Genetic Polymorphism

Introduction

Genetic polymorphism refers to the existence of multiple genetic forms within a population. It plays a central role in shaping **human biological diversity**, **disease susceptibility**, and **adaptive responses to environmental challenges**. As a dynamic feature of populations, polymorphism reflects the ongoing interaction between **evolutionary forces** and **human biology**. Anthropologists examine genetic polymorphism not just as a molecular phenomenon, but as a key to understanding **microevolution**, **population history**, and **adaptation to ecological and cultural environments**.

Understanding Genetic Polymorphism

Definition and Basic Characteristics

Genetic polymorphism is defined as the occurrence of two or more different alleles (alternative forms of a gene) at a specific **genetic locus**, each with a frequency of **at least 1%** in a given population. This distinguishes **polymorphism** from **rare mutations**, which occur sporadically and are often confined to individuals or small groups.

Key characteristics:

- It is **heritable** and **stable across generations**.
- It contributes to **phenotypic variation** in traits like skin color, metabolism, and immune response.
- It is often **maintained by natural selection, mutation, gene flow, or genetic drift**.

Molecular Forms of Genetic Polymorphism

Genetic polymorphism occurs at multiple levels of the genome, ranging from a **single DNA base** to **large structural variations**. These molecular forms of polymorphism provide the **raw material for evolution**, help us understand **population history**, and serve as critical tools in fields like **medical anthropology**, **population genetics**, and **forensic science**. Below are the major molecular forms of polymorphism, each with distinct characteristics and implications.

1. Single Nucleotide Polymorphisms (SNPs)

Definition and Mechanism

SNPs (pronounced "snips") are the **most common type** of genetic variation among humans. A **single nucleotide** (A, T, C, or G) in the genome is **altered** at a specific position and exists in **two or more forms** across individuals in a population.

For example:

- One person may have the sequence **AAGCCTA**, while another has **AAGCTTA**.
- The difference in a single base (C vs. T) is an **SNP**.

Key Features

- Occur approximately **once every 300 base pairs** in the human genome.
- Most are **bi-allelic** (have two variants).
- Generally **neutral**, but some affect gene regulation or protein structure.

Example

The **ALDH2** SNP variant common in **East Asian populations** leads to **alcohol flush reaction** and reduced alcohol metabolism, reflecting **genetic adaptation** and **cultural dietary patterns**.

2. Short Tandem Repeats (STRs) / Microsatellites

Definition and Mechanism

STRs (also called **microsatellites**) are sequences where a **short DNA motif (2–6 base pairs)** is **repeated multiple times** in tandem. The **number of repeats** varies significantly between individuals, making them **highly polymorphic**.

For example:

- At a given locus, one person may have $\mathbf{(CA)}_{10}$, while another may have $\mathbf{(CA)}_{15}$.

Key Features

- Found throughout the **non-coding regions** of the genome.
- High **mutation rate**, often due to replication slippage.
- Typically **multi-allelic**, making them highly informative for genetic studies.

Example

A study by the **University of Cambridge** used STRs to track **Y-chromosome diversity** in **Central Asian populations**, demonstrating descent from a **common male ancestor**, possibly **Genghis Khan**, reflecting **sociocultural dominance** influencing genetic structure.

3. Copy Number Variations (CNVs)

Definition and Mechanism

CNVs are structural variations in the genome where **sections of DNA (ranging from 1 kilobase to several megabases)** are **deleted, duplicated, or rearranged**. These variations can affect **gene dosage**, **expression levels**, and **phenotypic traits**.

Unlike SNPs and STRs, which are small-scale variations, CNVs represent **large-scale genetic changes** and are responsible for a **substantial amount of human genetic variation**.

Key Features

- Can involve **single genes or clusters** of genes.
- Often arise due to **unequal crossing-over** during meiosis or **replication errors**.
- May be **benign**, **adaptive**, or associated with **disease susceptibility**.

Example

The **AMY1 gene**, which encodes **salivary amylase**, exhibits CNV in relation to **dietary starch intake**. Populations with **high-starch diets** (e.g., **agricultural societies**) have more **copies of AMY1**, allowing better digestion of starch.

Summary of Molecular Polymorphisms in Anthropology

Type	Scale	Variation Type	Anthropological Use	Example
SNPs	Single base pair	Point mutation	Ancestry tracing, disease susceptibility	ALDH2 and alcohol intolerance
STRs	2–6 base pairs repeated	Tandem repeats	Forensics, kinship analysis	Y-STRs in Central Asian lineages

CNVs	1 kb to megabases	Deletions/duplications	Adaptation, phenotypic diversity	AMY1 copy number and starch diet

Mechanisms Behind Genetic Polymorphism

1. Role of Mutation and Inheritance

Mutation as the Source of Polymorphism

- **Mutation** is the **primary source of genetic variation**. It refers to random, heritable changes in the **DNA sequence**, such as:
  - **Point mutations** (e.g., SNPs),
  - **Insertions/deletions**,
  - **Chromosomal rearrangements**.
- When mutations occur in **germ cells**, they can be passed on to offspring, potentially becoming **established as polymorphisms**.

Establishment in the Gene Pool

- A new mutation may:
  - Be **neutral** (having no effect on fitness),
  - Be **beneficial** (increasing survival or reproduction),
  - Be **deleterious** (and removed by natural selection).
- If not strongly selected against, the allele may **persist through inheritance**, and over generations, become a stable **polymorphism** in the population.

Ancient vs. Recent Polymorphisms

- Some polymorphisms are **ancient**, predating the **divergence of human populations**. For example:
  - The **ABO blood group system** is shared among humans and other primates, indicating **deep evolutionary roots**.
- Others are **recent** and reflect **localized adaptation**:
  - For instance, the **sickle cell allele** (HbS) emerged in Africa and the Mediterranean and became common due to **malaria selection pressure**.

2. Why Polymorphisms Persist: Evolutionary Mechanisms

A. Heterozygote Advantage (Overdominance)

- **Definition**: This occurs when individuals who carry **two different alleles** (heterozygotes) at a locus have **higher fitness** than those with two copies of the same allele (homozygotes).
- **Example**: The classic case is **sickle cell trait**:
  - **Homozygous normal (HbA/HbA)**: Susceptible to malaria.
  - **Homozygous sickle cell (HbS/HbS)**: Develops sickle cell anemia.
  - **Heterozygous (HbA/HbS)**: **Resistant to malaria** with **milder health effects**.
- This balancing selection maintains **both alleles** in the population despite the harmful effects of the homozygous recessive condition.

B. Frequency-Dependent Selection

- **Definition:** The fitness of a genotype or phenotype depends on its **frequency relative to others** in the population.
- **Negative frequency-dependent selection** favors **rare alleles**, which increase in frequency until they become common, at which point their advantage may decline.
- **Example**: In host-pathogen dynamics, **rare immune gene variants** (e.g., HLA alleles) may evade common pathogens more effectively, maintaining **genetic diversity in immunity**.

C. Environmental Heterogeneity (Spatial and Temporal Variation)

- **Definition**: Different environments or ecological niches may favor different alleles, allowing **multiple variants to coexist**.
- **Local adaptation** occurs when certain alleles are advantageous only in **specific environmental contexts**.
- **Example**:
  - **Skin pigmentation genes** (like **MC1R**) vary with **UV radiation** exposure.
  - Darker skin is favored in **high-UV regions** (tropics) for **protection against folate degradation**, while lighter skin evolved in **low-UV regions** (Europe) for **vitamin D synthesis**.

D. Gene Flow and Admixture

- **Definition**: **Gene flow** is the movement of alleles between populations through **interbreeding.** It introduces **new alleles** and prevents **genetic isolation**, contributing to **polymorphism maintenance**.
- **Admixture** creates **genetic mosaics**, particularly visible in **diasporic** or **colonial** populations.
- **Example**:
  - The **B allele** in the **ABO system** was historically **absent** in Native American groups but introduced through **European and Asian admixture**, creating a **transient polymorphism**.

Summary Table: Mechanisms

Mechanism	Key Concept	Anthropological Example
Mutation and Inheritance	New alleles introduced and passed on	Sickle cell mutation (HbS), ALDH2 variant
Heterozygote Advantage	Heterozygotes have higher fitness	HbA/HbS genotype and malaria resistance
Frequency-Dependent Selection	Fitness changes with allele frequency	HLA gene variation and pathogen evasion
Environmental Heterogeneity	Local adaptation maintains variation	Skin color alleles and UV exposure
Gene Flow/Admixture	Introduction of alleles from other populations	ABO blood group variation in admixed groups

Types of Genetic Polymorphism

Balanced Polymorphism

Balanced polymorphism refers to a genetic situation in which **two or more alleles** are maintained **at stable frequencies** in a population's gene pool because each confers some **evolutionary advantage**, especially when present together in **heterozygous form**.

Unlike mutations that are either eliminated or fixed, **balanced polymorphisms persist over many generations**, often due to **natural selection** favoring **genetic diversity**.

Mechanisms Behind Balanced Polymorphism

1. Heterozygote Advantage (Overdominance): This is the **most common mechanism** in balanced polymorphism. It occurs when **heterozygous individuals (Aa)** have **higher biological fitness** than either of the **homozygotes (AA or aa)**. In such cases, natural selection maintains **both alleles** in the population because the heterozygote's **survival or reproductive success** is superior.

2. Frequency-Dependent Selection: Sometimes, the fitness of an allele depends on how **common or rare** it is. For example, a rare allele might offer resistance to a disease that affects those with the more common variant, thereby ensuring its persistence.

3. Environmental Variation: In **ecologically diverse environments**, different alleles might offer **advantages in different niches** or geographic areas. This allows for **spatially balanced polymorphism** maintained through **localized selective pressures**.

Example: Sickle Cell Trait and Malaria Resistance

Genetic Basis and Distribution

The **sickle cell trait** is a textbook example of **balanced polymorphism maintained by heterozygote advantage**. It involves two alleles of the **beta-globin gene** on chromosome 11:

- **HbA (Normal allele):** Produces normal adult hemoglobin.
- **HbS (Mutant allele):** A point mutation replaces **glutamic acid with valine** at position 6 of the beta-globin chain, causing hemoglobin to polymerize under low oxygen, distorting red blood cells into a sickle shape.

This polymorphism is commonly found in regions **endemic to malaria**, particularly:

- **Sub-Saharan Africa**
- **Middle East**
- **India (e.g., Orissa, Madhya Pradesh, Chhattisgarh)**
- **Parts of the Mediterranean**

Genotype-Phenotype Relationships

- **HbAA (Homozygous normal):** Normal red blood cells; susceptible to **Plasmodium falciparum** malaria.
- **HbSS (Homozygous sickle):** Develops **sickle cell anemia**, a severe and often fatal disease marked by **chronic anemia, pain, and organ damage**. Life expectancy is significantly reduced without modern medical care.
- **HbAS (Heterozygous):** Usually healthy, with **mild or no symptoms**, and **significant resistance to malaria**. The malarial parasite struggles to complete its life cycle in the **mildly sickled red blood cells**, giving HbAS individuals a **survival advantage** in malarial zones.

Example 2: G6PD Deficiency and Malaria Resistance

Genetic Background

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme involved in the **pentose phosphate pathway**, which protects red blood cells from **oxidative damage**. The **G6PD gene**, located on the **X chromosome**, exhibits polymorphic forms, some of which result in **enzyme deficiency**.

- G6PD deficiency is **X-linked**; therefore, **males (XY)** are more affected than **females (XX)**.
- Deficiency variants are especially prevalent in:
  - **Mediterranean countries**
  - **Africa**
  - **Middle East**
  - **South and Southeast Asia**

Clinical and Selective Effects

- Individuals with G6PD deficiency are **prone to hemolytic anemia** after consuming certain foods (like fava beans) or drugs (such as antimalarials or sulfa drugs).
- However, **G6PD-deficient red blood cells provide an inhospitable environment** for the **malaria parasite**, which relies on normal metabolic activity for survival.

Mechanism: Selection by Disease Pressure

Similar to the sickle cell example, **G6PD-deficient individuals are more resistant to malaria**, particularly **Plasmodium falciparum**. As a result:

- In **malarial zones**, even though G6PD deficiency can cause health problems, the **anti-malarial benefit** leads to **positive selection**.
- This results in **multiple G6PD-deficient alleles** being maintained in diverse populations—a case of **balanced polymorphism** driven by **pathogen pressure**.

Transient Polymorphism

Transient polymorphism refers to a **temporary state** in which **two or more alleles** exist within a population for a **limited time** before one becomes **dominant (fixed)** or is **eliminated** due to **natural selection**, **genetic drift**, or **demographic changes**.

Unlike **balanced polymorphism**, where multiple alleles are maintained by evolutionary forces such as heterozygote advantage, transient polymorphisms represent **shifting genetic states** during periods of **evolutionary change**.

Mechanism of Transient Polymorphism

The occurrence and eventual resolution of transient polymorphism are shaped by several interrelated mechanisms:

1. Introduction of a New Allele

A **new allele** may be introduced into a population through:

- **Mutation** (a novel genetic change arising within the population).
- **Gene flow** (migration or admixture from another population carrying a different allele).

This initial introduction creates a **polymorphic state**, where **more than one allele** is present at a genetic locus.

2. Selective Pressure or Neutral Drift

- If the **new allele** confers a **selective advantage** (e.g., resistance to a disease or environmental stress), it may **increase in frequency**.
- If it is **neutral**, its fate depends on **genetic drift**—random fluctuations in allele frequencies, particularly in **small populations**.

3. Resolution Through Fixation or Elimination

Over time, depending on environmental and demographic factors:

- The new allele may **reach fixation** (100% frequency), replacing the older allele.
- Or it may be **lost**, if it proves disadvantageous or if random drift eliminates it.

This temporary coexistence of alleles followed by **genetic resolution** defines the **transient nature** of this form of polymorphism.

Example: Blood Group B in Native American Populations

The **ABO blood group system**, controlled by a gene on **chromosome 9**, is one of the most studied polymorphic systems in human populations. It includes three alleles:

- **A** and **B**, both codominant.
- **O**, a recessive allele.

Prior to European colonization, **Native American populations** had an **extremely high frequency of the O allele**, with **near absence of the B allele**. The dominance of the O group has been attributed to:

- **Founder effects** during early migrations.
- **Isolation** due to geographical barriers.
- **Genetic drift** in small ancestral populations.

Post-Colonial Gene Flow and Transient Polymorphism

Following **European colonization** and later **Asian migration** into the Americas:

- The **B allele was introduced** into Native populations via **admixture**.
- This led to a temporary rise in **genetic diversity**, with a mixture of **A, B, and O alleles** now present.
- The population entered a phase of **transient polymorphism**.

Comparison Chart

Feature	Balanced Polymorphism	Transient Polymorphism
Allele Coexistence	Long-term coexistence	Temporary coexistence

Maintaining Force	Natural selection favoring heterozygotes or diversity	Selection, drift, or gene flow
Outcome	Stable equilibrium	Fixation or loss of one allele
Examples	Sickle cell trait, G6PD deficiency	Blood group B introgression, Insecticide resistance
Anthropological Importance	Reveals adaptation to pathogens and environments	Tracks gene flow, historical contact, human intervention