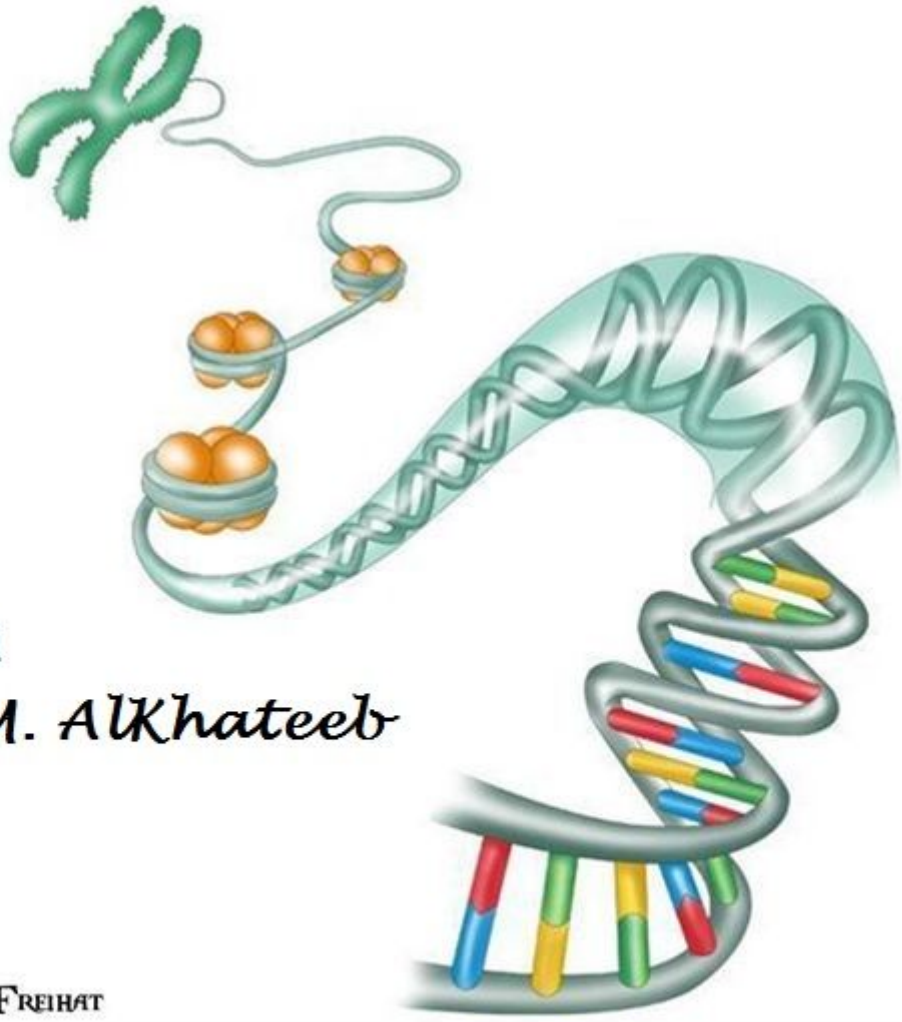
University of Jordan
Faculty of Medicine
Batch 2013-2019

Medical Committee
The University of Jordan

# Genetics & Molecular Biology

● Slides ○ Sheet ○ Handout ○ other.....



Lecture: 1

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Designed by Nadeen Al-Freihat

# Medical Genetics

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MG - Lec. 1

11th Feb 2015

# OBJECTIVE S OF THE COURSE

- Understanding of Basic genetics
- Be able to draw, and understand, a family tree
- Have awareness of when you should be considering a genetic condition
- Have a working knowledge of the most important genetic conditions
- Know how & when to refer to local specialist genetics services

# What's a ___?

- **Genetics** : Is the branch of biology that deals with heredity and variation in all living organisms
- **The subfields of genetics :**
  - Human genetics,
  - Animal genetics,
  - Plant genetics
  - Medical genetics

# What's a Medical Genetics?

- **Is the science or study of biological variation as it pertains to health and disease**
- **Any application of genetic principles to medical practice.**

**"Genetics – study of individual genes and their effects":**

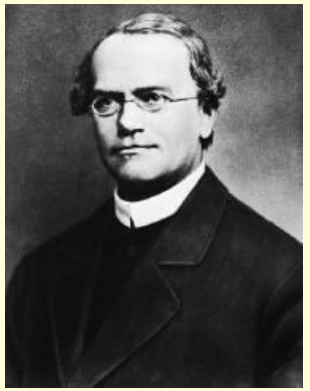
**Includes studies of inheritance, mapping disease, genes, diagnosis, treatment, and genetic counseling**

# History of Medical Genetics

- Early Genetics
- Mendel - 1860s
- Modern Experimental Genetics - 1900s
- Maize, drosophila, mouse
- Medical Genetics - 1960s to the present

# Mendel Inheritance

**Australian monk who formulated fundamental law of heredity in early 1860s.**



Gregor Mendel
(1822-1884)


- **Theories of inheritances**
- **Reshuffling of genes from generation to generations**

**He studied mathematics at University of Vienna**

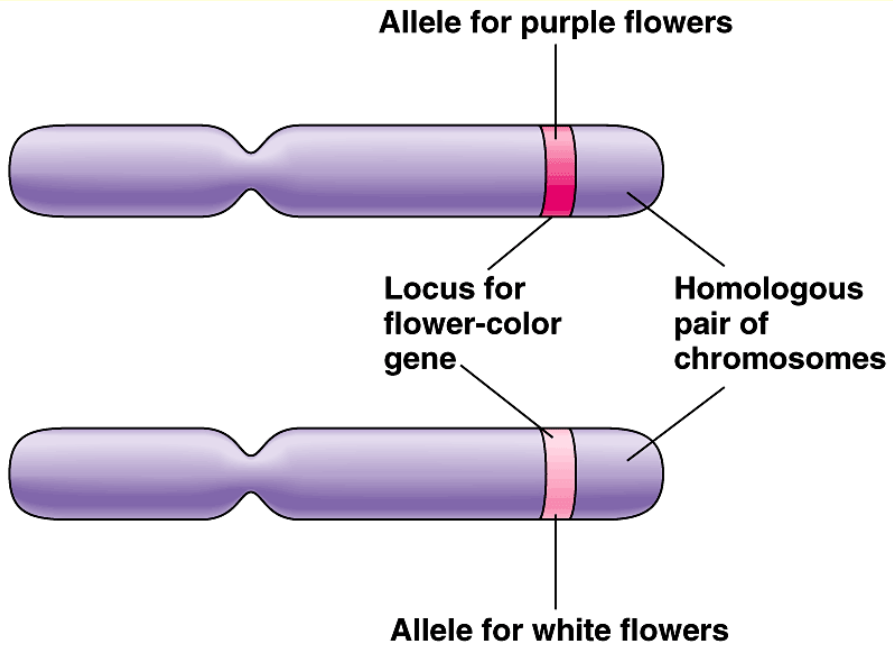
# Mendel studied seven characters in the garden pea

**Table 14.1 The Results of Mendel's $F_1$ Crosses for Seven Characters in Pea Plants**

| Character | Dominant Trait | x | Recessive Trait | $F_2$ Generation Dominant:Recessive | Ratio |
|---|---|---|---|---|---|
| Flower color | Purple | × | White | 705:224 | 3.15:1 |
| Flower position | Axial | × | Terminal | 651:207 | 3.14:1 |
| Seed color | Yellow | × | Green | 6,022:2,001 | 3.01:1 |
| Seed shape | Round | × | Wrinkled | 5,474:1,850 | 2.96:1 |
| Pod shape | Inflated | × | Constricted | 882:299 | 2.95:1 |
| Pod color | Green | × | Yellow | 428:152 | 2.82:1 |
| Stem length | Tall | × | Dwarf | 787:277 | 2.84:1 |

# Mendel deduced the underlying principles of genetics from these patterns

1. Segregation
2. Dominance
3. Independent assortment




# Genetics – history and key concepts…

**1860s** Mendel's work on peas allows the conclusion that traits are inherited through discrete units passed from one generation to the next

**1870s** Friedrich Miescher describes nucleic acids

**1909** The word 'gene' coined by Danish botanist Wilhelm Johannsen

**1910** Thomas Morgan's work on fruitflies demonstrates that genes lie on chromosomes

**1940s** Barbara McClintock describes mobile genetic elements in maize

**1944** Oswald Avery shows in bacteria that nucleic acids are the 'transforming principle'

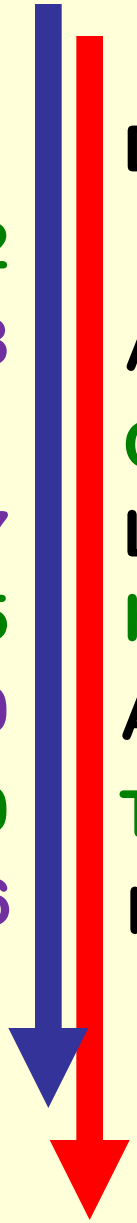
**1953** James Watson and Francis Crick publish the double helix model for DNA's chemical structure

**1958** Crick proposes the 'central dogma' for biological information flow: that DNA makes RNA makes protein

**1977** Phillip Sharp and Richard Roberts find that protein-coding genes are carried in segments

**2001** initial results from the Human Genome Project published

# A Conceptual History of Medical Genetics



| | |
|---|---|
| 1901 | Dominant inheritance of brachydactyly |
| 1902 | Inborn errors of metabolism |
| 1918 | Anticipation described |
| 1931 | Cytoplasmic inheritance of mitochondrial DNA |
| 1937 | Linkage of color blindness and hemophilia |
| 1955 | Human diploid chromosome number is 46 |
| 1970 | Amniocentesis for chromosomal disorders |
| 1970 | Tay-Sachs screening |
| 1976 | Human globin genes cloned |

# A Conceptual History of Medical Genetics

1985 PCR

1986 Duchenne muscular dystrophy gene

1986 Cystic Fibrosis gene

1987 Predictive genetic testing for Huntington Disease

1998 Decision to sequence entire human genome

1991 Medical genetics became an ABMS specialty

1991 Draft sequence for the human genome

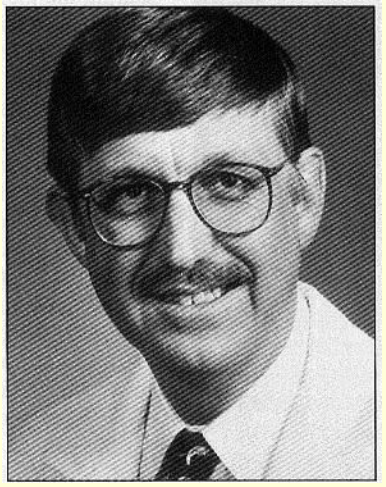
2001 Human genome sequence completed

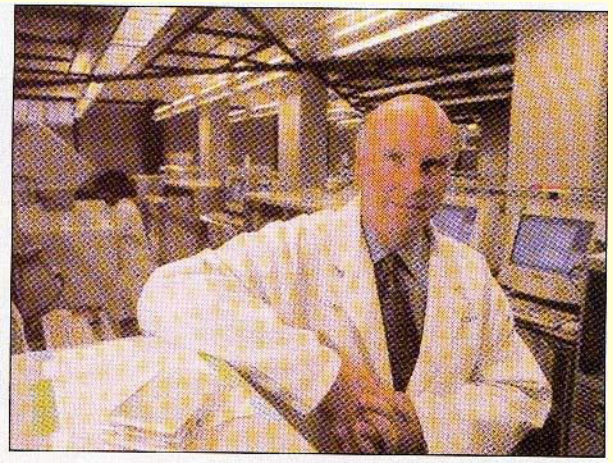
# Medical Genetics: 1950s to the present

- **DNA Genetics**
  - 1953 - Watson and Crick's Double Helix
  - 1992 –2003  Human Genome Project
  - 2003 -> the future of medical dx & tx
- **Prenatal Genetics**
  - 1970s - Prenatal Ultrasound & Amniocentesis
- **Inheritance of Genetically Complex Disorders**
  - Non-Mendelian Genetics
  - Genomic Imprinting
  - Triple Nucleotide Repeats
  - Mitochondrial Inheritance
  - 1990s - Neuropsychiatric Disorders, Diabetes, Cardiovascular
- **Interaction of genes with environmental triggers**

# Human Genome Project

- Proposed in 1985
- 1988. Initiated1990. Work begins.
- 1998. a 3-year plan to complete the project years early
- Published in Science and Nature in February, 2001





# What we've learned from our genome so far…

- There are a relatively small number of human genes, less than 30,000, but they have a complex architecture that we are only beginning to understand and appreciate.
  - ✓ We know where 85% of genes are in the sequence.
  - ✓ We don't know where the other 15% are because we haven't seen them "on" (they may only be expressed during fetal development).
  - ✓ We only know what about 20% of our genes do so far.
- **So it is relatively easy to locate genes in the genome, but it is hard to figure out what they do.**

# Human genome content

- 1-2 % codes for protein products
- 24% important for translation
- 75% “junk”
- Repetitive elements
  - Satellites (regular, mini-, micro-)
  - Transposons
  - Retrotransposons
  - Parasites

# Some Facts

- **In human beings, 99.9% bases are same**
- **Remaining 0.1% makes a person unique**
  - Different attributes / characteristics / traits
    - how a person looks
    - diseases he or she develops
- **These variations can be:**
  - Harmless (change in phenotype)
  - Harmful (diabetes, cancer, heart disease, Huntington's disease, and hemophilia )
  - Latent (variations found in coding and regulatory regions, are not harmful on their own, and the change in each gene only becomes apparent under certain conditions e.g. susceptibility to heart attack)

# Human Genetic Identity

- 99.9% identical
- 3,196,800,000 nucleotides identical
- 3,200,000 nucleotides different

# Human Genetic Variation

- Single base differences in genomes between any two individuals: 2-5 million
- Amino acid differences in proteomes between any two individuals: about 100,000

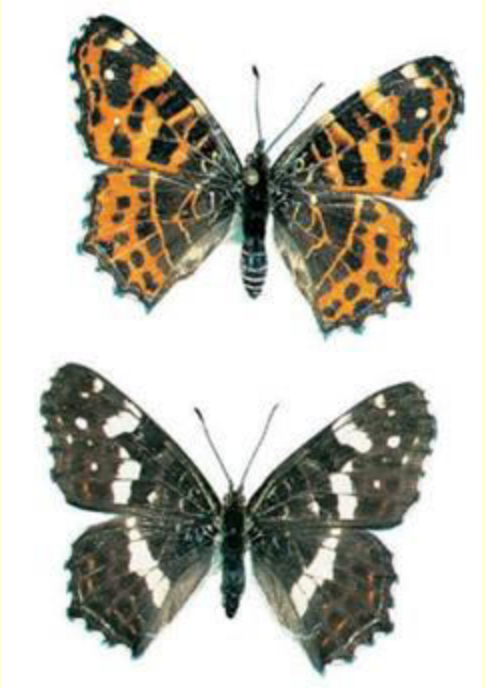
# GENETIC VARIATION

# VARIATION, SELECTION & TIME

- All living things from a simple Bacteria to Plants to Animals and Humans Are descendent of tiny simple single cell form 3.4 billion years ago.

- **Theory of evolution**: How the descendent of this primitive cell differentiated to millions of species share our plant to day

- All these changes are due to three simple ingredients:
  - **Variation**
  - **Selection**
  - **Time**




Lemon Box
Super Sarno
White Queen
Lime Green Salad
Super Snow White
Principe Borghese
Old Ivory Egg
Tangella
Sweet Olive
Persimmon
Taxi
Florida 91
Super Marzano
Vita Gold
Mixed tomatoes for market

# VARIATION

- Each offspring resemble his parents but each individual is unique
- Mutation and Recombination's introduce variation in each generation
- These two processes are constantly generating random diversity in the forms of life

# Evolution and Modern Humans: Human Diversity

Over the last 100,000 years human populations have expanded and diversified

- **Human morphology varies**
  - Height and body proportions
  - Skin color
  - Hair color and texture
  - Facial features
- **Human physiology varies**
  - Lactose absorption
  - Blood types
  - Susceptibility to diseases (i.e. &Tay-Sachs)

# Why is genetic variation important to a species?

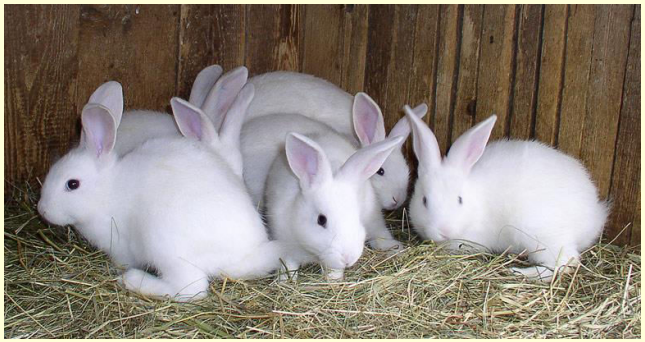
- If there is genetic variation, then some individuals in a species will be more fit than others. This ensures that some individuals of the species will survive and keep the species going.

- If there is no genetic variation, then all individuals will be exactly the same. This could be deadly if there is a change in the environment. The species could go extinct because none will be fit for the environment.

# Example:

- Which population of hares has a better chance of survival as a species?

**Population A**



**Population B**

## Population B

Because it has more genetic variation than population A so there will be some individuals that are more fit if the environment were to change. Thus the species has a higher chance of survival.

# GENETIC VARIATION

## Definitions

- ALLELES
- LOCUS
- HOMOZYGOTE
- HETEROZYGOTE
- GENOTYPE
- PHENOTYPE
- PLYMORPHIC
- POLYMORPHISM

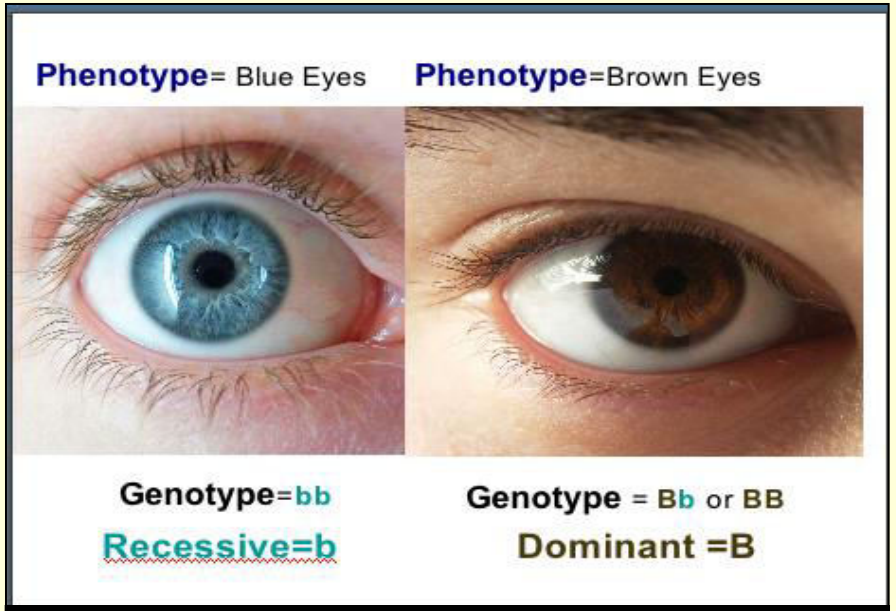
# Glossary & Definitions I

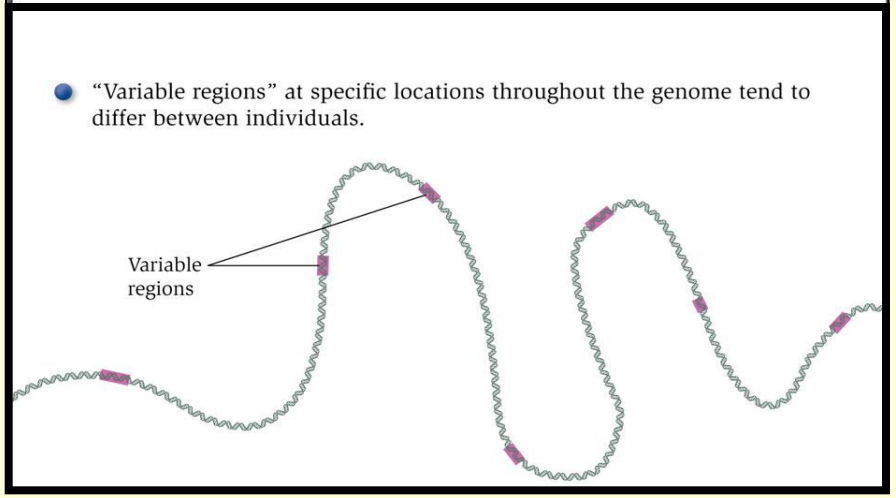
- **Character - a structure, function, or attribute determined by a gene or group of genes**
  - i.e. the appearance of the seed coat in Mendel's garden pea studies

- **Trait - the alternate forms of the character**
  - i.e "smooth" or "wrinkled" peas

# Glossary & Definitions II

- **Phenotype - the physical description of the character in an individual organism**
  - Eye Colors
- **Genotype - the genetic constitution of the organism**
- **Mutation** - a change in the genetic material, usually rare and pathological
- **Polymorphism** - a change in the genetic material, usually common and not pathological

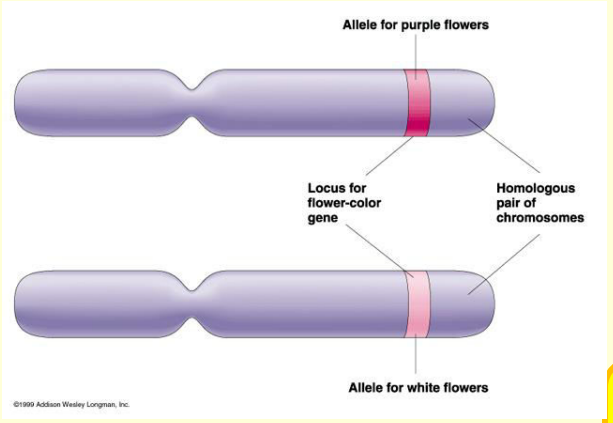


# Glossary & Definitions III

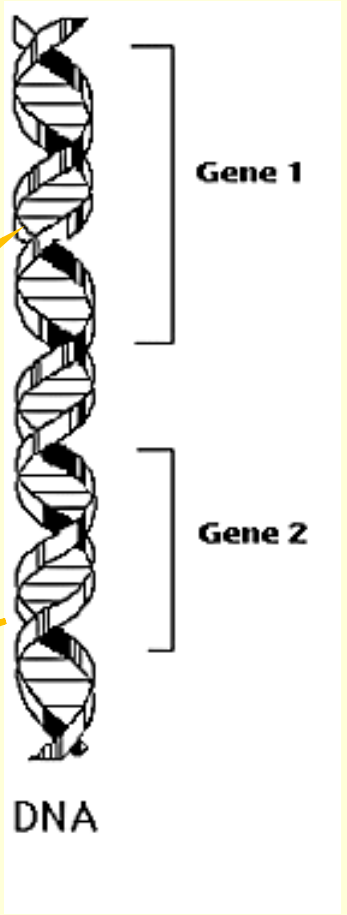
- **Locus** – location of a *gene/marker* on the chromosome.

- **Allele:** One of a number of alternative forms of the same genetic locus (for example a SNP)




**Locus1**
**Possible Alleles: A1,A2**

**Locus2**
**Possible Alleles: B1,B2,B3**



# Glossary and Definitions IV

- **Homozygote** - an organism with two identical alleles
- **Heterozygote** - an organism with two different alleles
- **Hemizygote** - having only one copy of a gene
  - Males are hemizygous for most genes on the sex chromosomes

# Glossary and Definitions V

- **Genome**: the complete genetic constitution of an organism, encoded in nucleic acids
- **Gene**: discrete DNA sequence encoding a protein
- **Linkage Disequilibrium (LD):** Non-random association of alleles that descend from single, ancestral chromosomes (i.e. usually close to each other)
- **Haplotype:** Combination of alleles at adjacent locations on a chromosome that are inherited together

# The Causes of Genetic Variations

- Evolution
- Gene Flow and Drift
- Gene Frequency
- Adaptation
- Natural Selection
- Mutation

# Evolution

- Evolution refers to change over time, or transformation over time.
- Evolution assumes that all natural forms arose from their ancestors and adapted over time to their environments, ⟹ leading to variation.
- In evolution, there are many rules the environment places upon the survival of a species.
- There are also numerous ways in which evolution occurs, the most noted are
  - Adaptation.
  - Natural Selection

# Examples of EVOLUTION

**Microevolution: Changes in gene frequencies from one generation to the next.**

**Macroevolution: Emergence of new varieties (e.g. species) of organisms.**

- You have to be better than the competitors to survive
- Evolution can greatly modify existing structure but it has to work within limits:
  - **The humans larynx set lower in the throat than in other mammals**
  - **Ice fish lost RBC… Survive in freezing environment**
  - **Tape warm parasite …. No digestive system using skin to absorbed the nutrients**

# GENETIC EVOLUTION

**Microevolution:** changes in gene frequencies from one generation to the next.

**Macroevolution:** emergence of new varieties (e.g. species) of organisms.

# Gene Flow

- **Gene flow refers to the passage of traits or genes between populations. The passage of genes from one population to another prevents high occurrences of mutation, and genetic drift.**
- **Can occur either with migration or with intermarriage / interbreeding**
- **Increases diversity within populations by introducing new alleles,**
- **Reduces differences between population spreading genetic material around**

**Even low levels of gene flow can keep two populations from diverging into different species**

# Adaptation and Adaptive Strategy

- The earth is rich in diverse environments and eco-systems. At the core of evolution is the way a specific species adapts to its environment.
- Examples

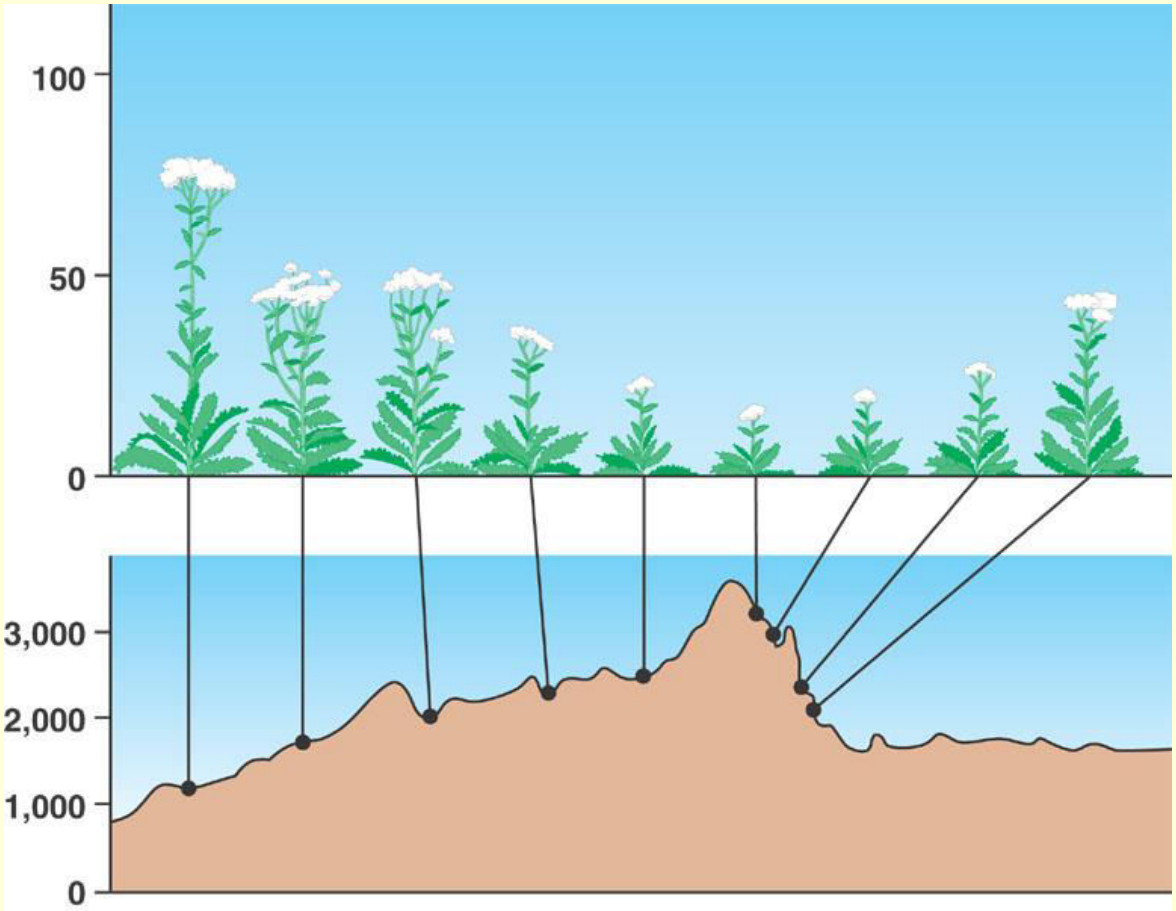
**Physiological Traits: Heat conservation**

- **Reduction of sweat production** – prevents heat loss through evaporation
- **Shivering –** muscles contract without synchronization
- **Less Radiation –** circulation limited to deeper capillaries

**Sickle cell anemia**. Heterozygous Sickle Cell Anemia genotype gives a higher resistance to malaria, Homozygous genotype is still a disadvantage.

# The phenotype is an interplay between genes and environment

- High elevation, 3,050 meters, in the mountains
- Intermediate elevation, 1,400 meters, in the foothills of the Sierra Nevada
- Low elevation, 30 meters above sea level



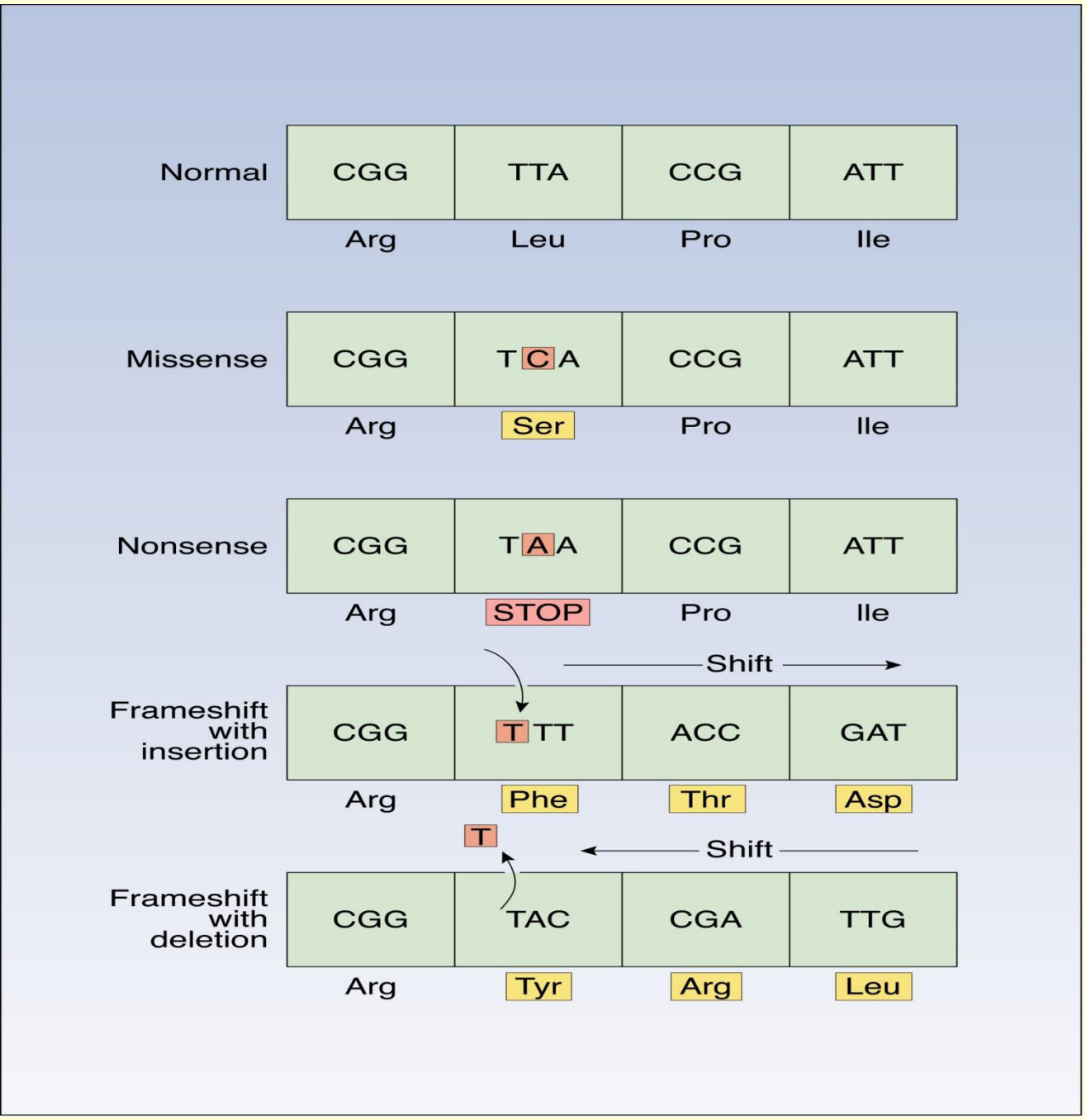
# NATURAL SELECTION

- Control which variations occurred and which variation eliminated
- Many species produce more many than can survive to adulthood
- Competition for the resources, predators the changing of environment eliminate most individuals
- Those with most favorable combination of genes they survive and pas there genes to their generations
- **Interval of a 100 or 200 year time span**
- **The best example of a quick change in the environment and a species ability to adapt concerns the color of the Gypsy Moths in England.**

**Natural selection • Stabilizing • Directional• Diversifying • Sexual selection**

# Mutation

- A permanent change in DNA sequence.
- Mutations in germ cells are heritable and may be transmitted to the next generation.
- Mutations are usually non-beneficial to an organism, however, they are almost always recessive and unless two mutations are coupled together the mutation will not be expressed.
- Mutations in somatic cells are not heritable, but may be transmitted to daughter cells.

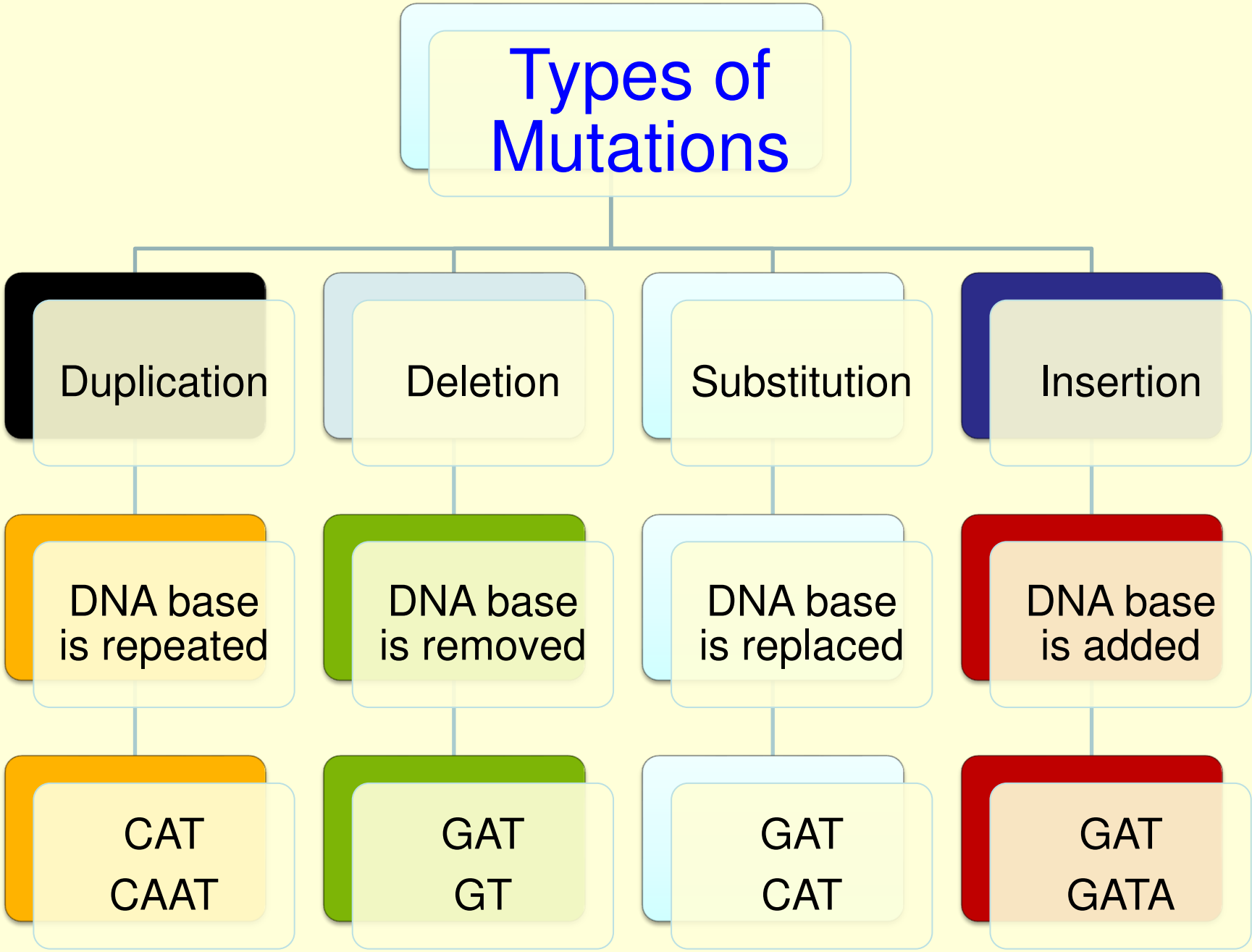



# Types of Mutation

**UAA, UAG, UGA**

**Mutation Cause**

**Elongation**


Types of Mutations
Duplication
Deletion
Substitution
Insertion
DNA base is repeated
DNA base is removed
DNA base is replaced
DNA base is added
CAT
CAAT
GAT
GT
GAT
CAT
GAT
GATA

# Effects of Mutations

## Harmful

(bad for organism)

EX: Hemophilia; blood doesn't clot

## Neutral

(does not hurt or help organism)

EX: humans having curly or straight hair

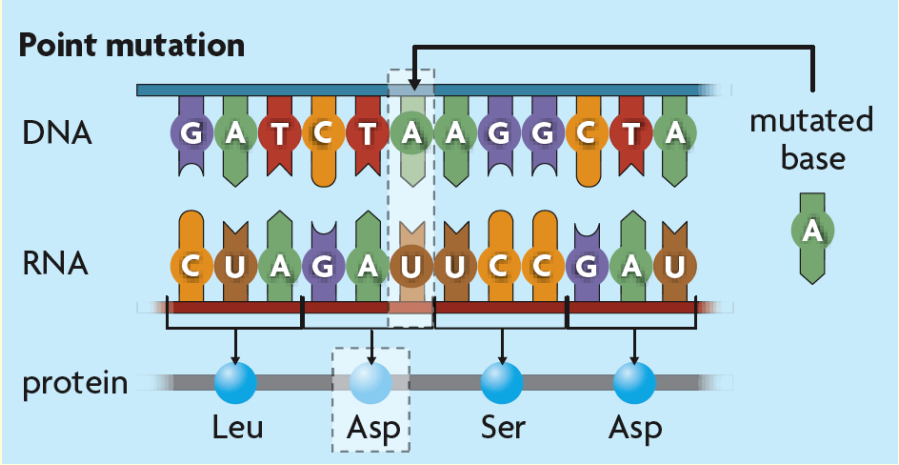
## Beneficial

(helps organism)

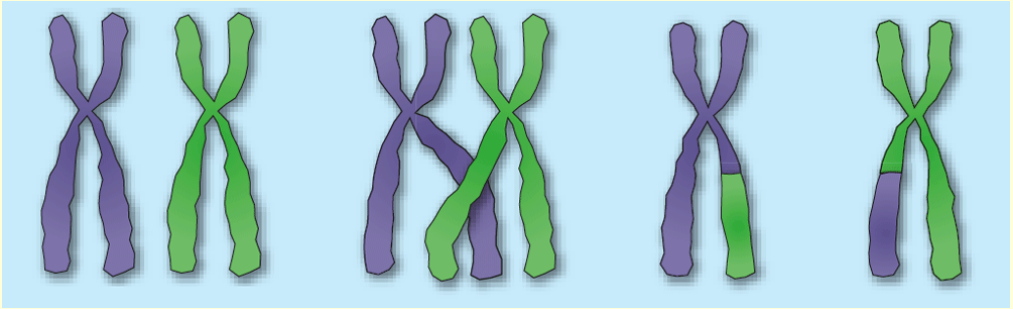
EX: extra muscle fiber in quadriceps

# Genetic variation comes from several sources.

- **Mutation is a random change in the DNA of a gene.**
  - Can form new allele
  - Can be passed on to offspring if in reproductive cells




- **Recombination forms new combinations of alleles.**
  - Usually occurs during meiosis
  - Parents' alleles arranged in new ways in gametes



# Variation Types

- **Macro:**
  - Chromosome numbers
  - Segmental duplications, rearrangements, and deletions
- **Medium:**
  - Sequence Repeats
  - Transposable Elements
  - Short Deletions, Sequence and Tandem Repeats
- **Micro:**
  - **S**ingle **N**ucleotide **P**olymorphisms (SNPs)
  - Single Nucleotide Insertions and Deletions

# GENETIC VARIATION

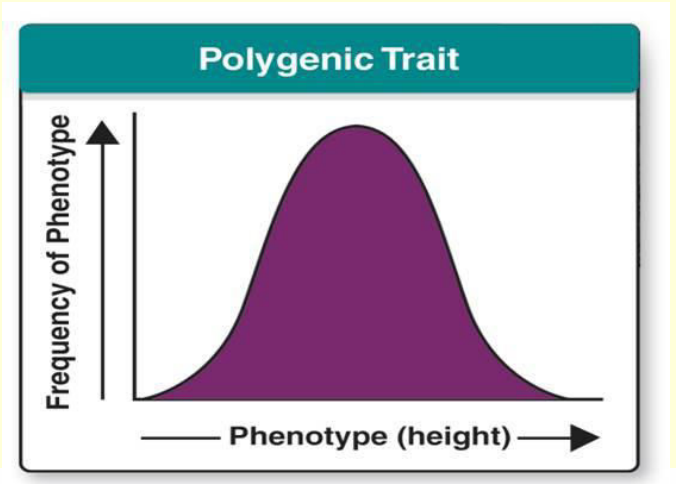
- The ultimate source of genetic variation is differences in DNA sequences. Most of those genetic differences do not affect how individuals function.
- Some genetic variation are:
  - Associated with disease,
  - Others improves the ability of the species to survive changes in the environment.
- Genetic variation, is the basis for evolution by natural selection.

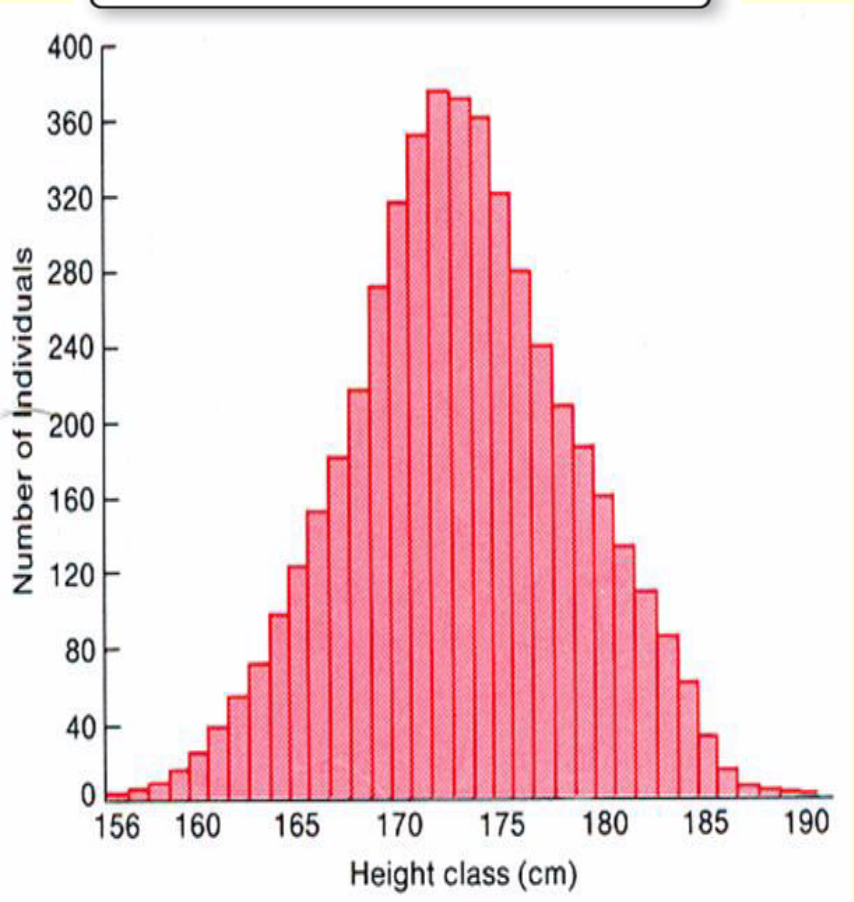
# Variations Types

- ***Quantitative Characters*** are those that vary along a continuum within a population.
  - ✓Quantitative variation is usually due to polygenic inheritance in which the additive effects of two or more genes influence a single phenotypic character.
  - ✓**Ex:** Tall and Shot person and in between.

**Genetic Variations Underlie Phenotypic Differences**

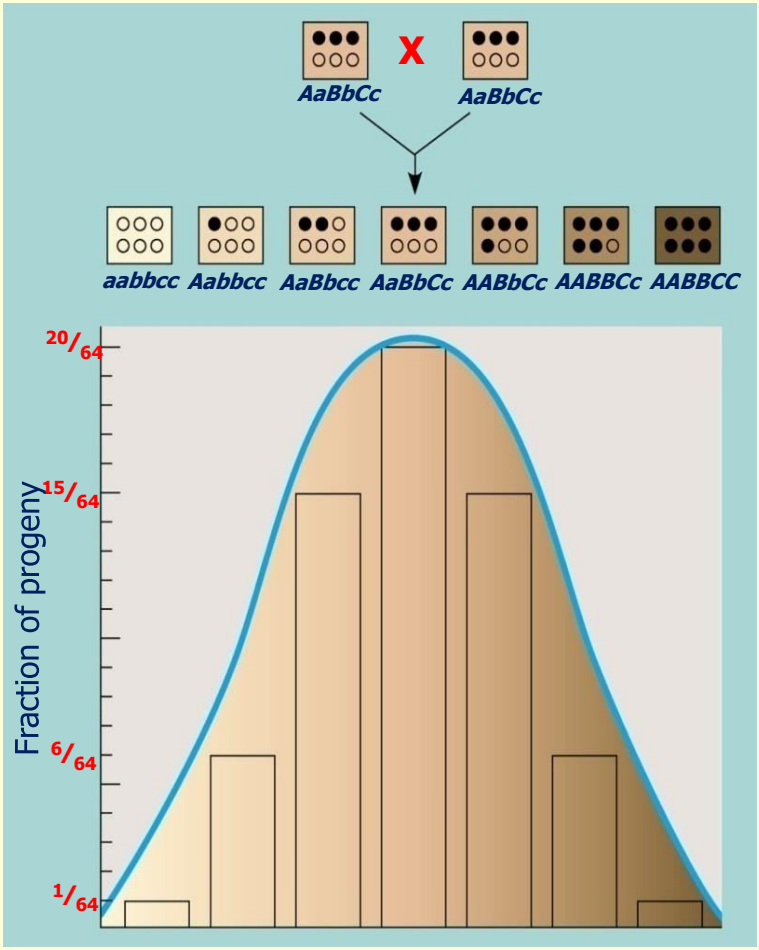
# Continuous trait / Discontineous Trait

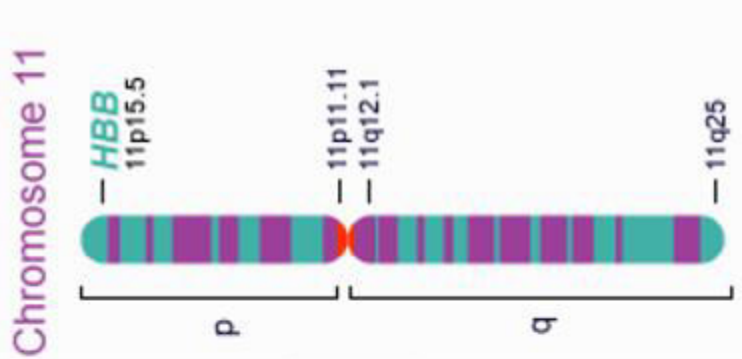



# Continuous trait Discontineous Trait

Skin color is determined by the additive effects of several incompletely dominant genes






Sequence for normal adult hemoglobin:

Nucleotide CTG ACT CCT GAG GAG AAG TCT

Wild-type Hemoglobin Protein

Normal Red Blood Cell

# Sickle Cell Anemia

Sequence for mutant hemoglobin:

Nucleotide CTG ACT CCT GTG GAG AAG TCT

Mutant Protein

Abnormal Red Blood Cell

# Process Shaping Genetic Variation an Linkage Disequilliperium

## GENETIC

- Mutagenesis
- Recombination
- Gene conversion

## DEMOGRAPHIC

- Population age
- Genetic drift
- Population dinamics
  - migration
  - bottlenecks

NATURAL SELECTION

# GENETIC VARIATION

- The ultimate source of genetic variation is differences in DNA sequences. Most of those genetic differences do not affect how individuals function.
- Some genetic variation are:
  - Associated with disease,
  - Others improves the ability of the species to survive changes in the environment.
- Genetic variation, is the basis for evolution by natural selection.

# Types of genetic variations

CCTAGTTGACTGATCGCGGGATTCACACACATGG

CCTGGTTGAC . . ATCGCGGGATTCACACACACACATGG

**InDels**
(insertions/deletions)
- two alleles
- > 1,000,000

**SSR – short sequence repeats**
(VNTR - variable number tandem repeats)
- **many alleles**
- **microsatellites (1-5)**
- **minisatellites (6-100)**
- **…**

**> 1,000,000**

**Single (point) base changes**
- two alleles

## SNPs

**Single Nucleotide Polymorphisms; > 10, 000, 000**

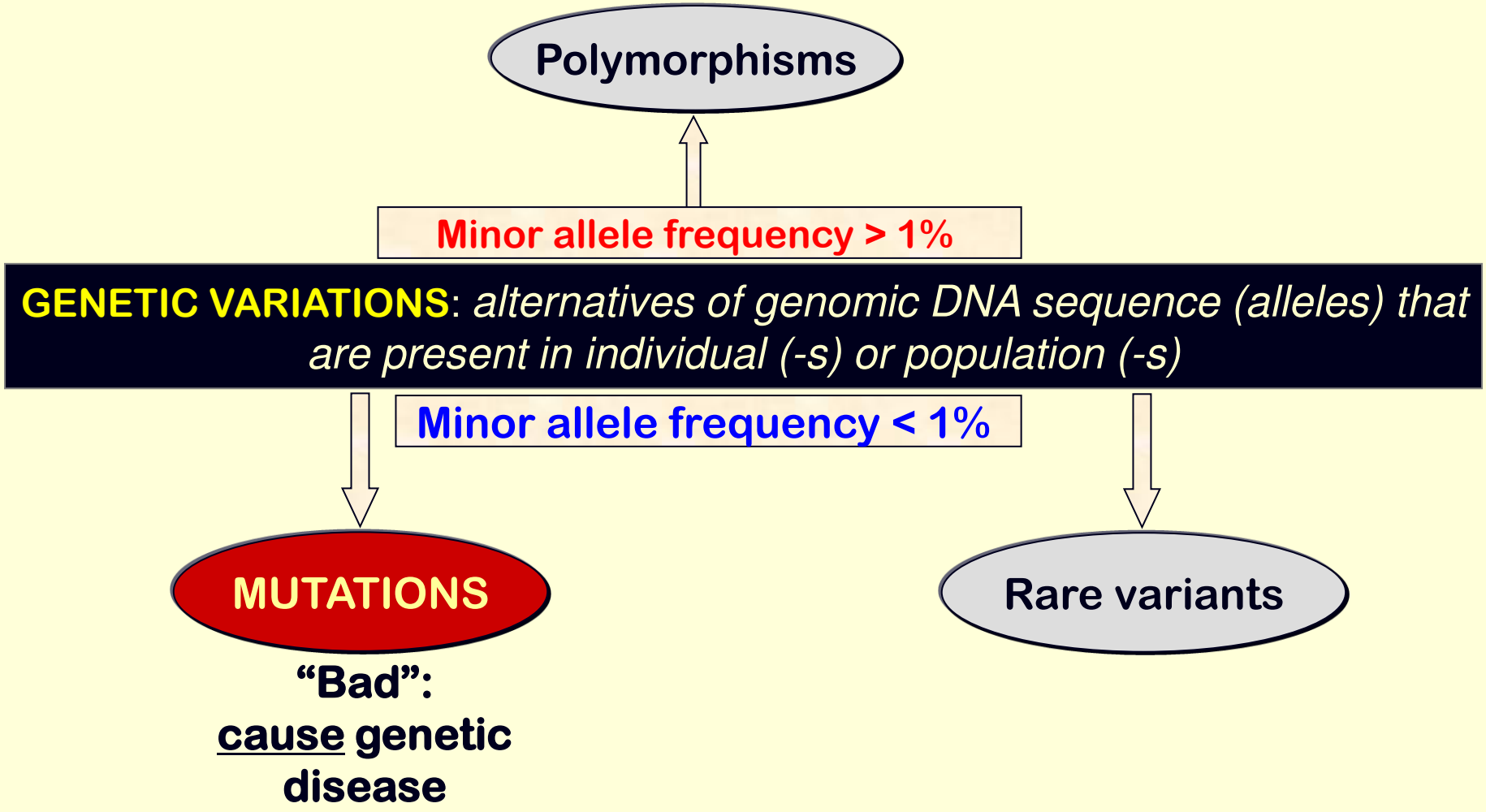
- **Inversions**
- **Duplications**
- **Translocations**
- **Transposon insertions**

**Variations exceeding 1000bp - STRUCTURAL VARIATIONS**
- **less than 3 million bp - submicroscopic; larger– microscopic**
- **InDels and duplications are called CNVs (copy number variations)**

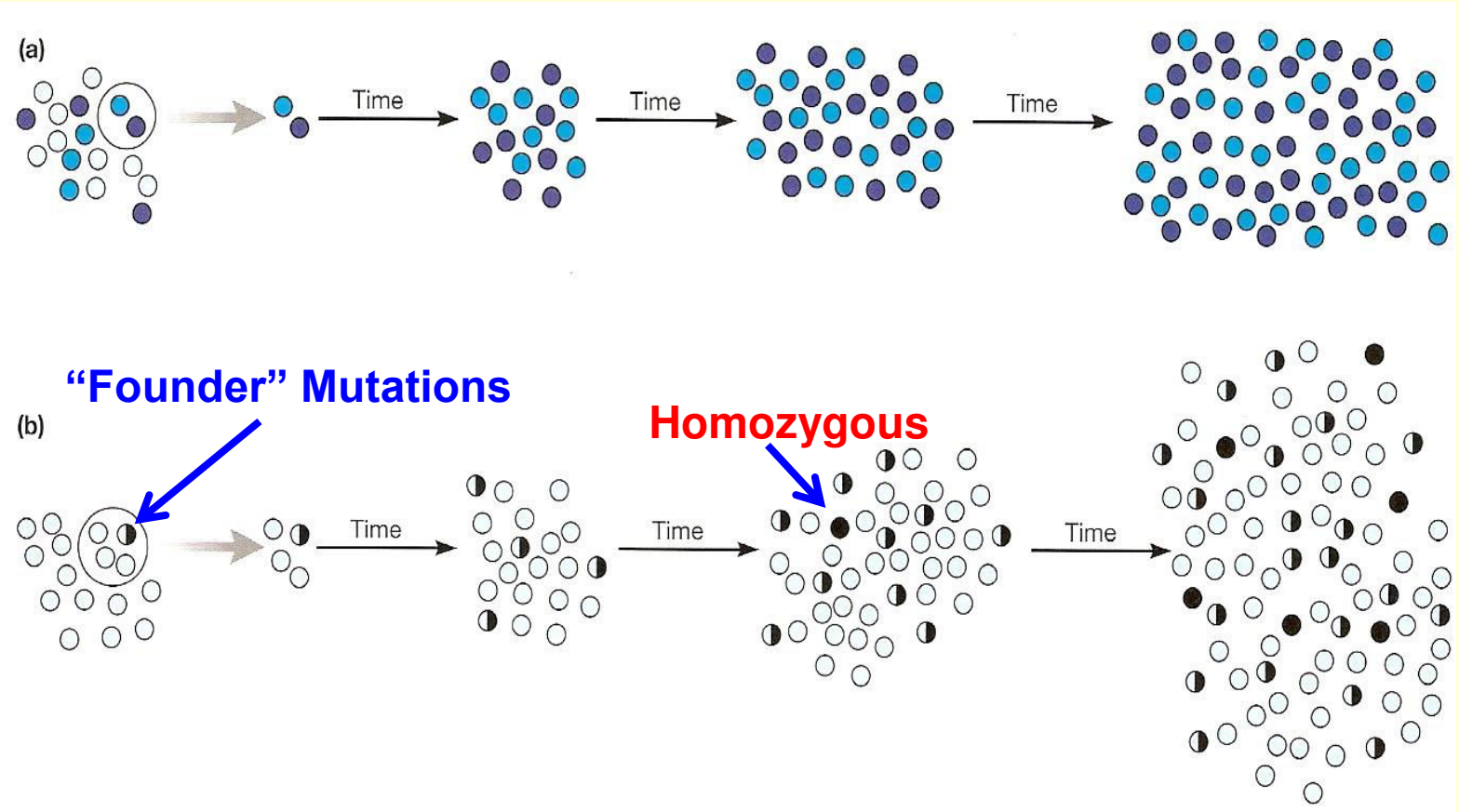
# Polymorphisms (common variation): majority – neutral

The rest:

- slightly "bad" (predispose to disease)
- slightly "good" (protect from disease)
- both slightly bad and good (predispose to and protect from certain conditions)



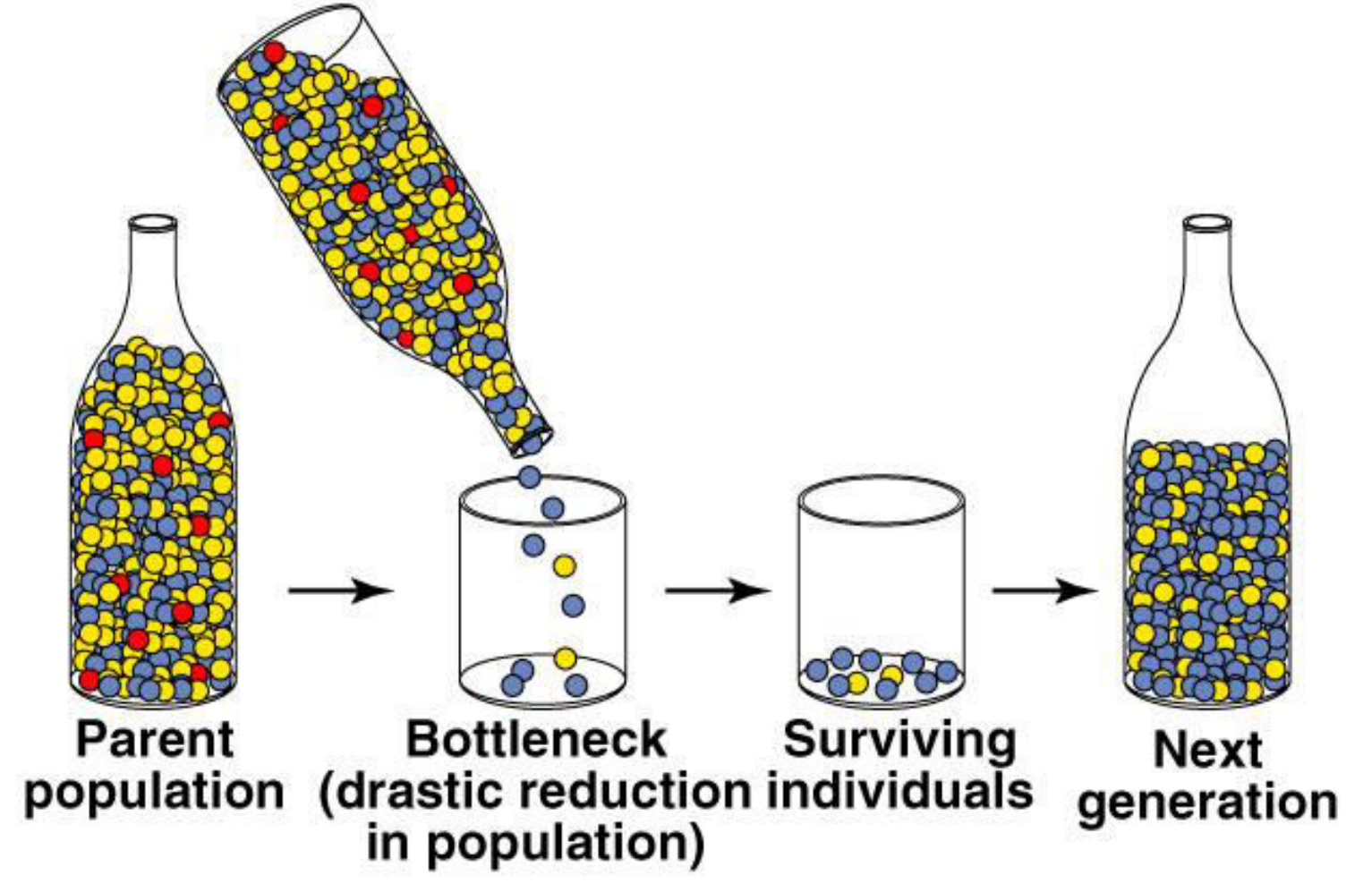
# (ii) Demographic processes: genetic drift and "founder" mutations




Bema Indians and Diabetes

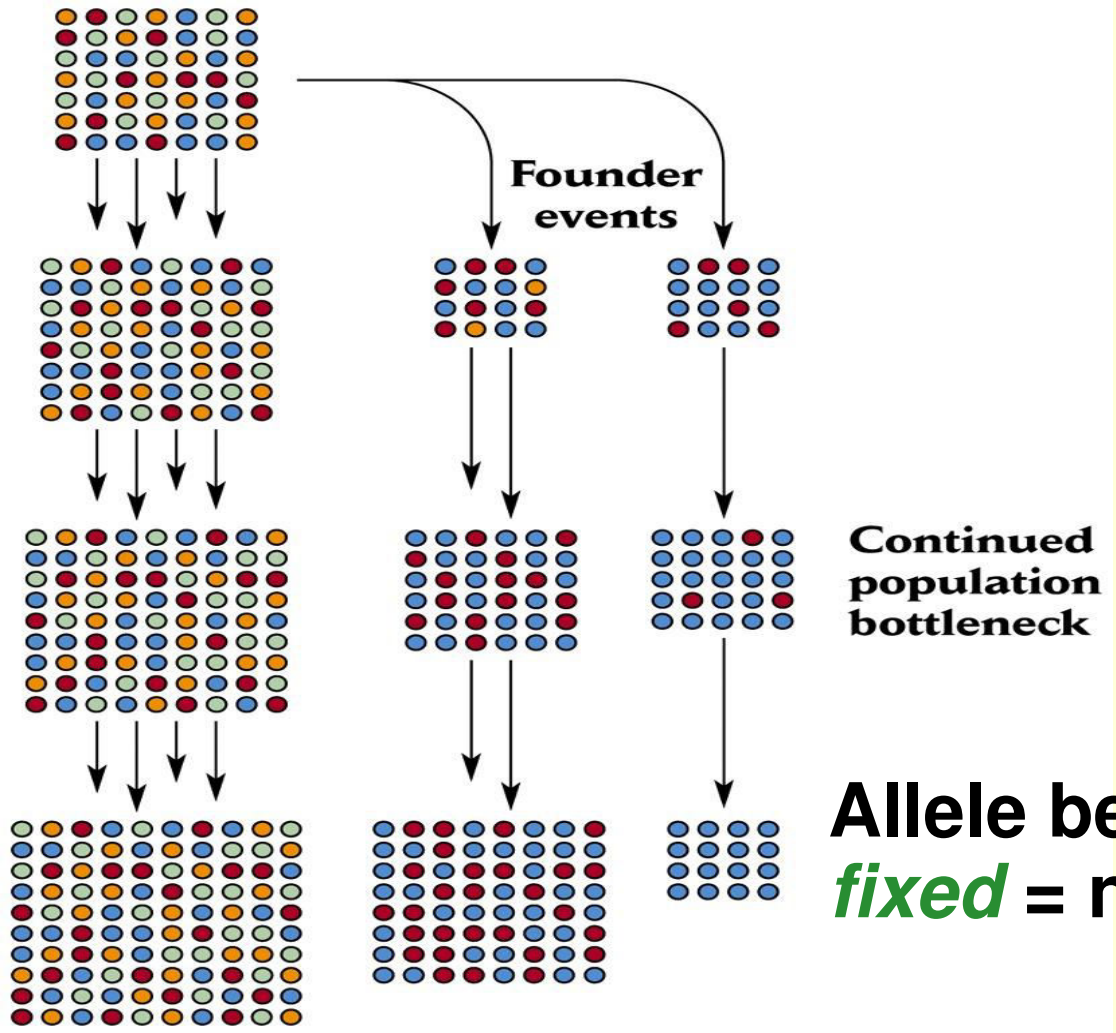
**Genetic Drift**

# Genetic Drift - Bottleneck Effect



**Small populations experience genetic drift, founder events, and population bottlenecks.**

**Each causes a loss in genetic variation.**




**+ genetic drift**

**Allele becomes *fixed* = no variation.**

# Genetic Variation in Nature

- Morphology, Physiology, Behavior
  - Size, color, shape of cell or body paespiration, digestion, excretion, etc.
  - Nutrient acquisition, reproduction, migration, etc.
- Enzyme polymorphism
  - Change in catalytic ability due to change in temperature, osmotic environment, pH,
- DNA sequence polymorphism
  - Changes in bases, codons, introns, exons, etc.
- Large, healthy populations exhibit a high level of genetic diversity
- Polymorphisms are the raw material for evolution

## Mutation

- Gene directly leads to disorder
- Mendelian pattern of inheritance
- Rare

## Polymorphism

- Gene confers an increased risk, but does not directly cause disorder
- No clear inheritance pattern
- Common in population

# Genetic Differences Among Individuals

DNA sequences can be **single-copy** or **repetitive** and can also be **clustered** or **interspersed**. In humans and in 23 pairs of chromosomes, we found that:

- 1.5 % of genome encodes polypeptides
- 5% of genome contains regulatory sequences
- 50% of the genome contains unique DNA sequences
- 50% of the genome contains repetitive DNA sequences
- 99.9% of genome is shared among all humans

# TAKE HOME MESSAGE:

**Genetic variation increases a species' chance of survival**

Variation = good ↑ survival

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