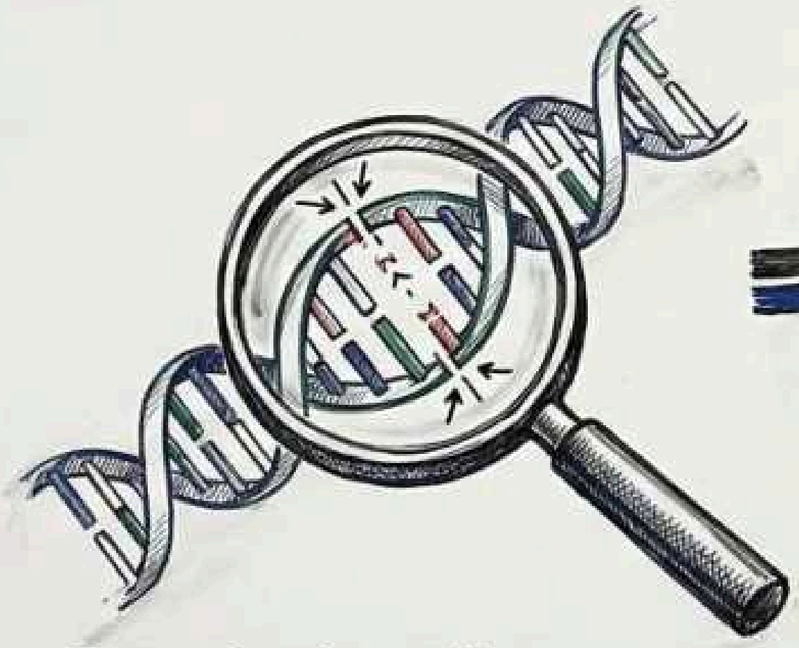
¶ 6.1

Our journey scales from single gene edits to entire population dynamics.

Part 1: Gene Editing



- How scientists edit genes
- Medical and ethical implications

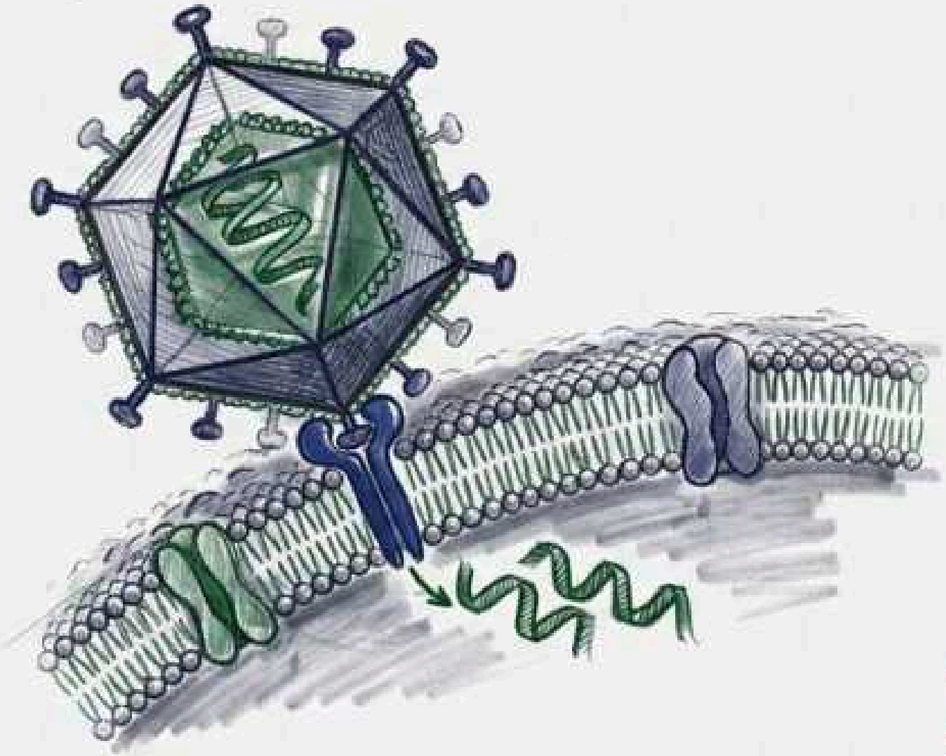
Part 2: Population Genetics



- How genes behave over time
- The foundation of evolutionary biology

The long prehistory of genetic intervention was defined by slow progress and profound setbacks.

¶ 6.2



Severely shook the field, demanding decades of careful work to rebuild safe therapies.

1990

First approved trial for a rare immune disorder using viral carriers (gene therapy).

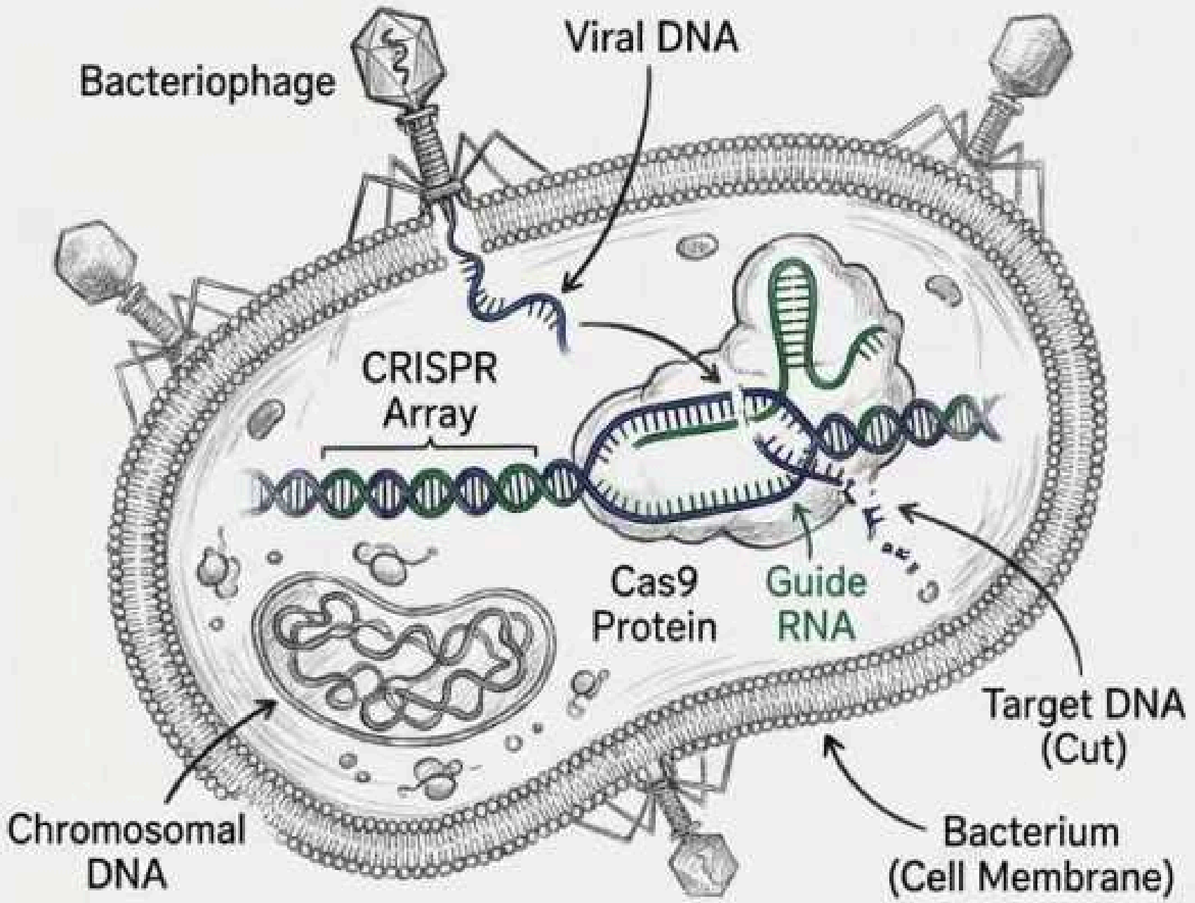
1999

Tragic death of Jesse Gelsinger in a clinical trial.

The great breakthrough repurposed an ancient bacterial immune defense system.

¶ 6.3

CRISPR: The Bacterial Immune Defense



2012 Jennifer Doudna & Emmanuelle Charpentier discover Cas9 protein can be directed by guide RNA to cut specific DNA

Next step Feng Zhang & George Church prove the mechanism works in human cells

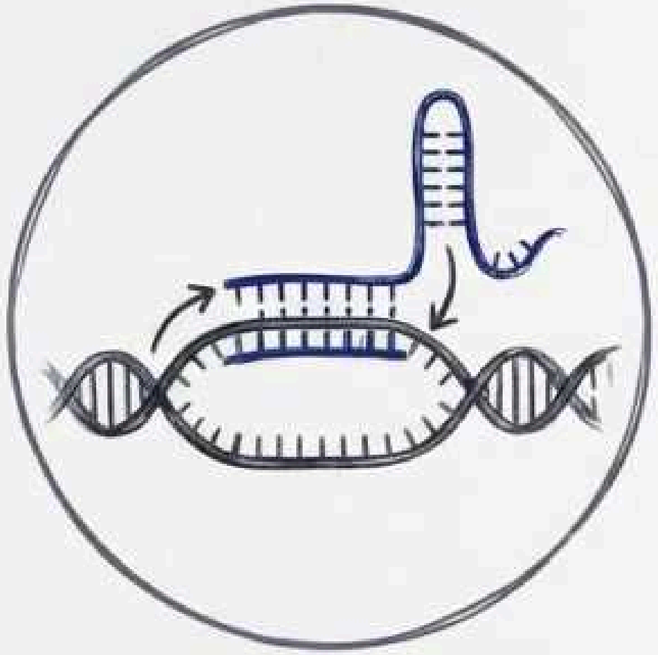


2020 Nobel Prize in Chemistry

¶ 6.4

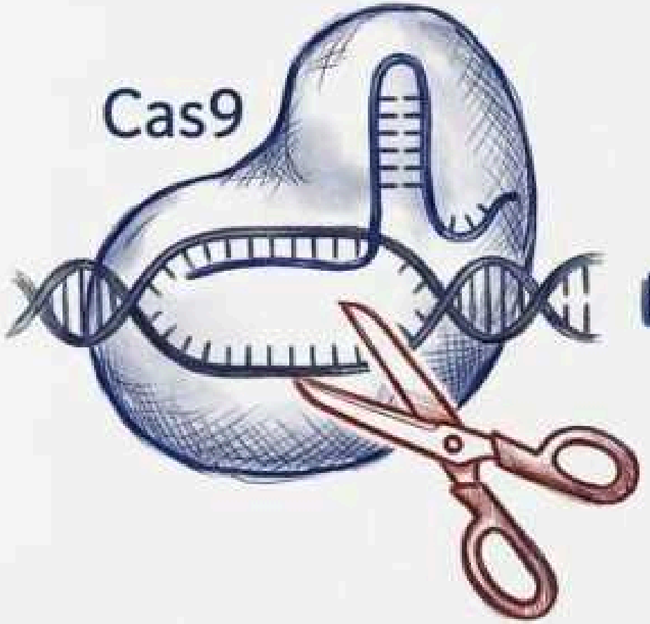
The mechanism relies on targeted cutting followed by cellular repair.

1. Targeting



Guide RNA matches a target sequence.

2. Cutting



Cas9 protein cuts both strands.

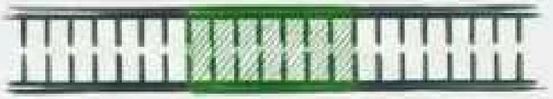
3. Repairing

A. Disabled



Careless repair. DNA ends joined haphazardly, disabling the gene.

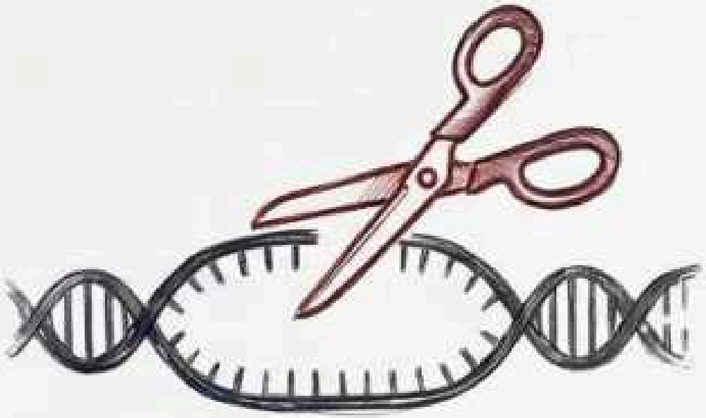
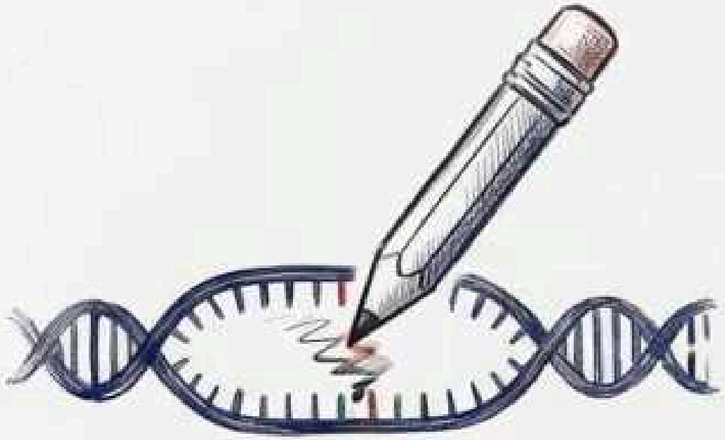
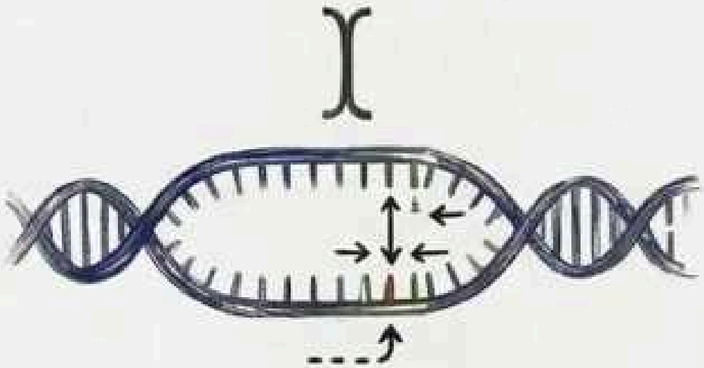
B. Edited



Template copy. Cell uses a supplied template to introduce a precise, chosen change.

¶6.5

Newer editing tools refine the original mechanism to minimize unwanted cellular damage.

Standard CRISPR	Base Editors (Liu et al.)	Prime Editors
		
Cuts both DNA strands.	Changes a single DNA letter without double-strand cuts.	Makes precise small insertions and deletions.

The Off-Target Threat. Editors acting at the wrong location remain a major concern requiring rigorous testing for every therapy.

CRISPR is already functioning as an effective but demanding modern medicine.

¶ 6.6

Extraction.

Blood stem cells are removed from the patient.

Editing.

Cells are edited to switch on fetal hemoglobin production.

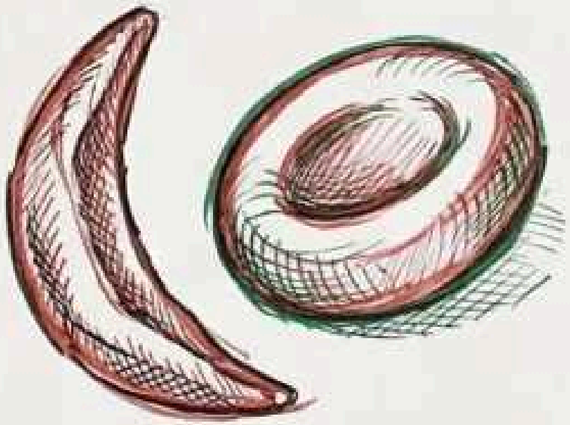
Return.

The edited cells are infused back into the patient.

Effect.

Treatment effectively cures the condition, though it remains highly costly and physically demanding.

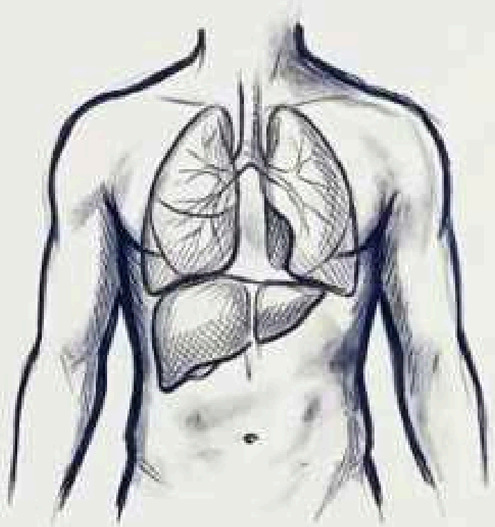
Casgevy:
First CRISPR therapy approved in UK & US (Late 2023) for sickle cell and related blood disorders.



A deep biological and ethical distinction separates somatic from germline editing.

¶ 6.7

Somatic Editing

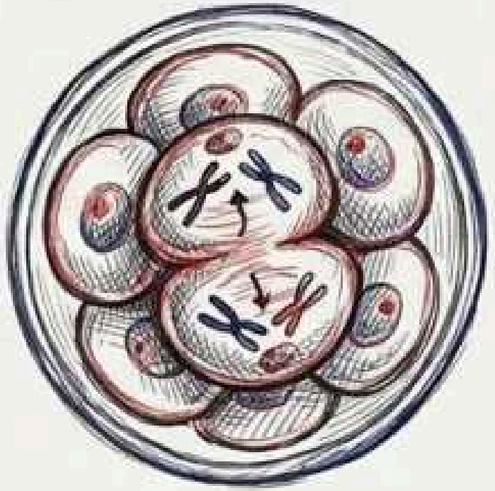


Changes cells in one patient's body.
Not passed to children.



Widely accepted by scientific bodies and countries.

Germline Editing



Changes eggs, sperm, or embryos.
Inherited by all future generations.



Demands extreme caution.

The ethical boundary was violently tested by unauthorized human germline editing.

Event (2018): He Jiankui (researcher in China) announced the birth of twin girls from embryos he edited to confer HIV resistance.

Backlash:
- Condemned as scientifically unsafe.
- Deemed medically unnecessary.
- Ruled ethically unjustified.

Consequence:



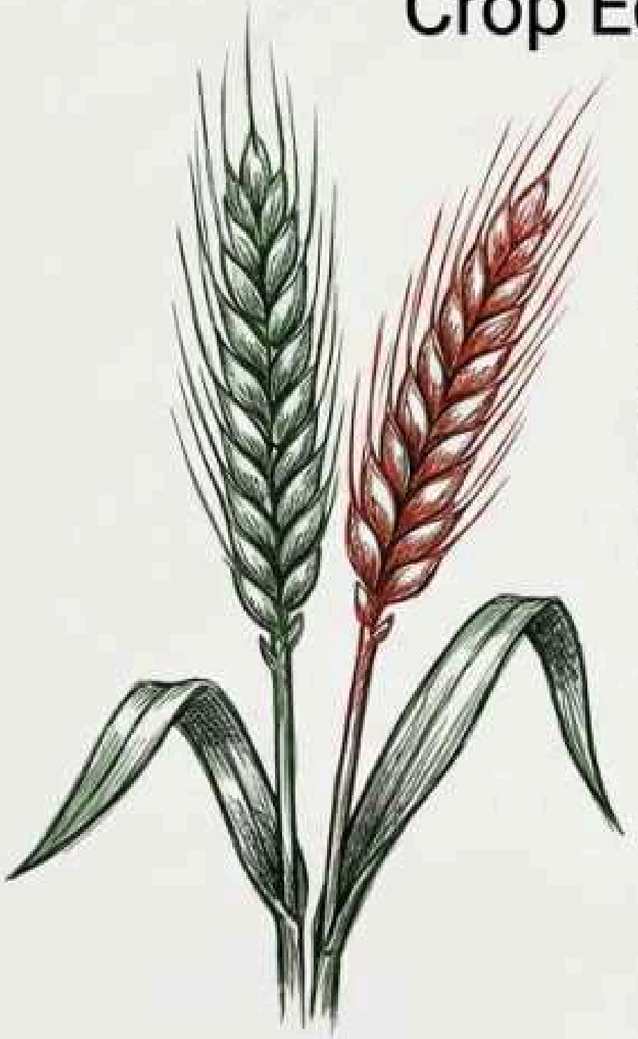
Three-year prison sentence from a Chinese court.

Aftermath: Triggered massive demands for stronger international oversight.

Editing tools are now reshaping agriculture and wild ecological systems.

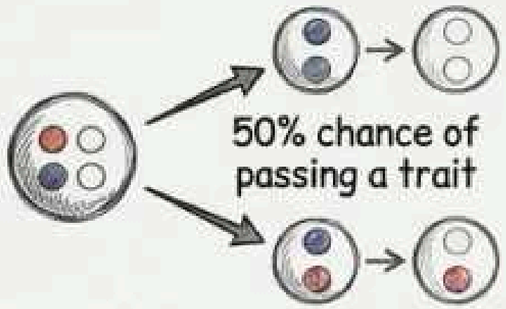
¶ 6.9

Crop Editing

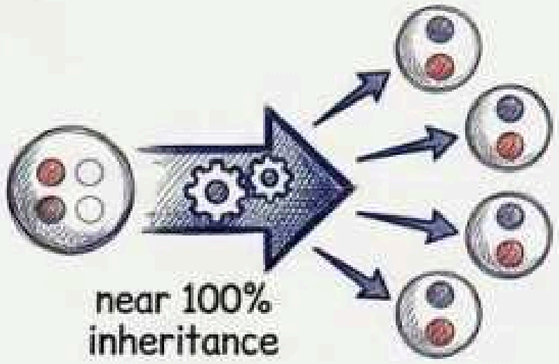


Editing crops produces varieties with disease resistance and longer shelf lives.

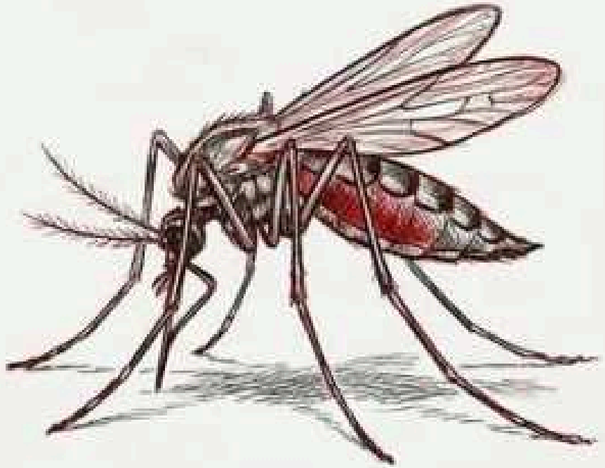
Gene Drives



Standard Inheritance



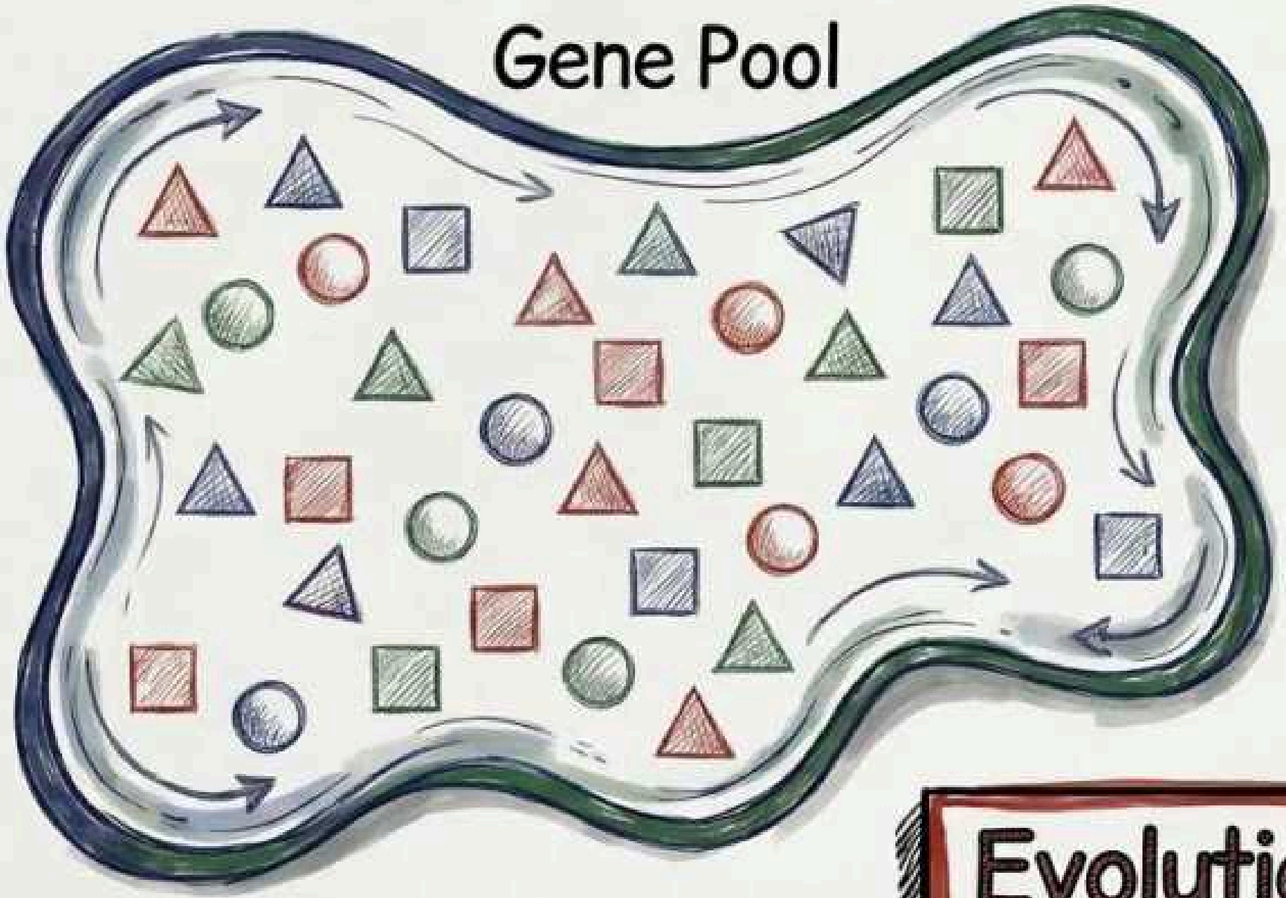
Gene Drive



Gene drives to suppress mosquitoes raise profound questions about releasing engineered elements into wild nature.

Population genetics tracks how alleles behave across entirely interconnected groups.

¶ 6.10



Population: A group of interbreeding individuals.

Gene Pool: The complete set of all alleles in that population.

- **Allele Frequencies**: The
  - proportion of each allele among all copies of a gene.

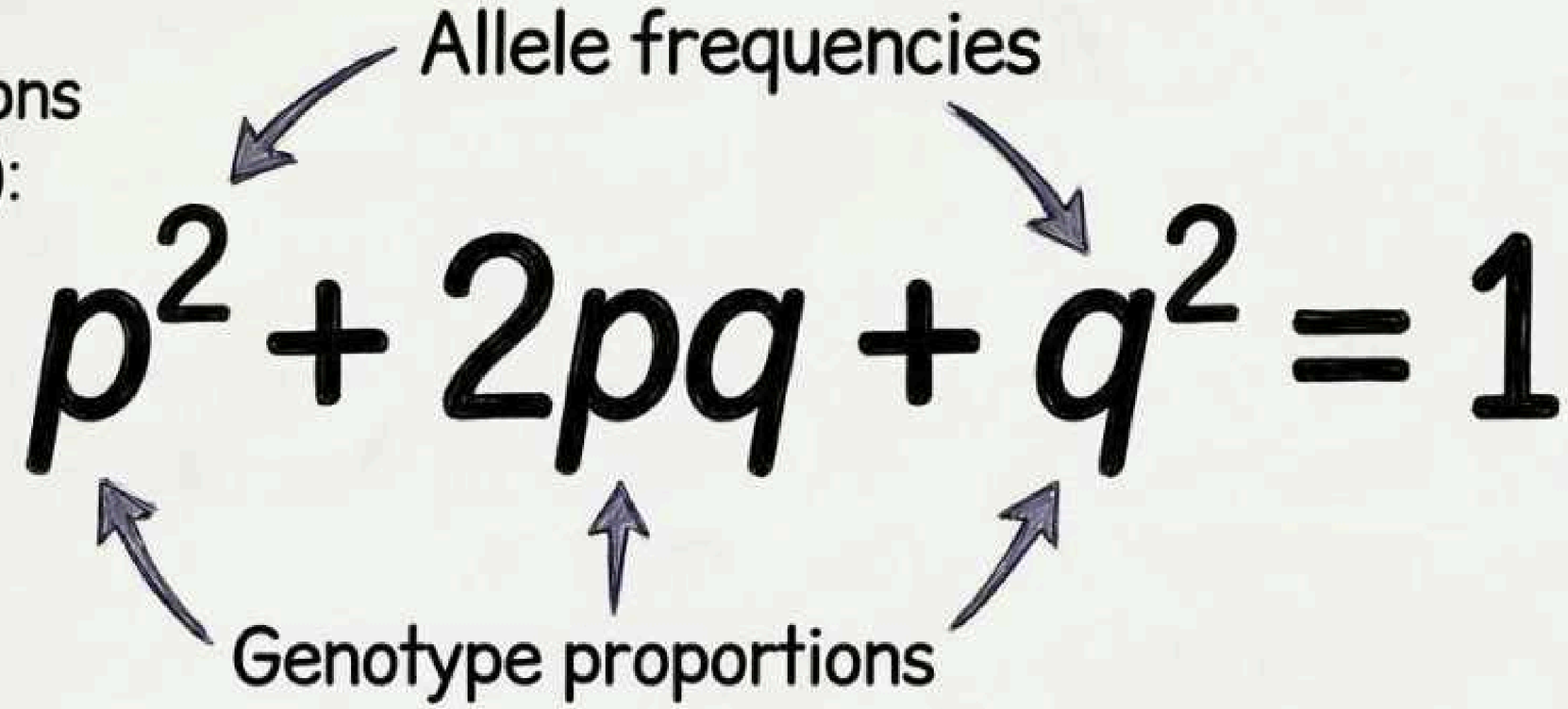
Evolution = A change in allele frequencies across generations.

The Hardy-Weinberg principle establishes the mathematical baseline of a stable population.

¶ 6.11

The 5 Baseline Conditions (Constant Frequencies):

- Large population
- Random mating
- No mutation
- No migration
- No selection



Discovered independently (1908) by G.H. Hardy (mathematician) and Wilhelm Weinberg (physician).

Calculating carrier frequencies reveals where rare recessive alleles hide.

Problem: A recessive disease affects 1 in 10,000 babies.

Step 1: $q^2 = \frac{1}{10{,}000}$ (Disease frequency)

Step 2: $q = \frac{1}{100}$ (Recessive allele frequency)

Step 3: $p = \frac{99}{100}$ (Dominant allele frequency)

Step 4: $2pq \approx \frac{1}{50}$ (Carrier frequency)

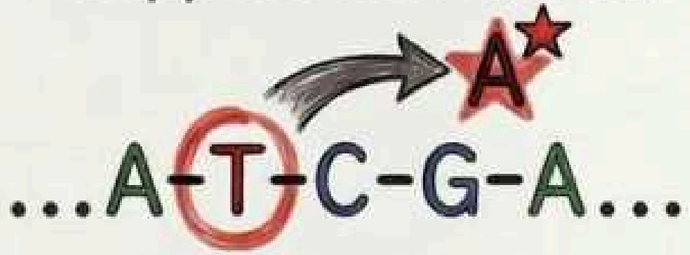
Insight: Most copies of a rare recessive allele are safely hidden inside healthy carriers.

Real populations depart from the baseline through four distinct evolutionary forces.

¶ 6.13

Mutation

Supplies new alleles.



Natural Selection

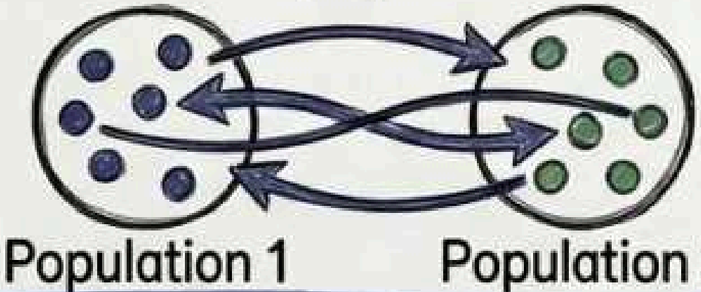
Favors alleles that raise survival and reproduction.



Departures from Hardy-Weinberg

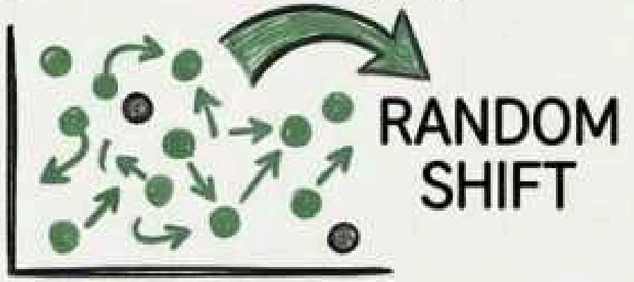
Gene Flow

Movement of alleles through migration makes populations more alike.



Genetic Drift

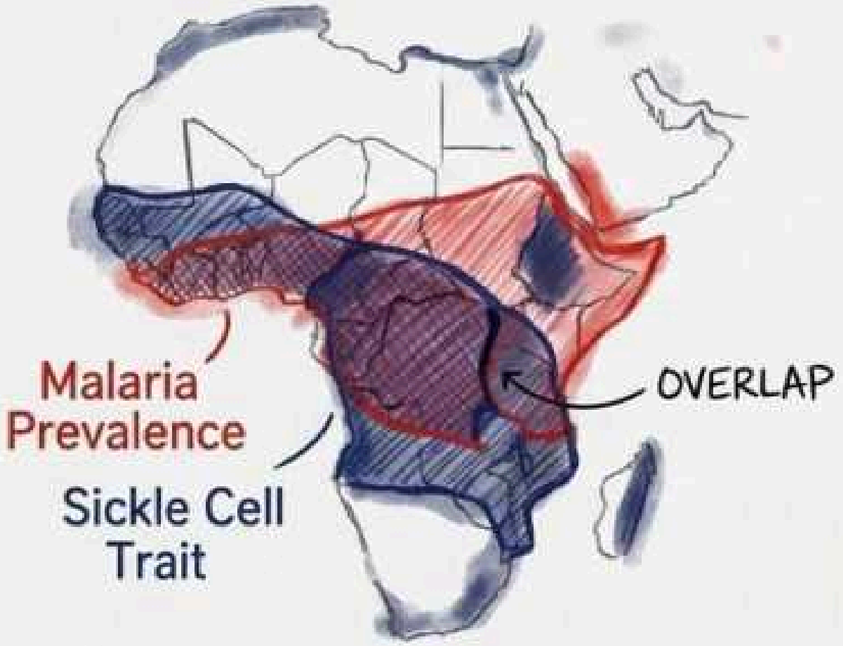
Random change in frequencies, strongest in small populations.



Natural selection adapts populations through specific environmental pressures.

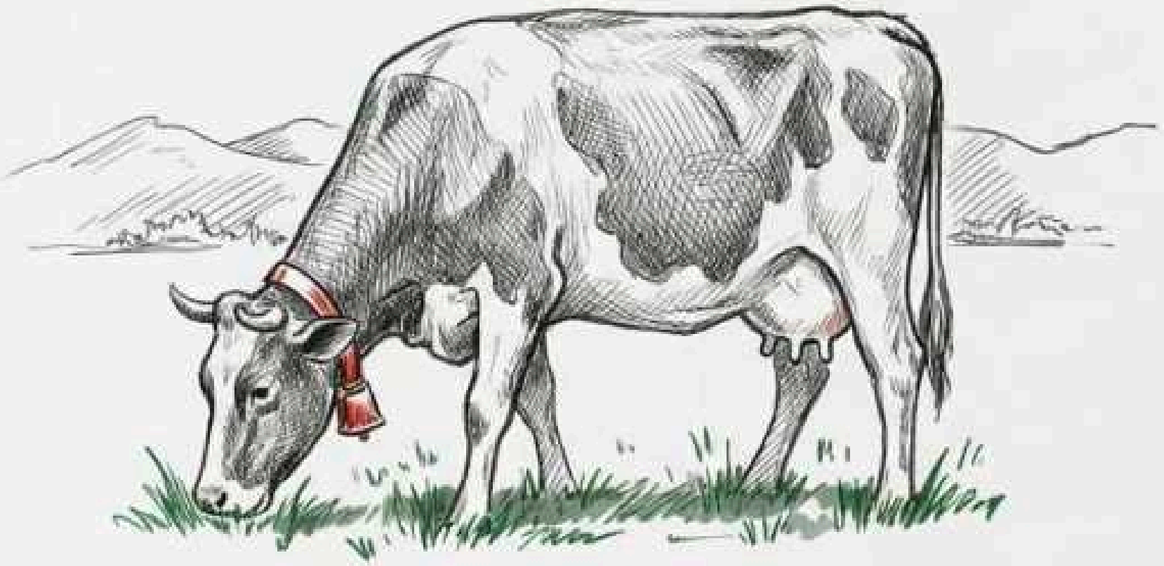
¶ 6.14

Balancing Selection: Sickle Cell



Carriers are protected from severe malaria, while two copies cause disease. The allele remains common precisely where malaria is widespread.

Directional Selection: Lactase Persistence



The ability for adults to digest milk spread rapidly and specifically among historical dairy-herding peoples.

Genetic drift drives random, drastic changes when populations shrink.

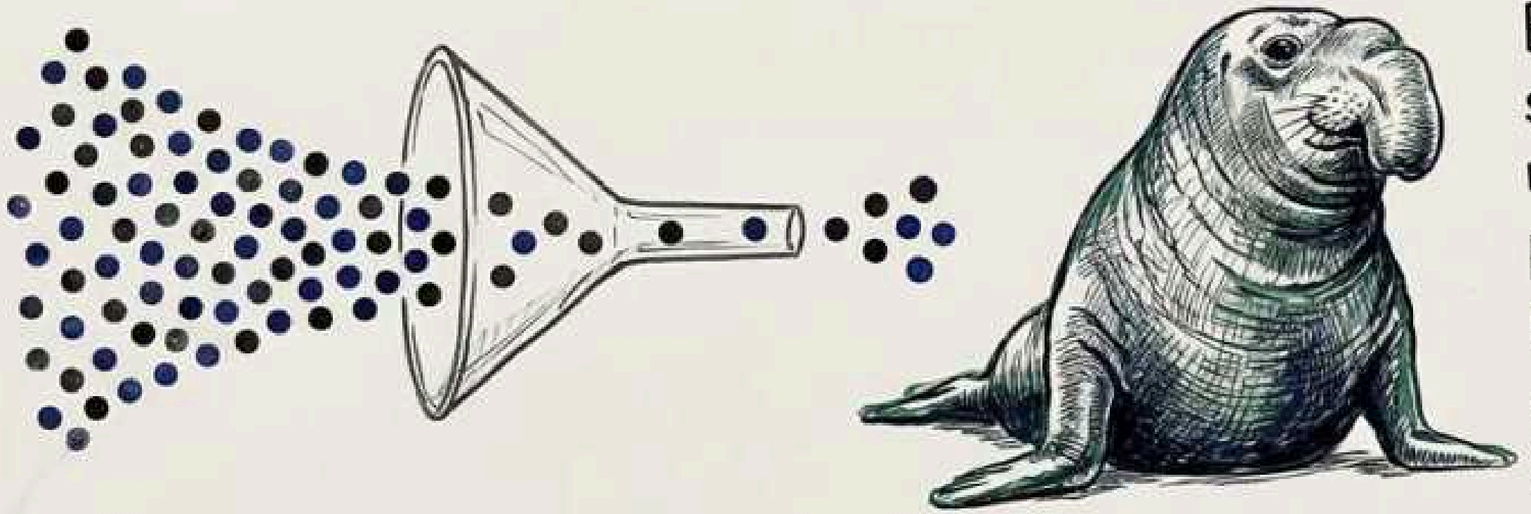
¶ 6.15

The Founder Effect



Founder Effect: A few individuals start a new population with only a sample of original alleles.

The Bottleneck Effect

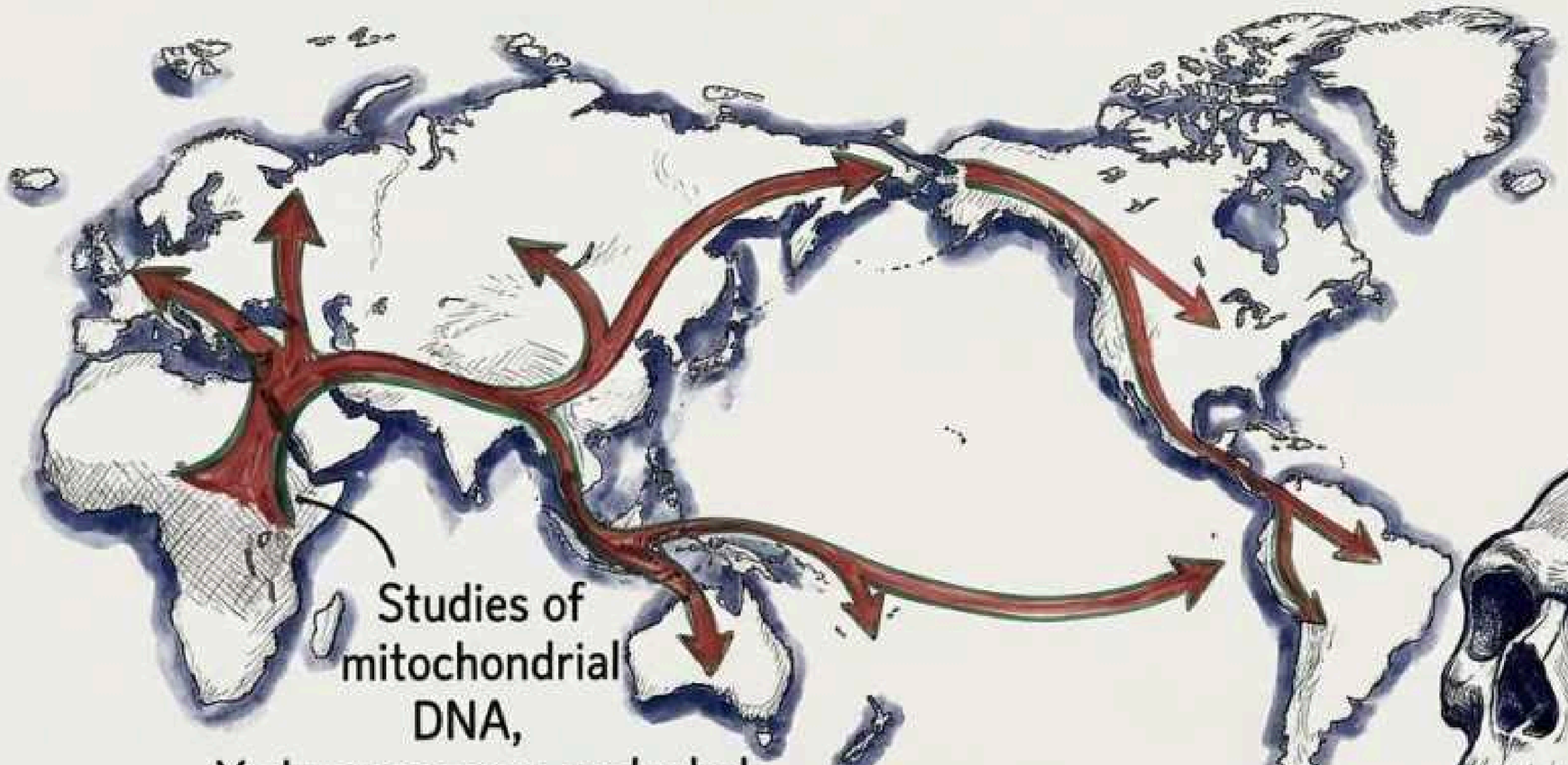


Bottleneck Effect: Population shrinks sharply, recovering with reduced variation.

Example: Northern elephant seals hunted to ~20 animals in the 1890s now number in the tens of thousands, but show strikingly little genetic diversity.

¶ 6.16

Genomic data reconstructs the deep history and migration of modern humans.



Studies of mitochondrial DNA, Y chromosomes, and whole genomes prove an Out-of-Africa origin.

African populations hold the highest global genetic diversity.

Ancient DNA

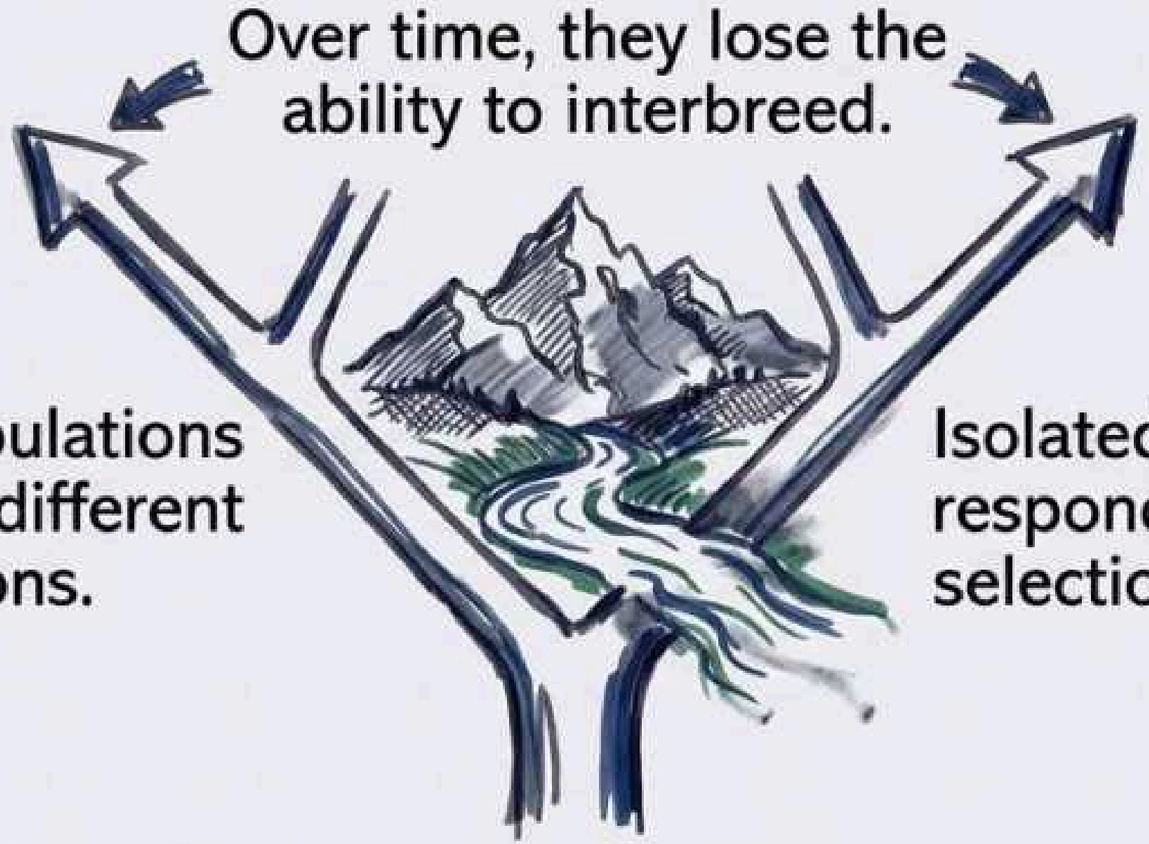
Pioneered by Svante Pääbo (2022 Nobel Prize).



Ancient DNA proved many modern people carry a few percent of Neanderthal ancestry.

Accumulated genetic isolation ultimately fractures populations into distinct species.

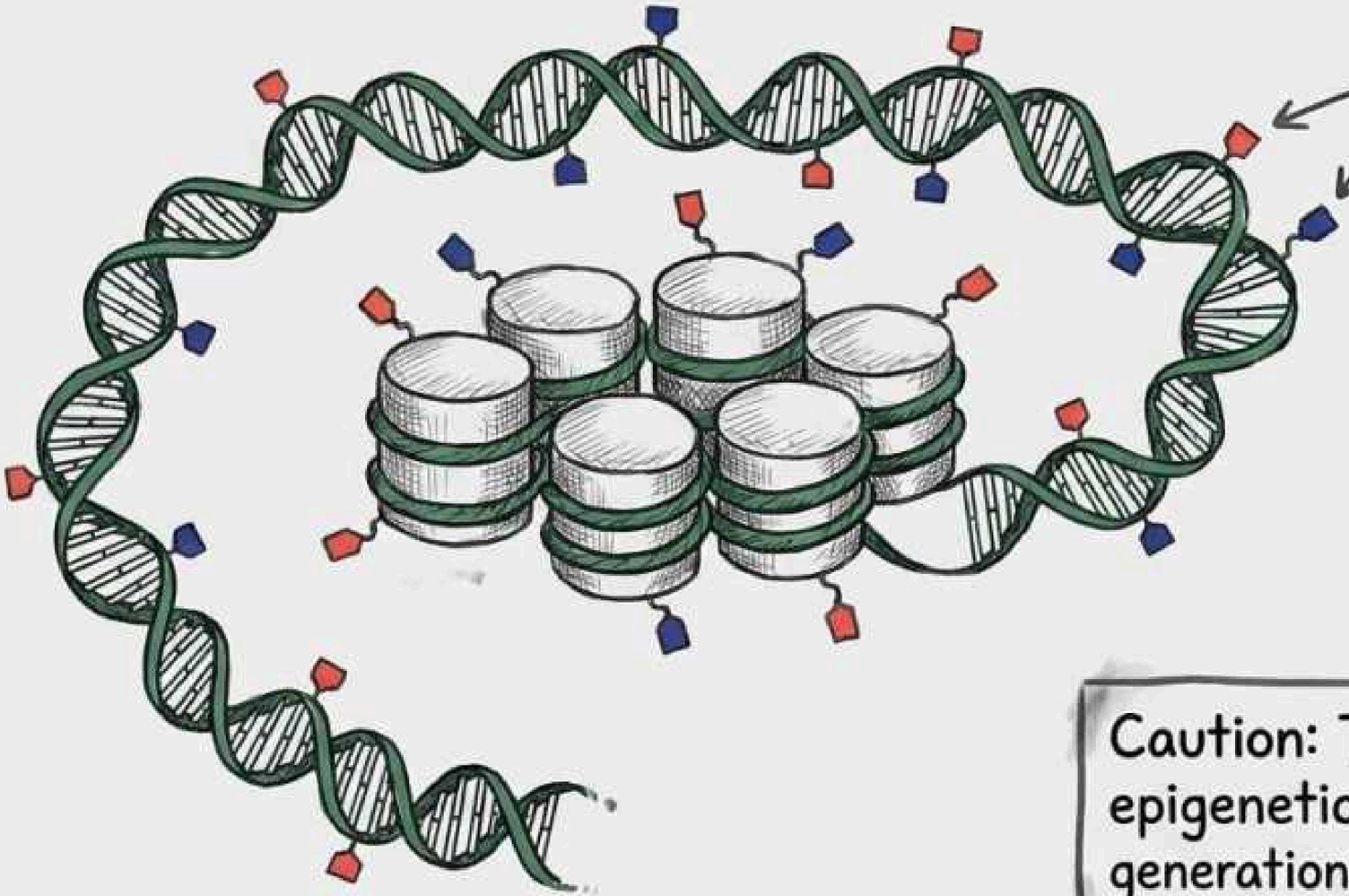
¶ 6.17



This mechanism supplies the strongest evidence for the universal tree of life.

Epigenetics reveals how chemical marks control genes without altering the underlying code.

¶ 6.18



Chemical marks
(ON/OFF switches)

This mechanism explains how cells with identical genomes can develop into entirely different tissues.

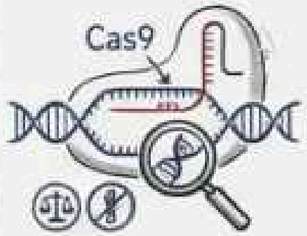
Caution: The extent to which these epigenetic marks are passed across generations in humans remains hotly debated. Claims should be treated with care.

Together, heredity and evolution explain how life persists and changes.

¶ 6.19

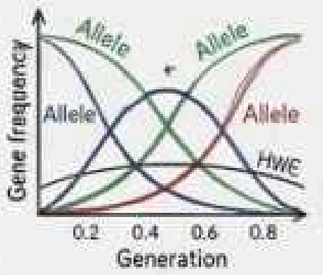
The mechanics of the single gene drive the evolution of the entire population.

Gene Editing (CRISPR)



- Precise alterations.
- Emerging disease cures balanced against sharp smarp ethical lines around germline changes.

Population Genetics



- Alleles shift via mutation, selection, drift, and flow, moving away from the steady Hardy-Weinberg baseline.

¶ 6.20

Final Assessment: Apply the mechanics of editing and the math of populations.

1. A recessive condition affects 1 in 4,000 people. Using Hardy-Weinberg, how would you estimate the carrier frequency?

2. Why is it mathematically and biologically difficult for natural selection to completely remove a rare recessive allele from a population?

3. Why does the scientific community treat germline editing with drastically different oversight than somatic therapy?

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