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GENETIC VARIATION

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MGL-2

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

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

GENETIC VARIATION

- **One of the benefits of understanding human genetic variation at a molecular level is its practical value for helping us understand and treat disease.**

- **The development of effective gene-based therapies is an exciting outcome of human genetic research.**

- **Studying the genetic and environmental factors involved in multifactorial diseases will lead to increased ability of diagnosis, prevention, and treatment of disease.**

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.

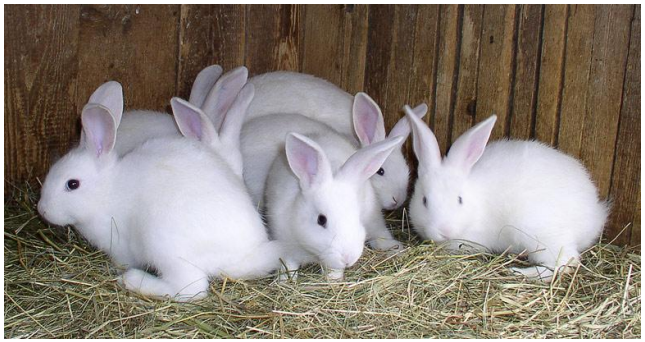
Example:

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

Population 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.

Population A



Population B

Bottle Neck

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

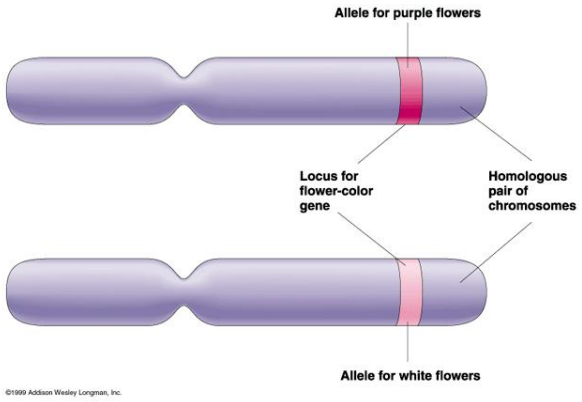
Glossary & Definitions II

- **Phenotype - the physical description of the character in an individual organism**
  - i.e a green pea
- **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

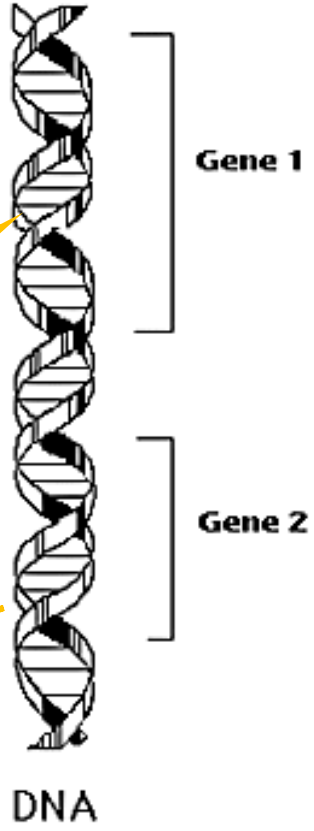
- **Locus** – location of a *gene/marker* on the chromosome.

- **Allele** – one variant form of a gene/marker at a particular *locus*.



Locus1
Possible Alleles: A1,A2

Locus2
Possible Alleles: B1,B2,B3



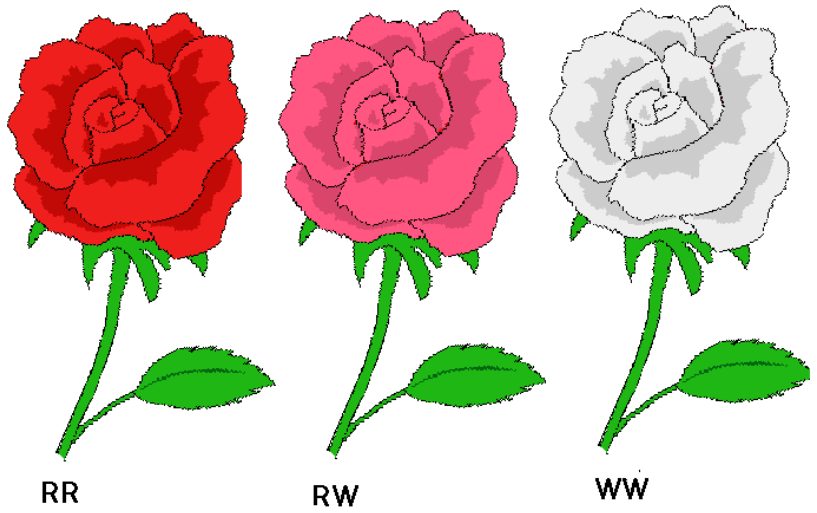
Glossary and Definitions IV

- **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

- **Dominant trait** - a trait that shows in a heterozygote

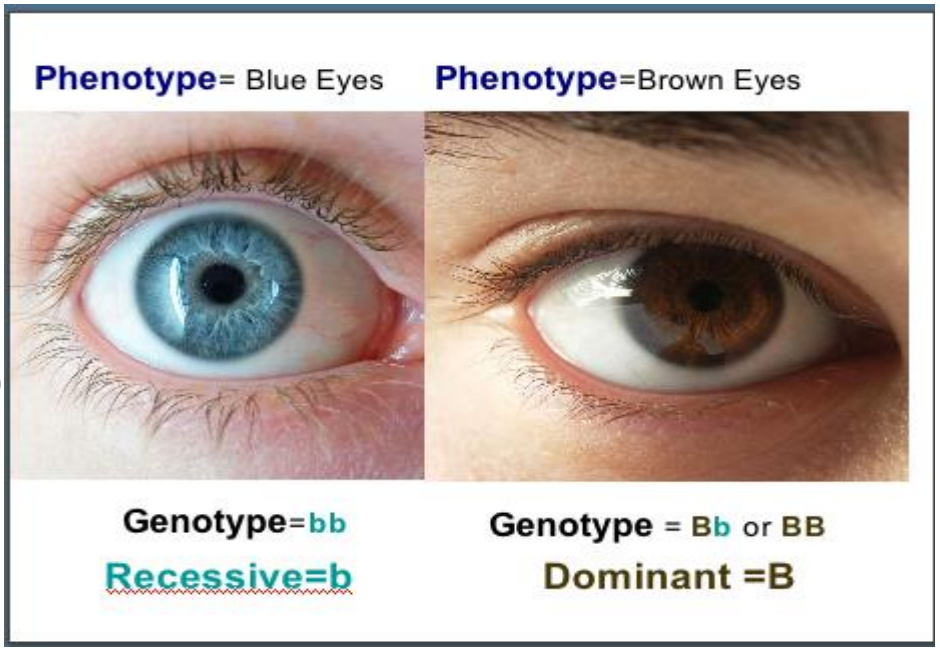
- **Recessive trait** - a trait that is hidden in a heterozygote



Phenotype / Genotype

- An organism's physical appearance based on an interaction of its genes and environment
- **Ex**: fur color, eye color, # toes, hair texture, speed, intelligence

- The genes (DNA) an organism has
- Ex: BB or Bb or bb for eye color



GENETIC VARIATION

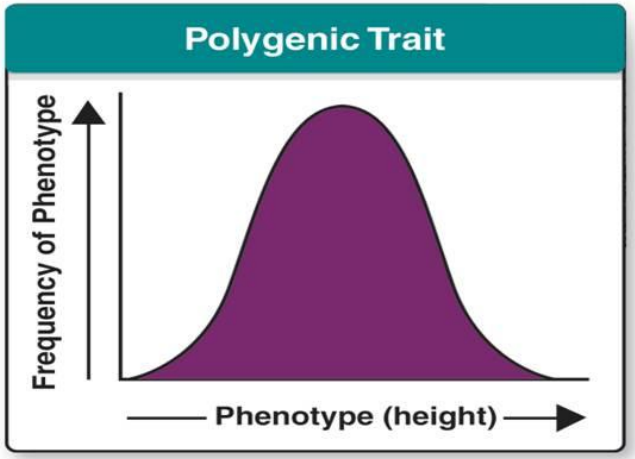
- The ultimate source of genetic variation is differences in DNA sequences. Most of those genetic differences do not affect how individuals function.
- Some genetic variation are:
  - Associated with disease,
  - Others improves the ability of the species to survive changes in the environment.
- Genetic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

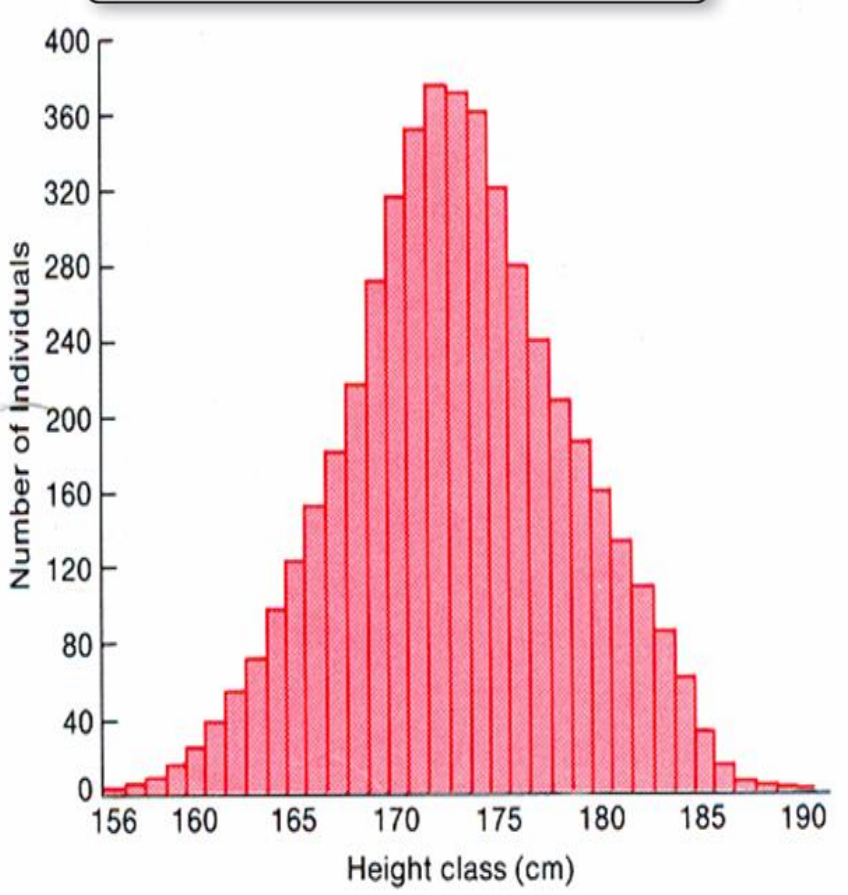
Variations Types

- ***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

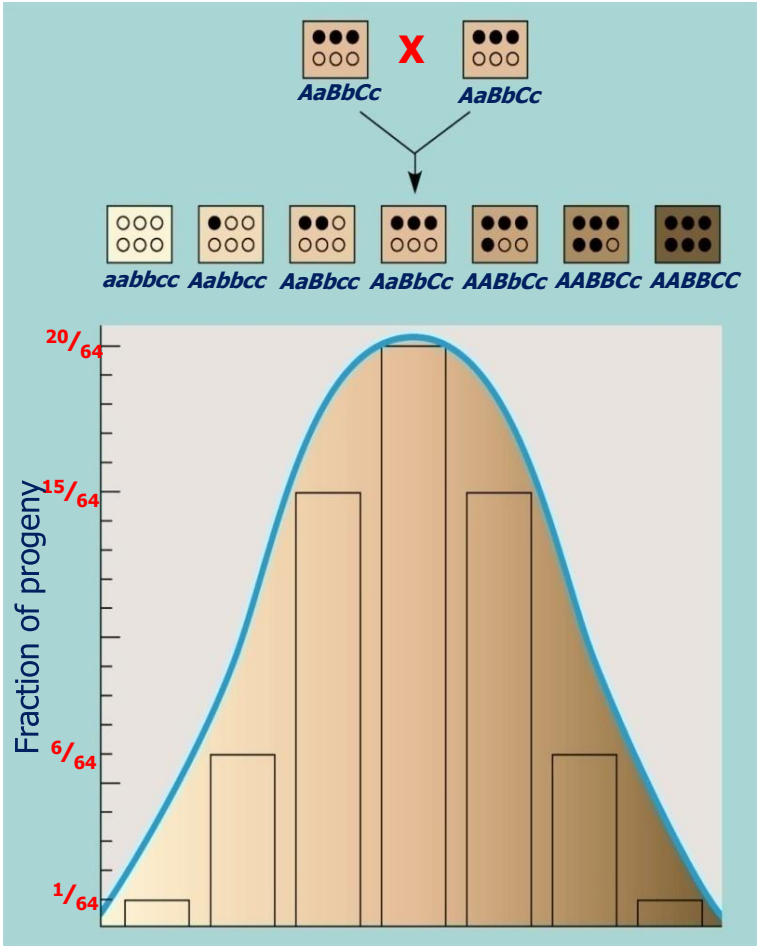
Continuous trait / Discontineous Trait





Continuous trait Discontineous Trait

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



Variations Types

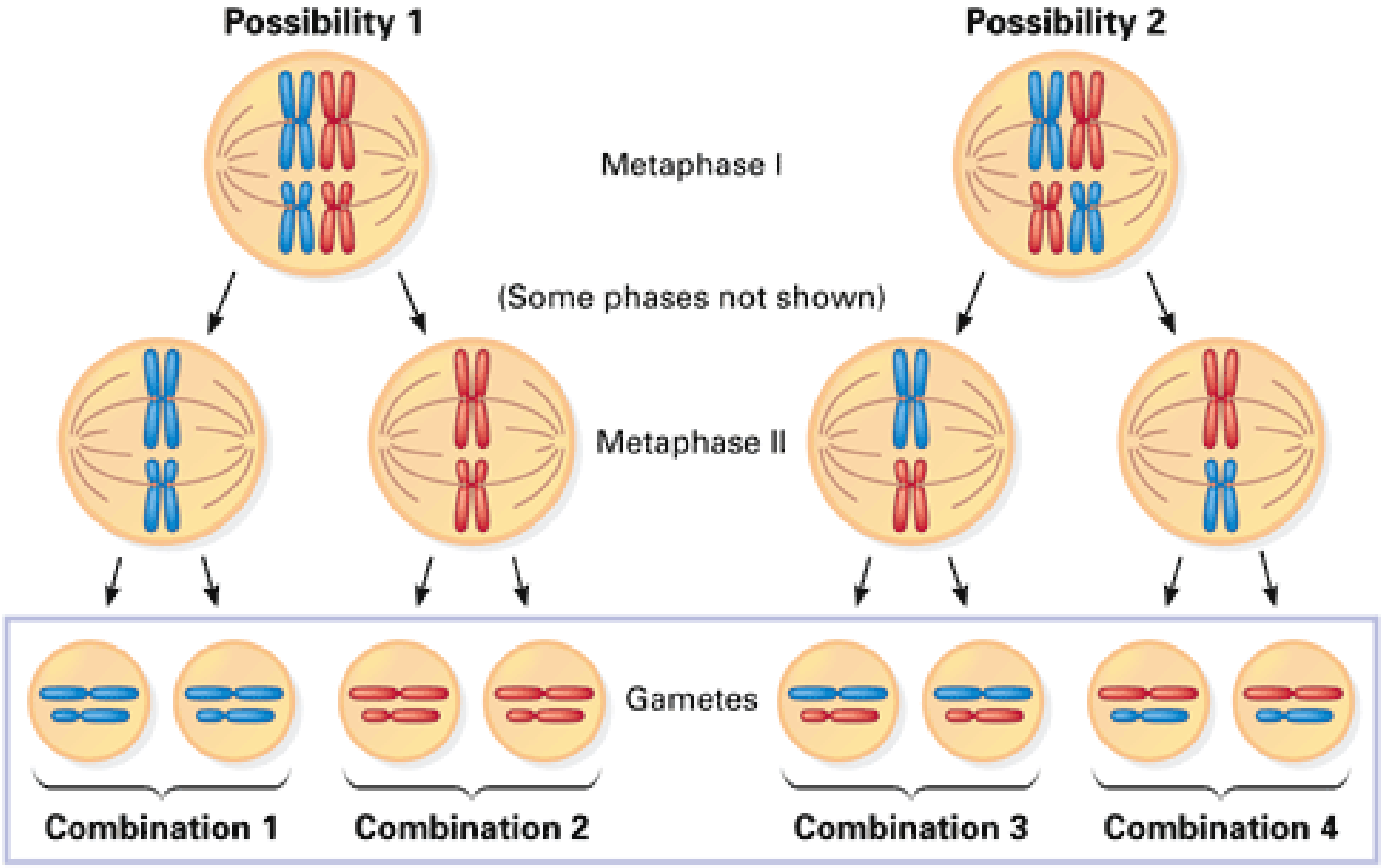
- ***Discrete characters***:

✓ flower color, are usually determined by a single locus with different alleles with distinct impacts on the phenotype

Measurement of Variation

1. Assortments of Chromosomes

- Meiosis contributes to genetic variety.
- How the chromosomes in each homologous pair (tetrads) line up and separate at metaphase I is a matter of chance, like the flip of a coin.
- So, the assortment of chromosomes that end up in the resulting cells occurs randomly. In this example, four combinations are possible

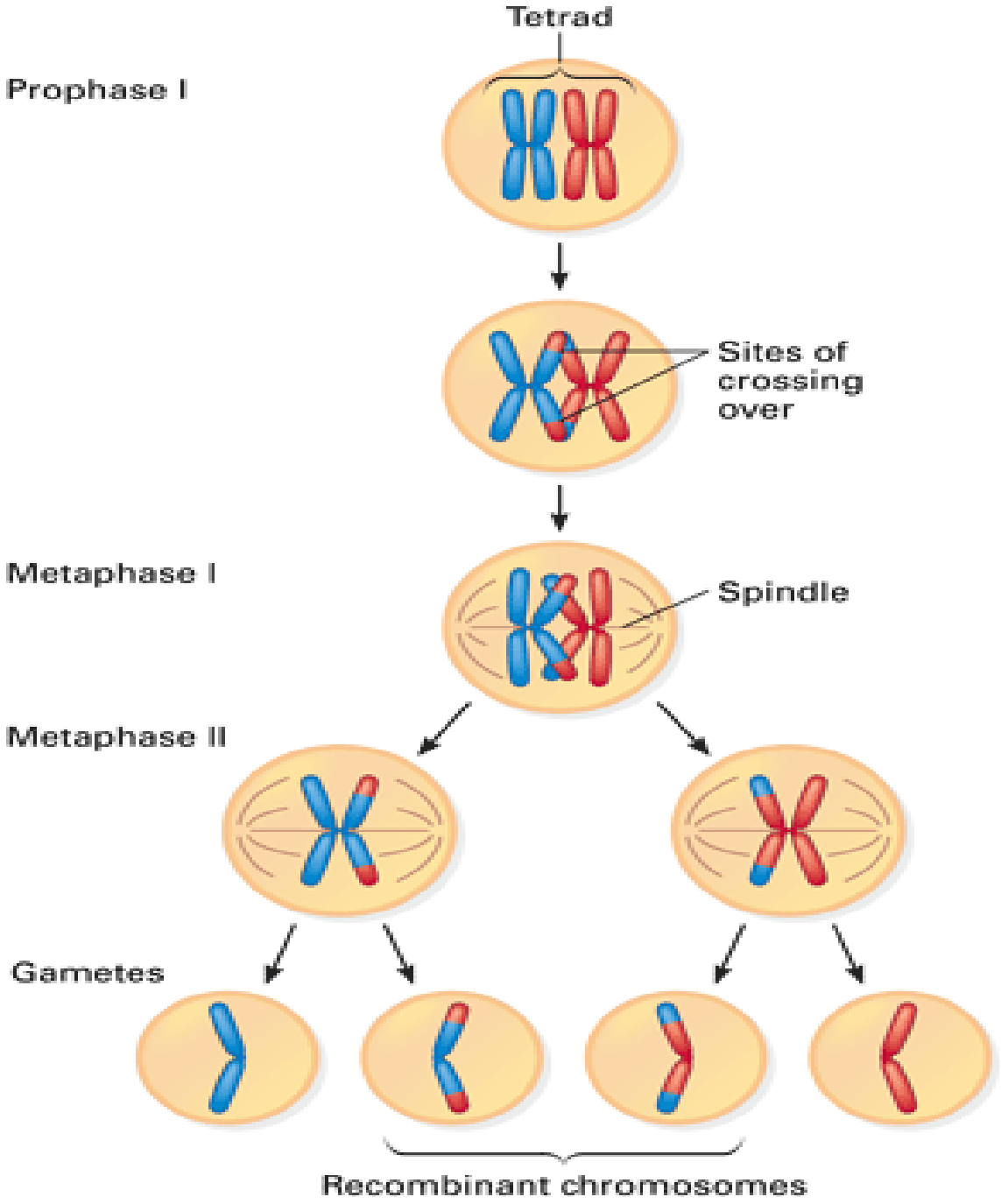

Possibility 1
Possibility 2
Metaphase I
(Some phases not shown)
Metaphase II
Gametes
Combination 1
Combination 2
Combination 3
Combination 4

- If you know the haploid number for an organism, you can calculate the number of possible combinations in the gametes
- The possible combinations are equal to 2^n, where n is the haploid number.
- For the organism if $n = 2$, so the number of chromosome combinations is 2^2, or 4. For a human, $n = 23$, so there are 2^{23}, or about 8 million, possible chromosome combinations!

Measurement of Variation

2. Crossing Over

- Crossing Over exchange of genetic material between homologous chromosomes. This exchange occurs during prophase I of meiosis
- When crossing over begins, homologous chromosomes are closely paired all along their lengths. There is a precise gene-by-gene alignment between adjacent chromatids of the two chromosomes.
- Segments of the two chromatids can be exchanged at one or more sites



Crossing over can produce a single chromosome that contains a new combination of genetic information from different parents, a result called Genetic Recombination

The Causes of Genetic Variations

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

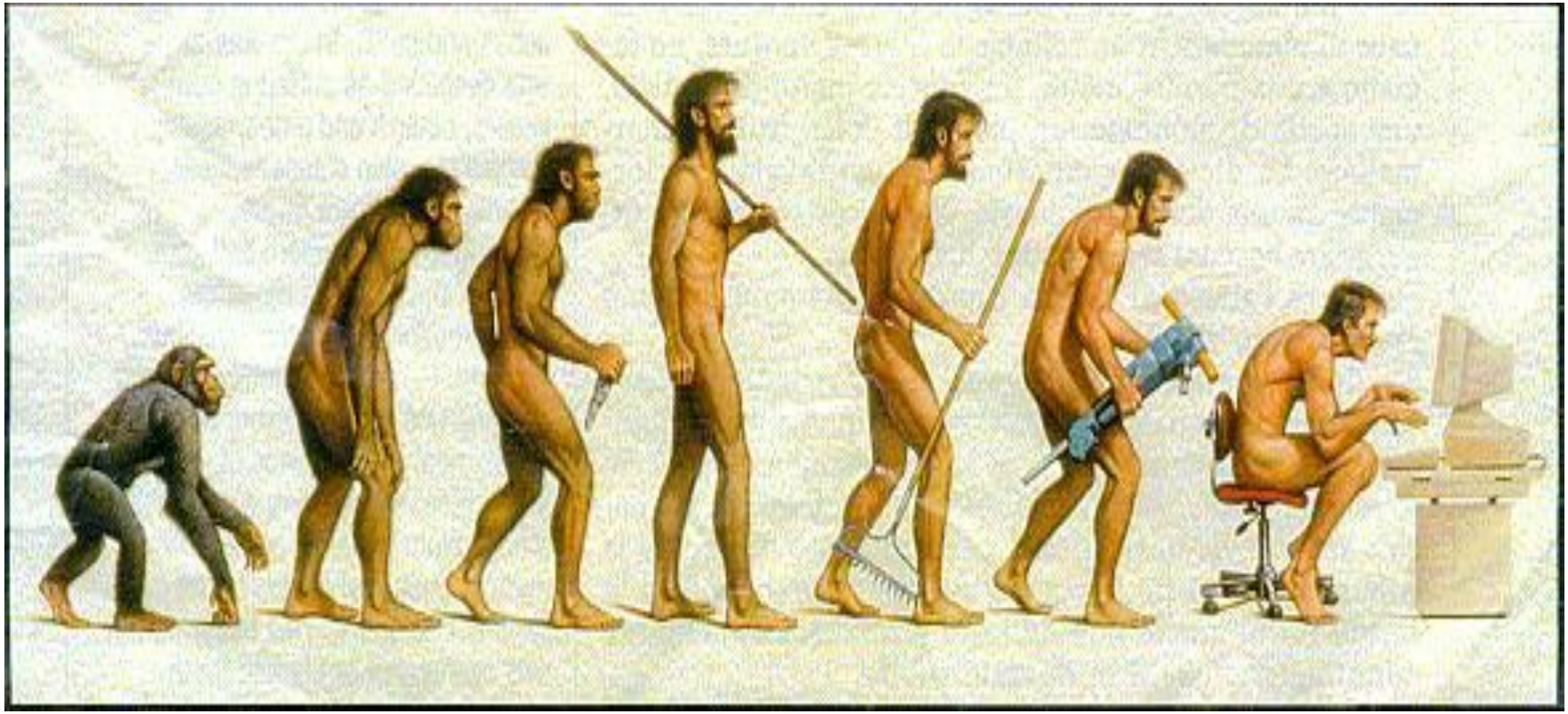
Evolution

- 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

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

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

EVOLUTION



Examples of EVOLUTION

- 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:

Genetic Evolution is a two stage process.

1: Production and redistribution of heritable **variation;**

2: Natural selection and other evolutionary mechanisms act on variation

(no change possible without variation)

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 and Gene Drift

- 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.
- In genetic drift, random variation occurs because the genetic population is small, leading to the proliferation of specific traits within a population.
  - Bema Indians and Diabetes
- To prevent genetic drift, genetic material must be shared between differing populations, even so, variations can occur.

Gene Flow

- 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. An example in humans is sickle cell anemia.
- Heterozygous Sickle Cell Anemia genotype gives a higher resistance to malaria,
- Homozygous genotype is still a disadvantage.
- Adaptation occurs on many levels.

Examples of Adaptation

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
- Long term adaptation - reduced surface area
  - Allen's Rule - Animals in warmer climates have longer extremities than those of the same species in cold climates
  - Bergmann's Rule- Animals in cold climates have larger body size than those of the same species in warm climates

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

Natural Selection

- The Adaptive Strategy of an organism is not the only thing which creates biological changes.
- 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.
- An example of sexual selection is found in peacocks. Male peacocks have large tails that were sexually selected for by female peacocks.

FOUR MAIN MECHANISMS DRIVING GENETIC EVOLUTION

- **Mutation**
- **Gene flow due to migration**
- **Genetic drift**
  - **Bottlenecks / founder effects**
- **Natural selection**
  - **Stabilizing**
  - **Directional**
  - **Diversifying**
  - **Sexual selection**

Drift and Selection

The two forces that determine the fate of alleles in a population

- **Drift**
  - **Change in allele frequencies due to sampling**
  - **a 'stochastic' process**
  - **Neutral variation is subject to drift**

- **Selection**
  - **Change in allele frequencies due to function**
  - **'deterministic'**
  - **Functional variation may be subject to selection (more later)**

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.

Mutation

Types and rates of mutation

Type	Mechanism	Frequency
Genome mutation	chromosome missegregation (e.g., aneuploidy)	10^{-2} per cell division
Chromosome mutation	chromosome rearrangement (e.g., translocation)	6 X 10^{-4} per cell division
Gene mutation	base pair mutation (e.g., point mutation, or small deletion or insertion	10^{-10} per base pair per cell division or 10^{-5} - 10^{-6} per locus per generation

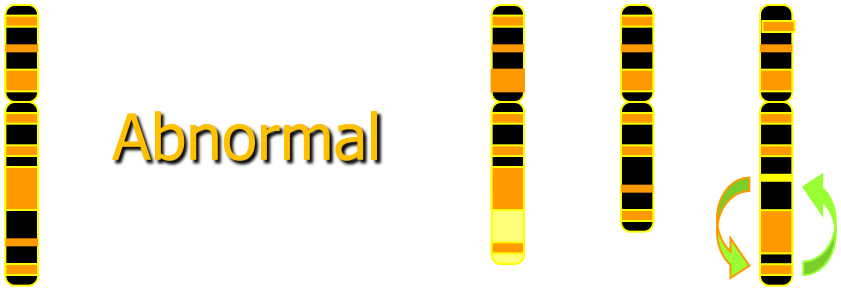
Types of Mutation and their Estimated Frequencies

Genome

(1/100 per cell div.)

Chromosome

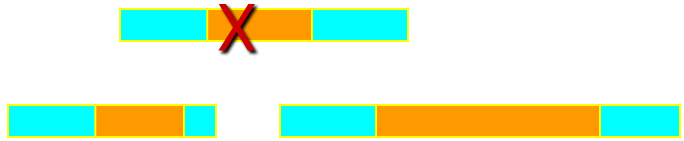
(1/ 1700 per cell div.)



Gene

normal

(1/10^{10}/bp per cell div.)



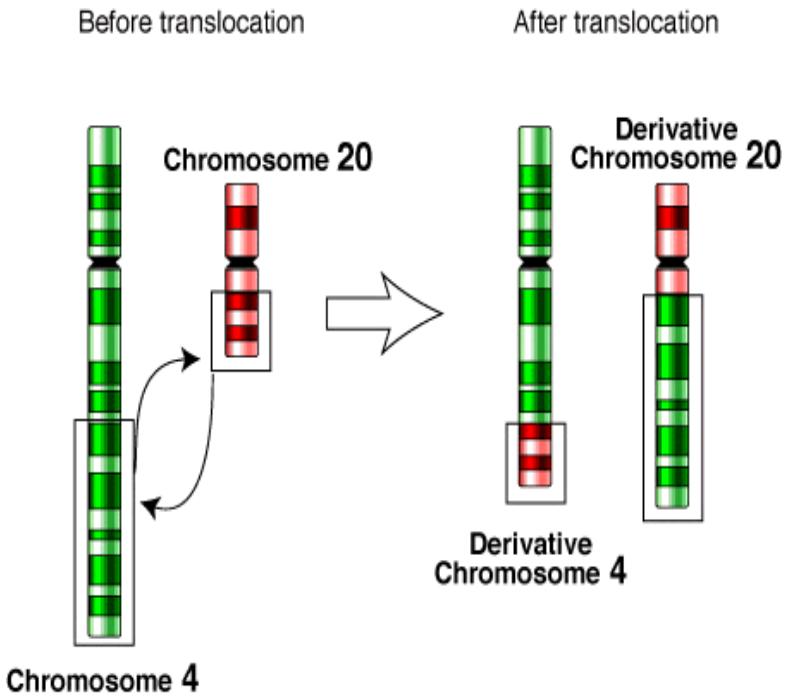
Small Scale Mutations

ATC**G**GAATAAAC

ATC**T**GAATAAAC

- Nucleotid Substitution
- Deletions or insertions

Large Scale Mutation



- Translocation
- Gain/Loss

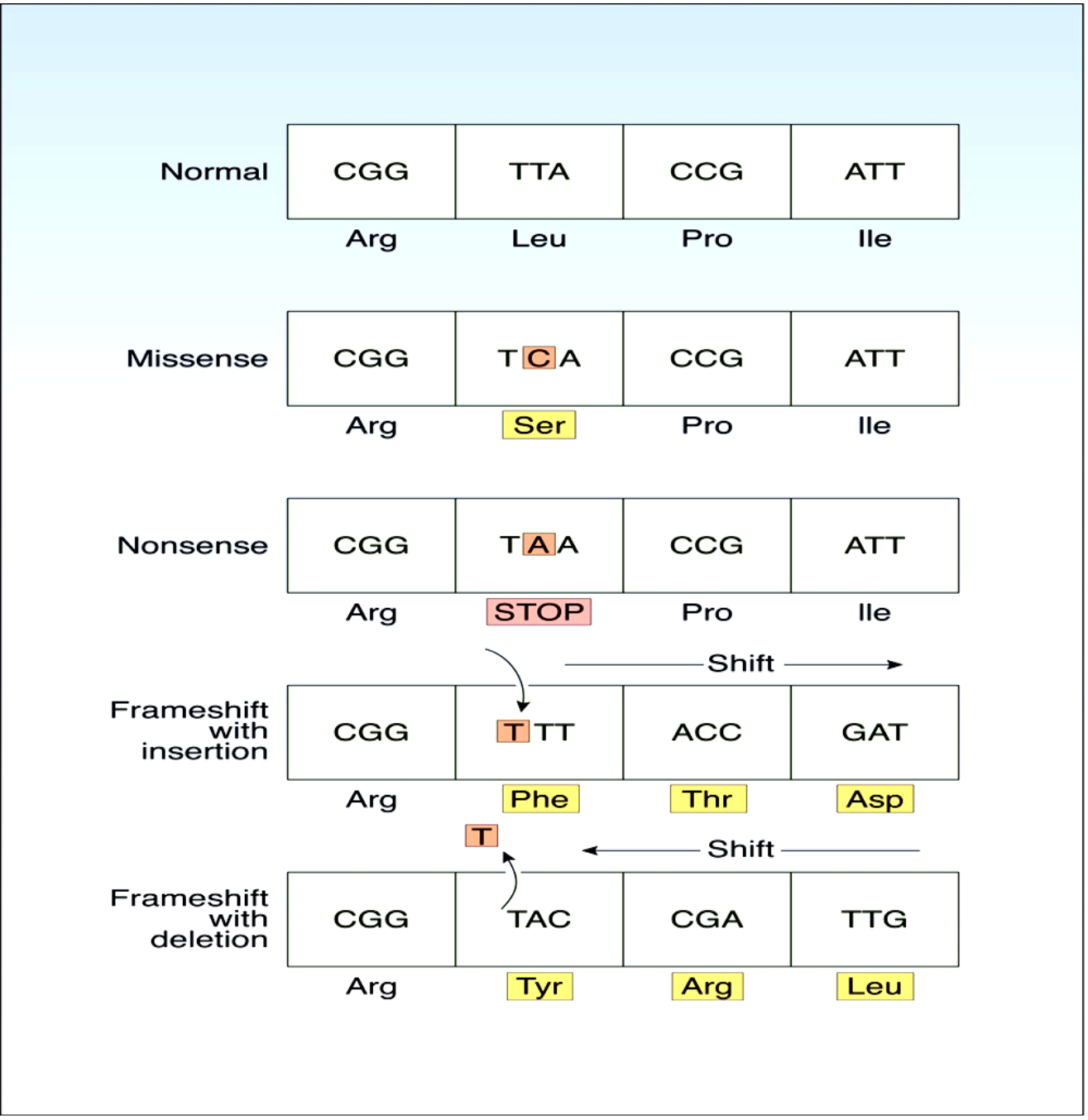
The DNA Between Individuals is Identical.

All differences are in the 0.1% of DNA that varies.

A
C
C
G
T
C
C
A
G
G

A
C
C
G
T
G
C
A
G
G

It's hard to believe sometimes!



UAA, UAG, UGA

Mutation Cause

Elongation

Forms of genetic variations

Single nucleotide substitution: replacement of one nucleotide with another

Microsatellites or minisatellites: these tandem repeats often present high levels of inter- and intra-specific polymorphism

Deletions or insertions: loss or addition of one or more nucleotides

Changes in chromosome number, segmental rearrangements and deletions

Microsatellite

di-, tri-, and tetra-nucleotide repeats

TGC**CACACACACACACACACA**GC
TGC**CACACACACA**------GC

TGC**TCATCATCATCA**GC
TGC**TCATCA**------GC

TGC**TCAGTCAGTCAGTCAG**GC
TGC**TCAGTCAG**--------GC

- The second abundant genetic variation in the human genome
- Usually have no functional effect, but some do

Minisatellite

6 - 64 bp repeating pattern

1 tgattggtct ctctgccacc gggagatttc cttatttgga ggtgatggag gatttc**agga**
61 **atttttagg** aatttttta atggattacg ggattttagg gttctaggat tttaggatta
121 tggtatttta ggatttactt gattttggga ttttaggatt gagggatttt agggtttcag
181 gatttcggga tttcaggatt ttaagttttc ttgattttat gattttaaga ttttaggatt
241 tacttgattt tgggatttta ggattacggg attttagggt ttcaggattt cgggatttca
301 ggattttaag ttttcttgat tttatgattt taagatttta ggatttactt gattttggga
361 ttttaggatt acgggatttt agggtgctca ctatttatag aactttcatg gtttaacata
421 ctgaatataa atgctctgct gctctcgctg atgtcattgt tctcataata cgttcctttg

These occur at more than 1000 locations in the human genome

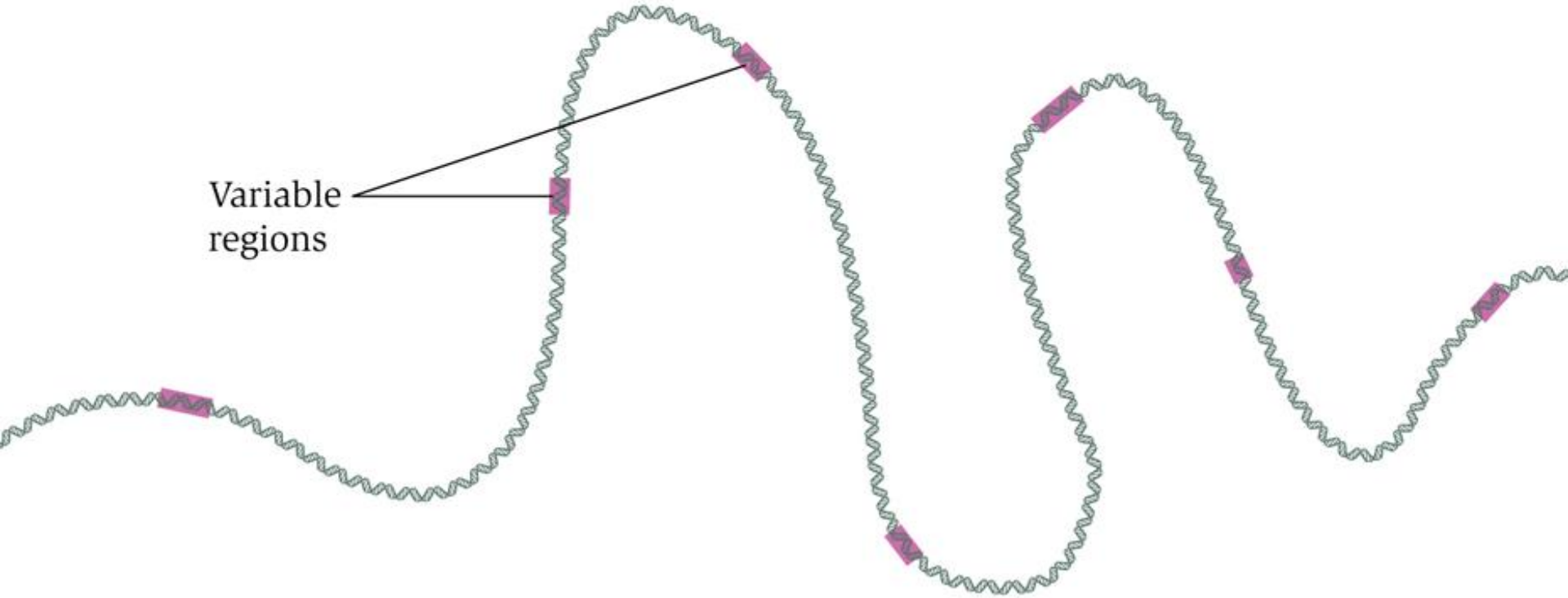
Usually have no functional effect

POLYMORPHISM

Some loci vary considerably among individuals if a locus has two or more alleles whose frequencies each exceeds 1% in a population

DNA DIFFERENCES BETWEEN INDIVIDUALS

- "Variable regions" at specific locations throughout the genome tend to differ between individuals.



Classification of SNPs

- **1. Coding SNPs**
  - **Synonymous:** when single base substitutions do not cause a change in the resultant amino acid
  - **Non-synonymous:** when single base substitutions cause a change in the resultant amino acid

- **2. Non-coding SNPs** that influence gene expression

- **3. Non-coding silent SNPs**

How many variations are present in the average human genome ?

- SNPs appear at least once per 0.3-1-kb average intervals.
- Considering the size of entire human genome ($3.2X10^9$ bp), the total number of **SNPs is around to 5-10 million**
- Potentially polymorphic microsatellites are **over 100,000 across** the human genome
- The **insertion/deletions** are very difficult to quantify and the number is likely to fall **in between SNPs and microsatellites**

Human Genetic Variation

Most abundant type:

SNPs-Single Nucleotide Polymorphisms

GATTTAGATCGCGATAGAG

GATTTAGATCTCGATAGAG

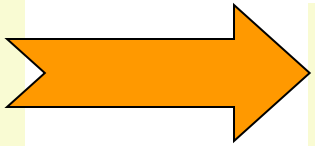
^

about 90% of all human genetic variations

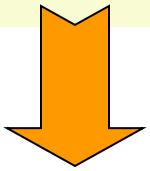
Life cycle of SNP

(long way from mutation to SNP)

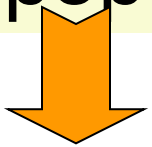
Appearance of new variant by mutation



Survival of rare allele



Increase in allele frequency after population expand



New allele is fixed in population as novel polymorphism

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

TAKE HOME MESSAGE:

Genetic variation increases a species' chance of survival

Variation = good ↑ survival