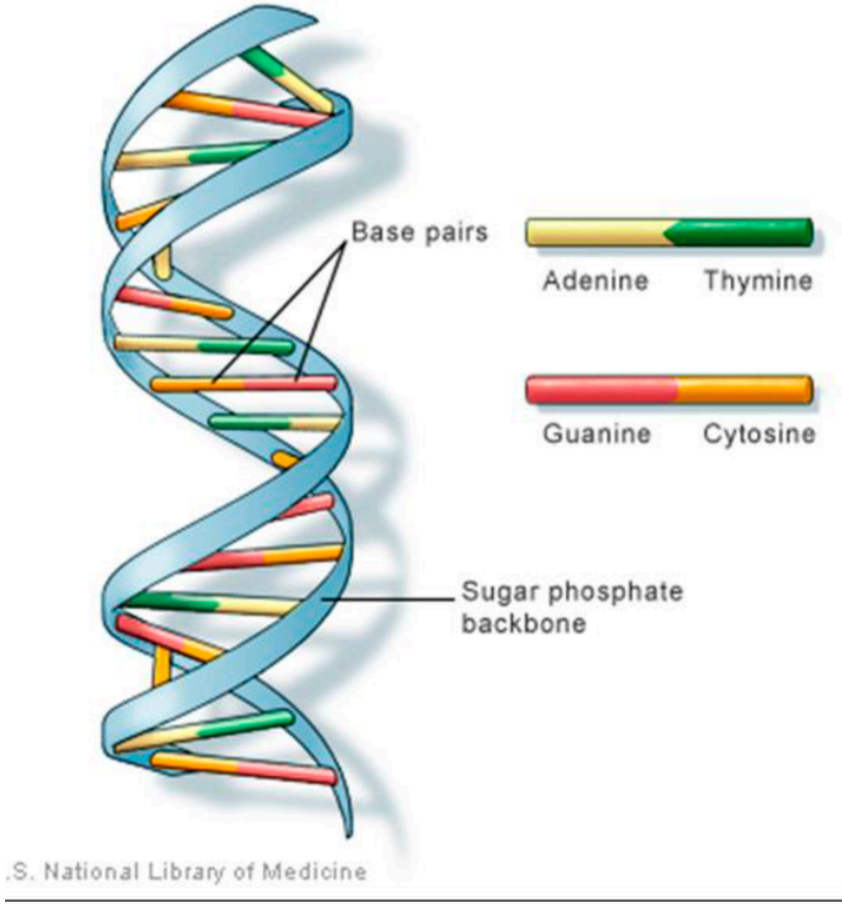


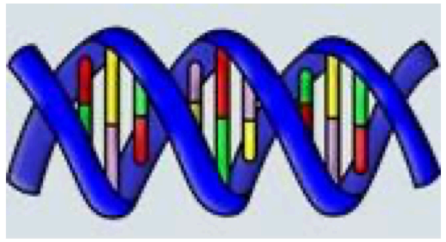
Image: Dr. Paterson's Notes on Genetics, via Lei Sun (U of T), GitHub

DeoxyriboNucleic Acid (DNA)

- DNA is the basic biological material of interitance; 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: ATGC.
- A-T and G-C matching: information on one strand is sufficient.
- ‘Size’ of the genome: ≈ 3 billions of DNA base pairs



DeoxyriboNucleic Acid (DNA)



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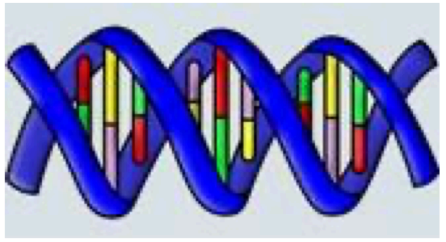

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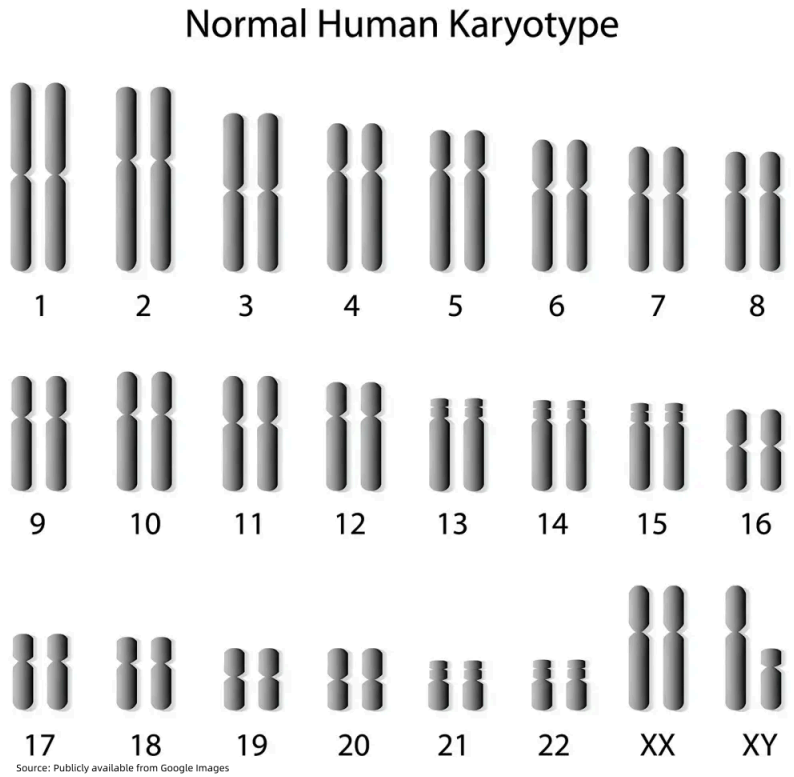
Source: Created by Fan Wang

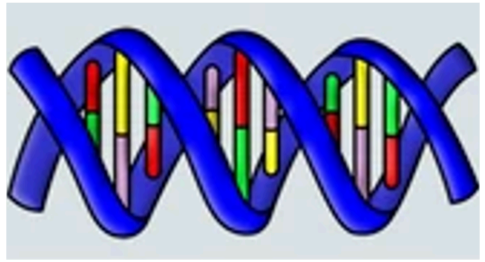
Chromosomes

- Each chromosome has a double helix structure: two long strands of DNA, bounded 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**:



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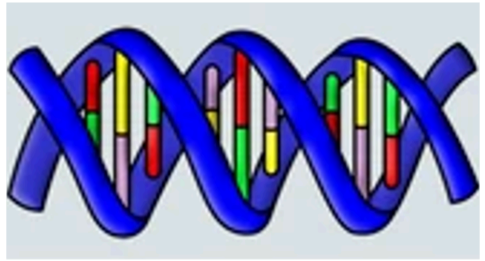

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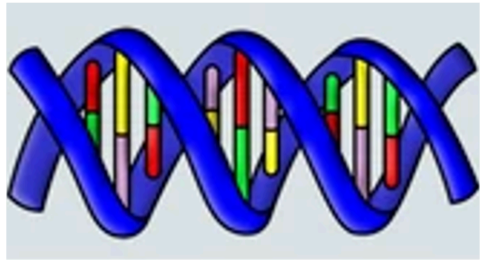

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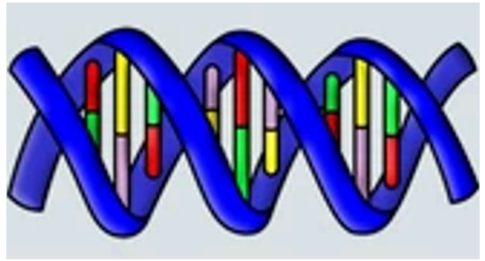

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G A G G A G T G A A G T G

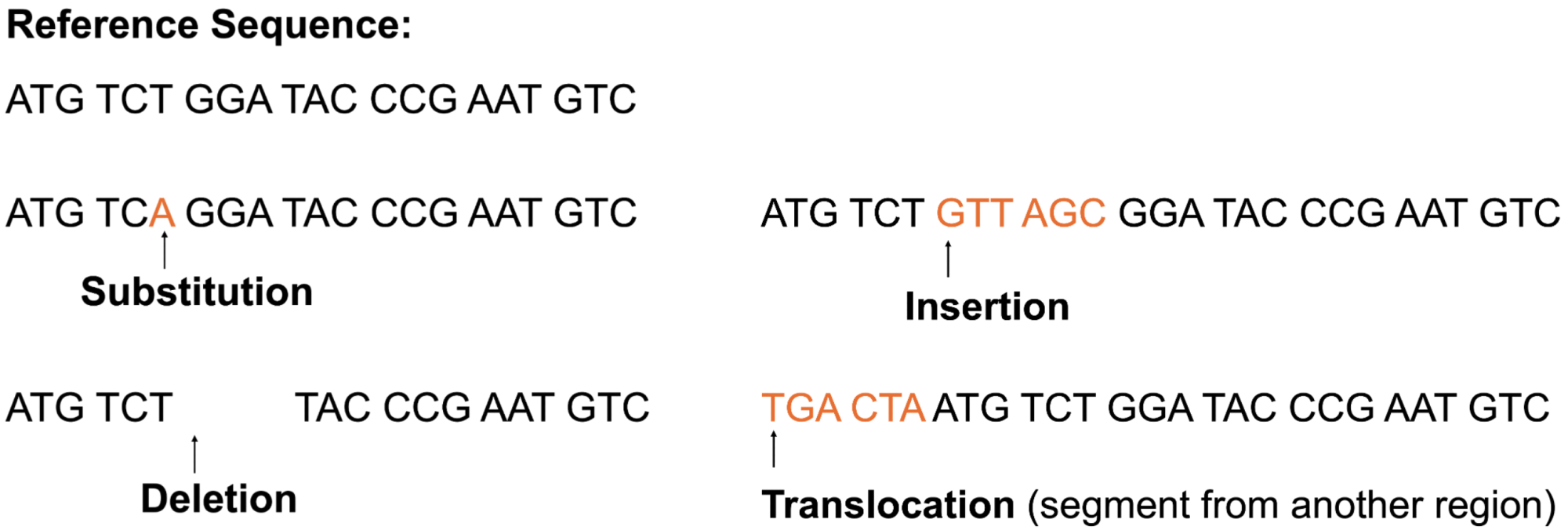
Source: Created by Fan Wang

Human Genome

- 3 billion nucleotides (A,C,G,T) in the whole human genome.
  – 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**.

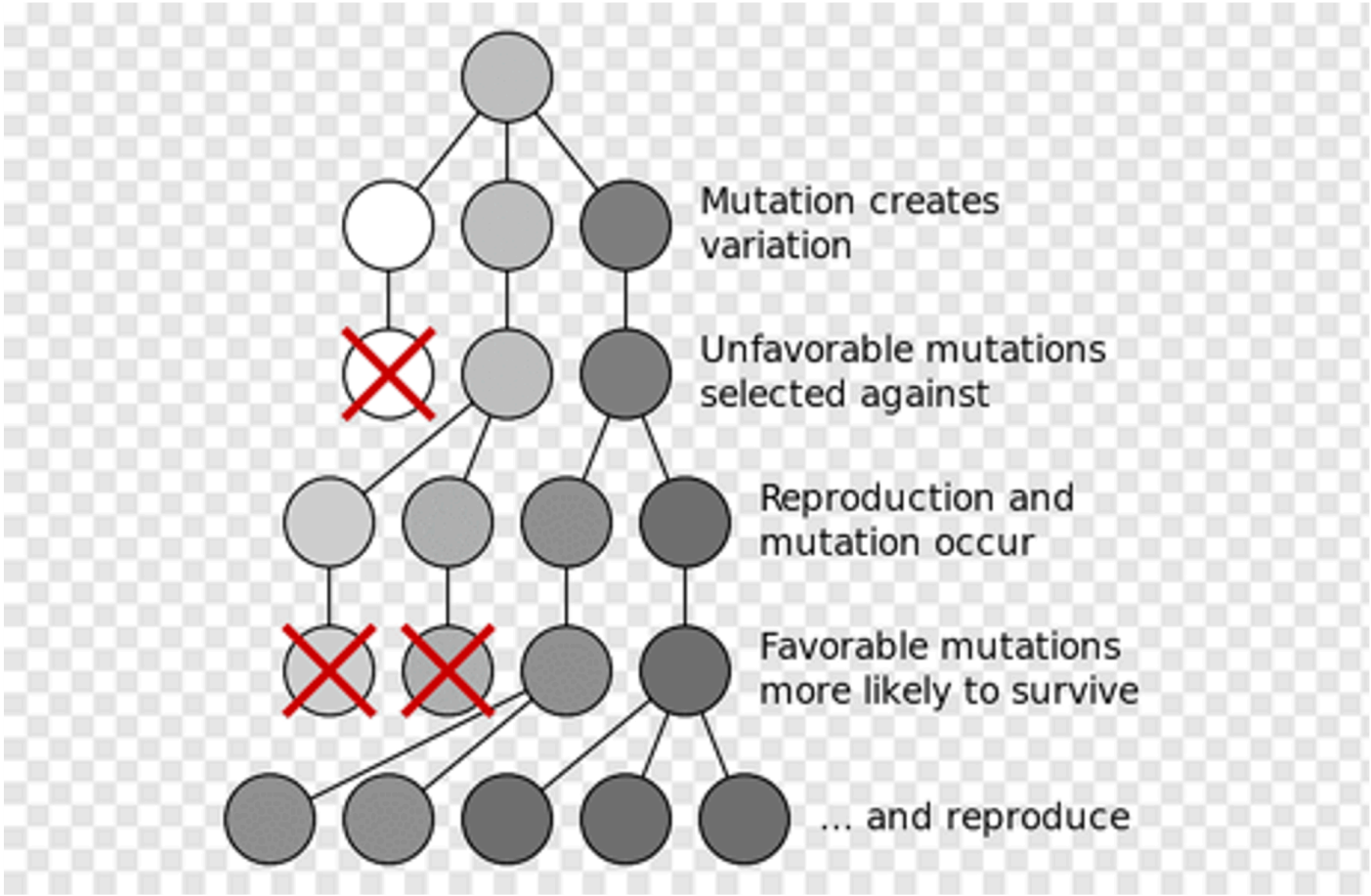


Source: Created by Fan Wang

Effects of Mutations

- Mutations can be very detrimental to an organism.
    - May cause proteins to malfunction.
    - cells 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



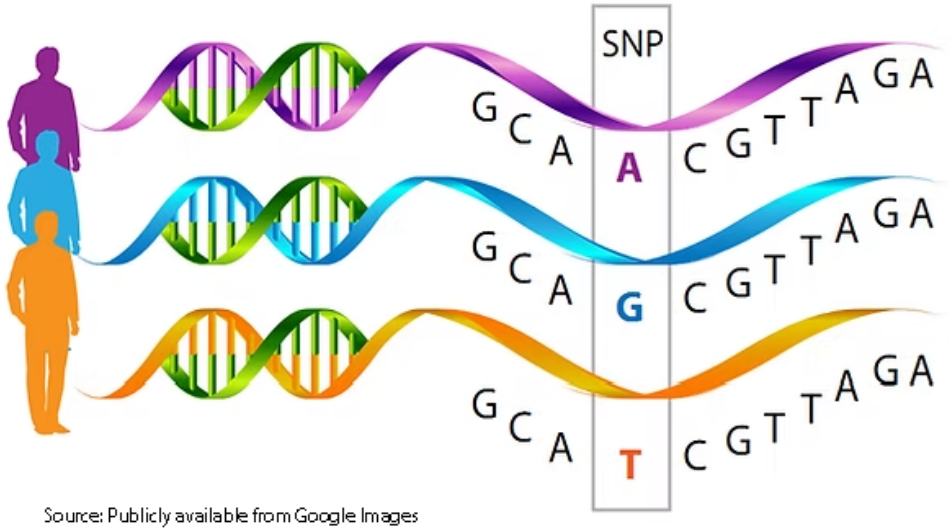
Source: Publicly available from Google Images

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 term: 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 $\rightarrow \approx$ 10 million SNPs.



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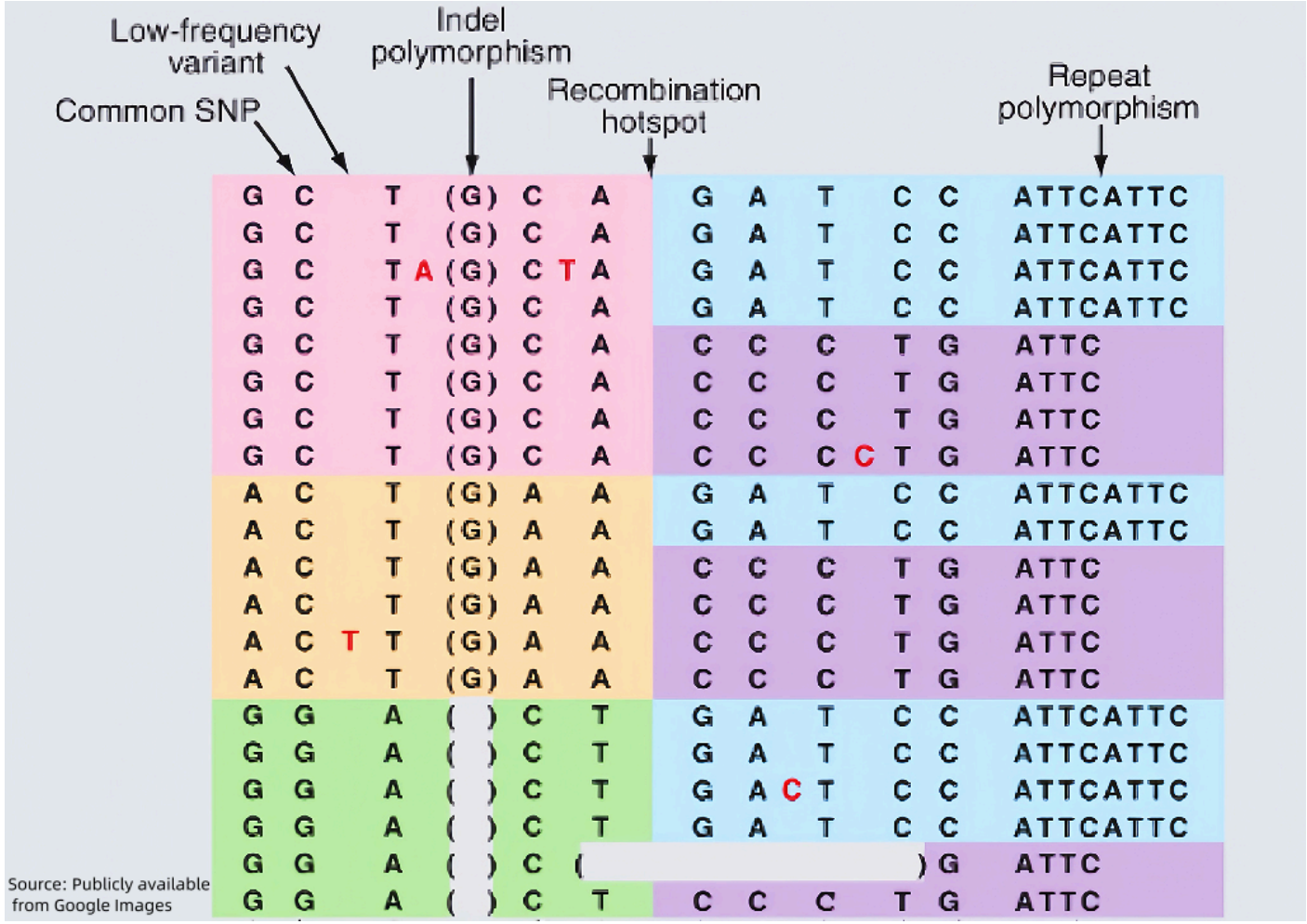
Types of Genetic Variants

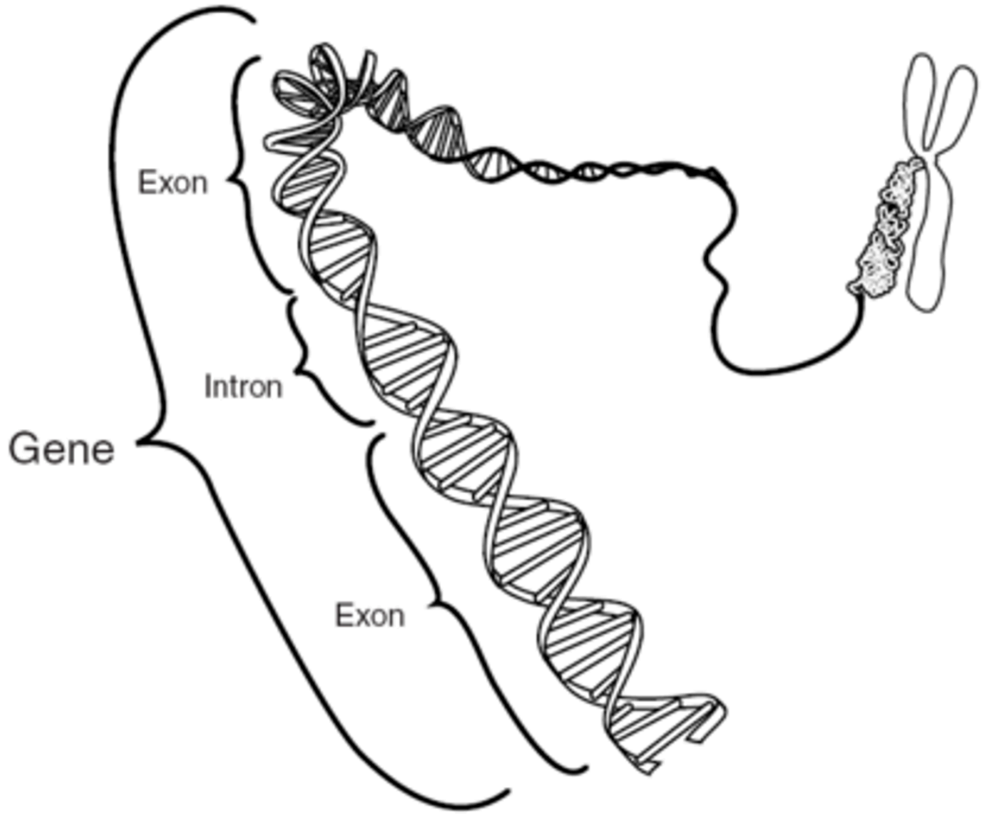
- **Variable number of tandem repeats (VNTR)**: Specific DNA sequences that are repeated immediately adjacent to each other a variable number of times.
    - e.g. 16, 14 and 11 repeats of CA.
    - **Microsatellites** consist of small sequences (1-6) which are repeated.
    - The number of repeats can 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 in between two specific base pairs
- **Structural variants**: duplications, deletions, inversions, translocations
- **CNV (copy number variants)**: large insertions/ deletions

Types of Genetic Variants



Genes

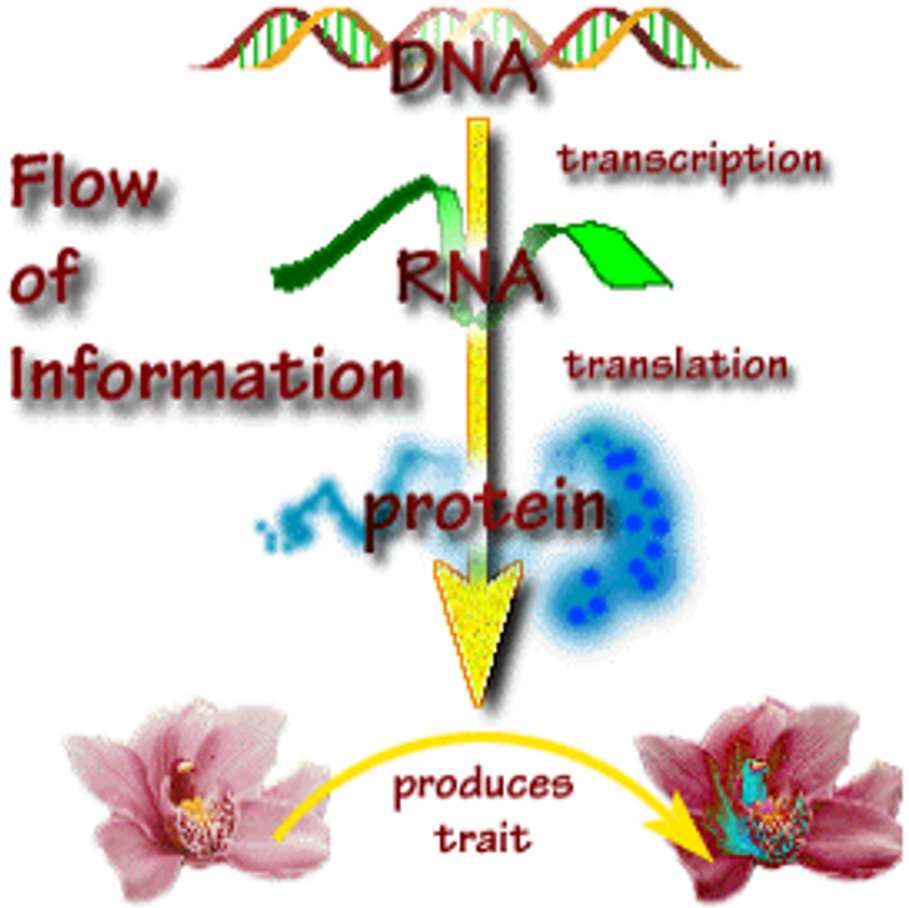
- A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that **encodes a specific functional product** (a protein or RNA molecule).
- A gene is a segment of DNA consists of several coding segments (**Exons**), separated by non-coding sequences (**Introns**)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



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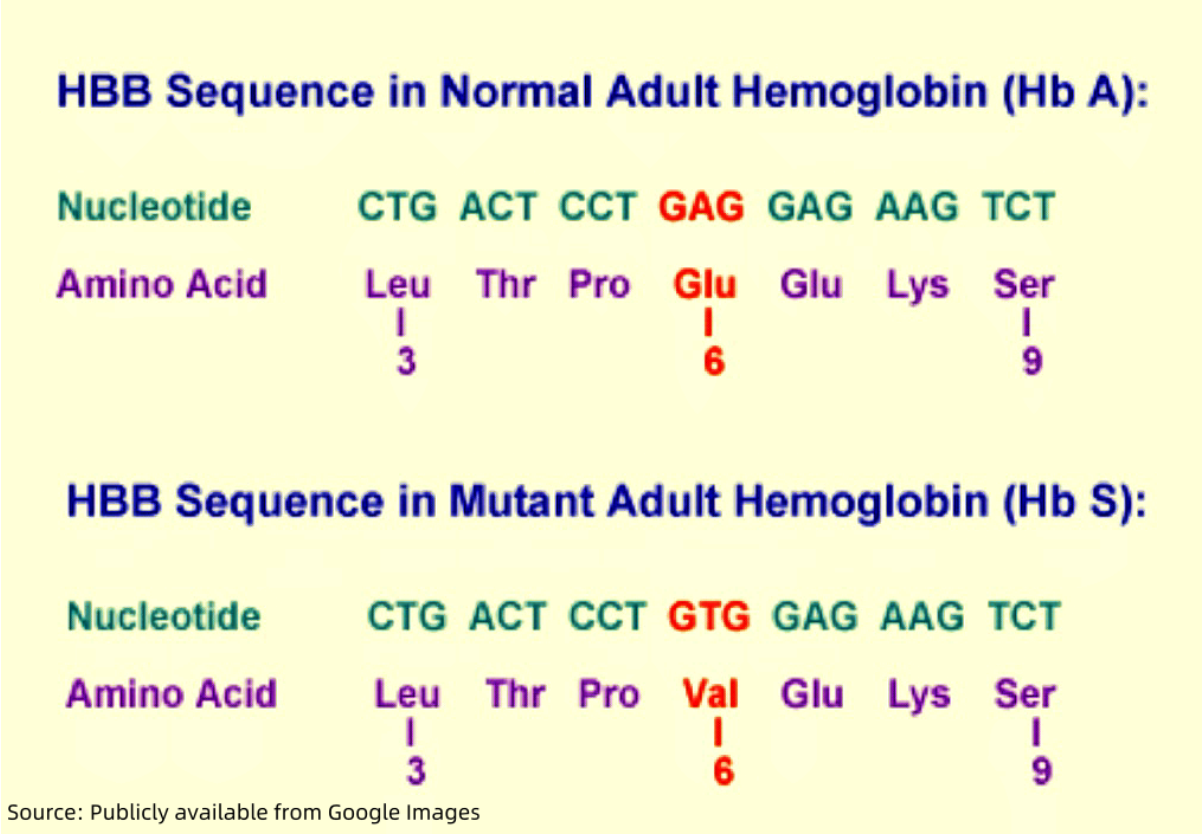
Proteins

- 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



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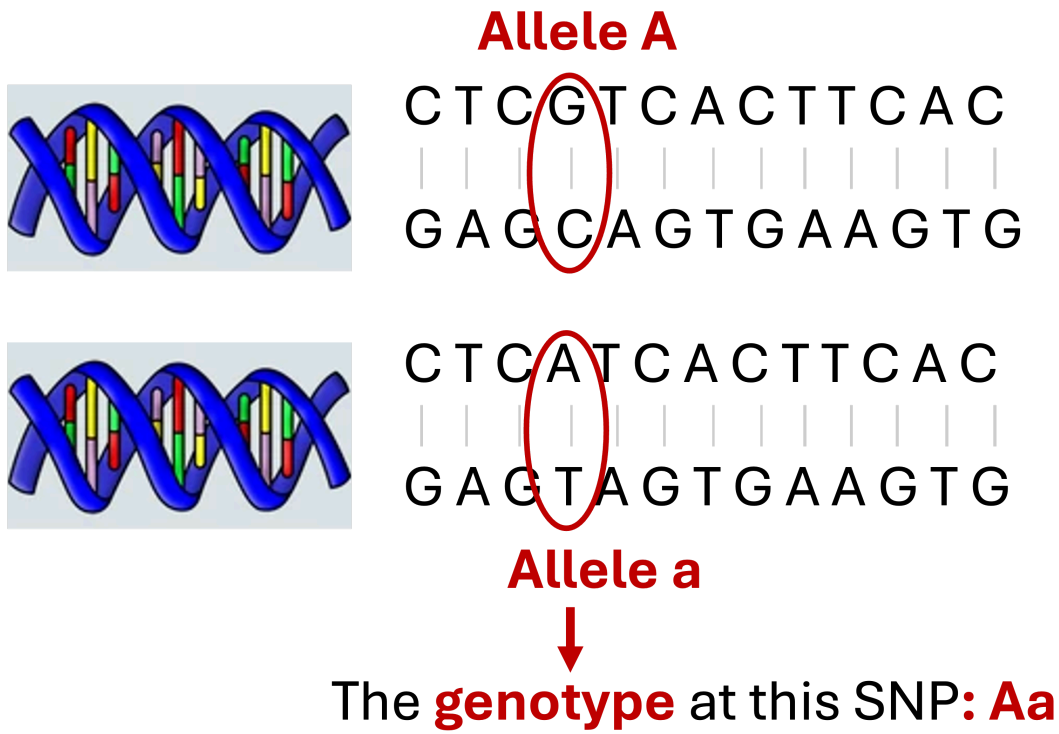
Alleles and Genotypes

Genotype: the two alleles at each chromosomal location (a pair of chormosome) 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).

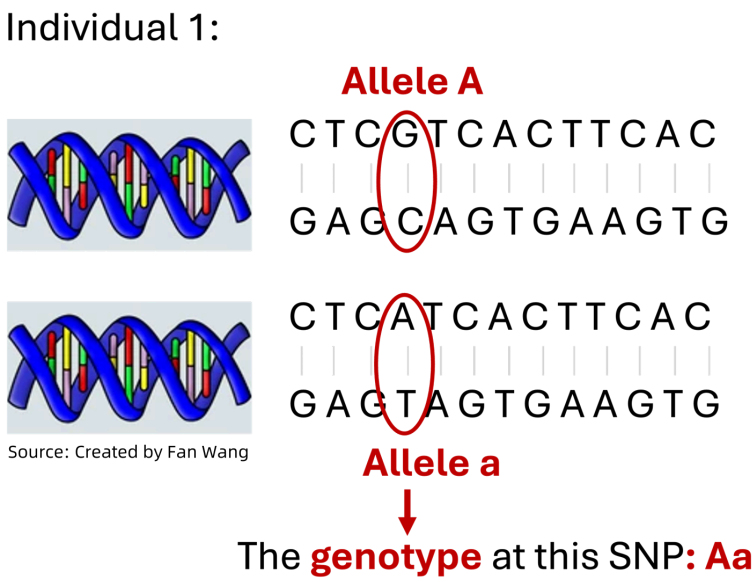
Individual 1:

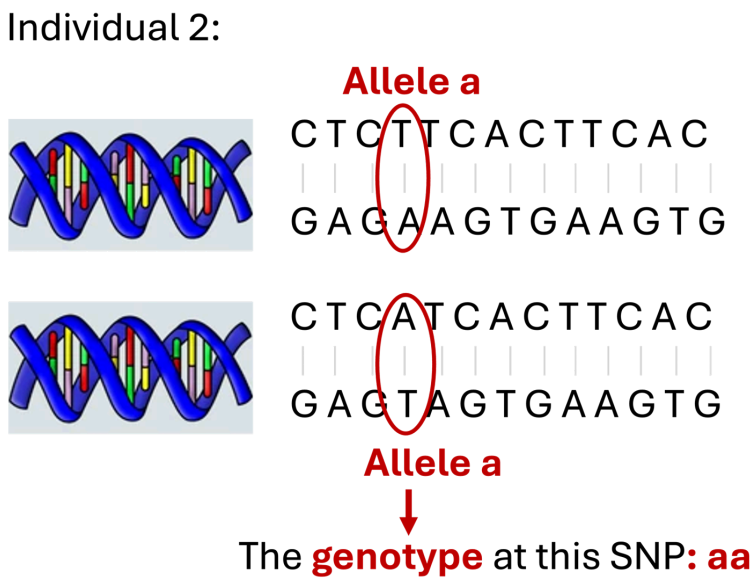


Source: Created by Fan Wang

Alleles and Genotypes

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

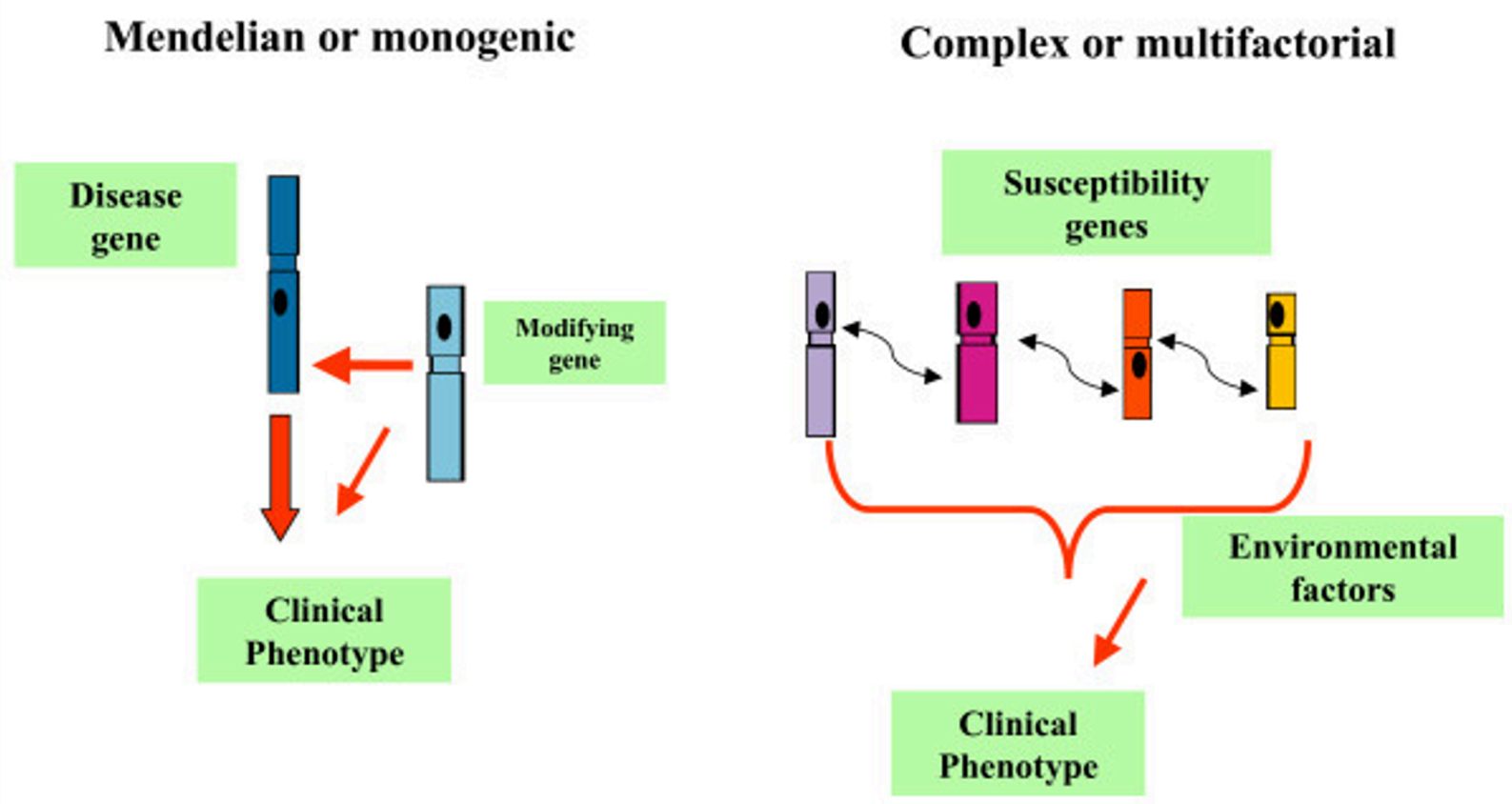




Recap

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

Mendelian vs. Complex diseases



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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 pentrance function in genetics)**.

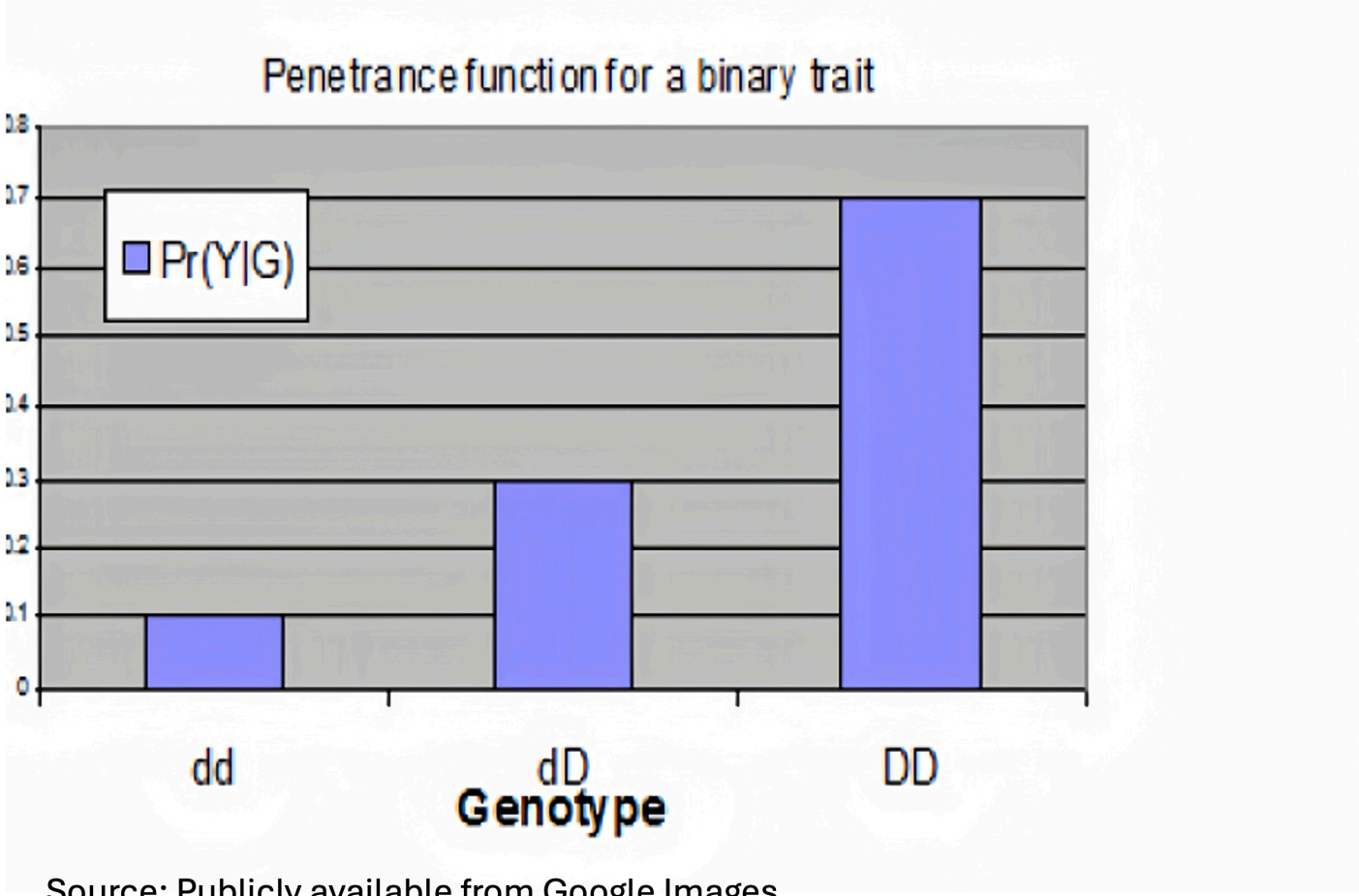
Simple disease models - Binary traits

- 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 **only hold rarely for simple Mendelian diseases**.
- More realistic are stochastic models with reduced penetrance and phenocopies.

Simple disease models - Binary traits

- Reduced penetrance: the probability is less than 1 above.
    - e.g. in the recessive model $\mathrm{P}(\mathrm{Y}=1 \mid \mathrm{DD})<1$.
- Phenocopy means probability $P(Y=1 \mid dd)>0$
    - 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.

Pentrance function for binary trait



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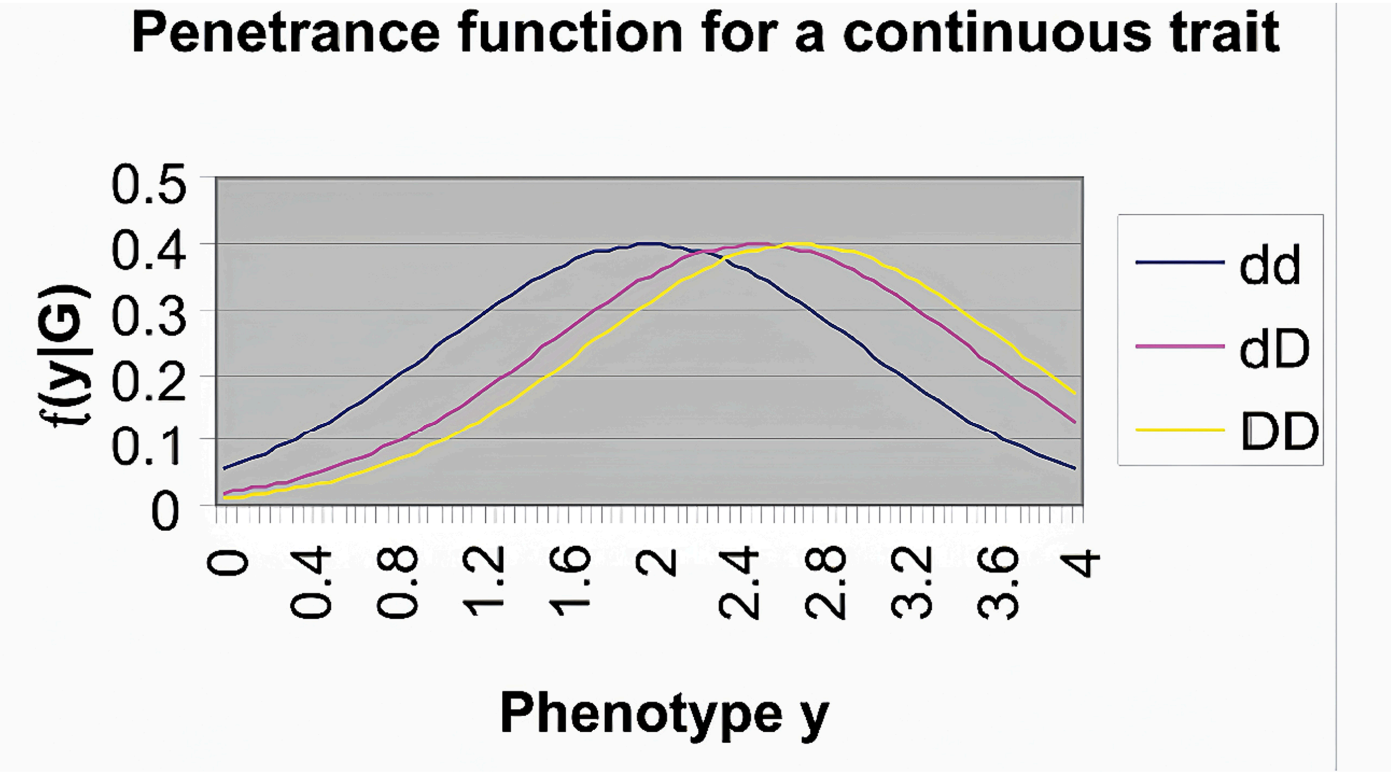
Quantitative traits

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

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

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

Pentrance function for a continuous trait



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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

Tutorial I : Navigating the genetic dataset

- The goal is to help beginners understand how genotype data is stored and accessed (in PLINK), and prepare them for downstream tasks like GWAS and QC.
- Introduces the structure, content, and usage of PLINK binary genotype datasets, using a toy dataset with 4,000 individuals and more than 300K SNPs in PLINK.

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?