KARYOTYPE

The complete set of chromosomes that an organism possesses is called its karyotype and **usually presented as a picture of metaphase chromosomes lined up in descending order of their size**.

A karyotype **is an ordered display of magnified images of an individual's chromosomes arranged in pairs**. ì

Karyotype allow for the observation of:

- homologous chromosome pairs,
- chromosome number
- chromosome structure

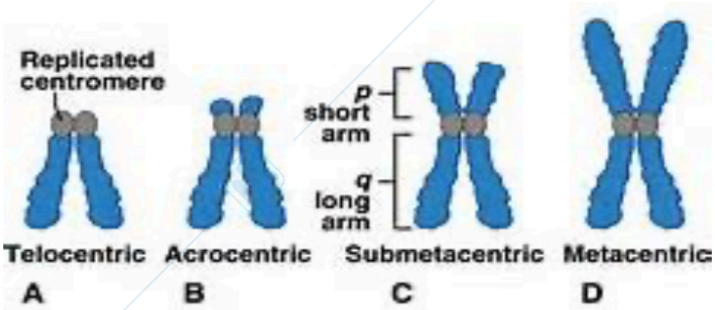
A human karyotype consists of 46 chromosomes.

POSITION

Each chromosome has two arms, labeled *p* (the shorter of the two) and *q* (the longer). Many remember that the short arm 'p' is named for the French word "petit" meaning 'small', although this explanation was shown to be apocryphal.

They can be connected in either metacentric, submetacentric, acrocentric or telocentric manner.

A. **Telocentric**: the centromere is at or very near the end of the chromosome
B. **Acrocentric**: the centromere is near one end, producing a long arm and a knob, or satellite, at the other.
C. **Submetacentric**: the centromere is displaced toward one end, creating a long arm and a short arm (on human chromosomes, the short armi s designated by the letter p and the long arm by the letter q).
D. **Metacentric**: the centromere is locaded approximately in the middle, and so the chromosome has two arms of equal length.



PROCEDURE OF CHROMOSOME PREPARATION FROM PERIPHERAL BLOOD

1. Inoculate approximately 0.5 mL of heparinized whole blood into a glass or plastic tube with 10 mL of medium.
2. Incubate the culture at 37°C in 5% CO_2 atmosphere for 72 hr.
3. Add 0.5 µg/mL of KaryoMAX Colcemid Solution to each culture tube.
4. Incubate the culture for an additional 15–30 min.
5. Transfer the culture to a centrifuge tube and spin at 500 x *g* for 5 min.
6. Remove the supernatant and re-suspend the cells in 5–10 mL of hypotonic 0.075M KCl.
7. Incubate at 37°C for 10–12 min.
8. Spin at 500 x *g* for 5 min.
9. Remove the supernatant, agitate the cellular sediment and add drop-by-drop 5–10 mL of fresh, ice-cold fixative made up of 1 part acetic acid to 3 parts methanol. Leave in 4°C for 10 min.
10. Repeat steps 7 and 8.
11. Spin at 500 x *g* for 5 min.
12. Resuspend the cell pellet in a small volume (0.5–1 mL) of fresh fixative, drop onto a clean slide, and allow to air dry.

At this stage, the preparation can be stained with Orecin or Giemsa. Giemsa banding has become the most widely used technique, and the most common method to obtain this staining is to treat slides with Trypsin-EDTA (0.5%)

CHROMOSOME BANDING

Chromosomes are stained with various dyes enabling the chromosome segments to be identified.
I cromosomi sono colorati con vari coloranti che consentono di identificare i segmenti cromosomici

Most methods can distinguish 550 bands/haploid set.
High resolution methods can distinguish up to 850 bands/haploid set that can allow identification of small interstitial deletions.
La maggior parte dei metodi può distinguere 550 bande / set aploide.
I metodi ad alta risoluzione possono distinguere fino a 850 bande / set aploide che possono consentire l'identificazione di piccole delezioni interstiziali.

AMNIOCENTESIS VS CHORIONIC VILLUS SAMPLING (CVS)

- **Amniocentesis** usually done at 14-16 wks. Cells must be cultured for several weeks before tests can be done.

Needle inserted through abdomen to extract amniotic fluid. The amniotic fluide is centrifugate and the fetal cells are located at the bottom of the medical test tube. The cells wait for several weeks in a colture and then analyse and we obtain the karyotyping.

- **CVS** can be done at 8-12 wks. Can perform tests on cells immediately.

Suction tube inserted through cervix to extract chorionic villus tissue from the placenta. After several hours it's obtained the karyotyoping.

- **FISH** fluorescence in situ hybridization

Fluorescent probes are used to localize genes, characterise chromosome alterations as translocations, deletions but also number chromosomes.

TYPES OF CHROMOSOMAL ANOMALIES: ATERATIONS IN STRUCTURE AND NUMBER

There are many types of chromosome anomalies.They can be organized into two basic groups:

1. **NUMERICAL**: animalies in the number of chromosomes are called aneuploidies and consist in the presence of more or less copies of a chromosome.

They result from an alteration in the separation (non-disjunction) of chromosomes during the formation of gametes and in most cases involve the autosomal chromosomes. These types of anomalies are almost always lethal for the fetus that is aborted, while when they are compatible with life they are associated with specific conditions.

Among the aneuploidies of **autosomes** are:
a) Down syndrome (Trisomy 21): 47 chromosomes (+1 on chromosome 21)
b) Patau syndrome (Trisomy 13): 47 chromosomes (+1 on chromosome 13)
c) Edwards syndrome (Trisomy 18): 47 chromosomes (+1 on chromosome 18)

Among the aneuploidies of the **sex chromosomes** are:
a) Turner syndrome
b) Klinefelter syndrome
c) Triple X syndrome

There are also cells called polyploids, which are cells that contain multiples of the entire series of chromosomes (multiple karyotype). **Polyploidy** is a condition in which the cells of an organism have more than two paired (homologous) sets of chromosomes. True polyploidy occurs in humans, although it occurs in some tissues (especially in the liver).

2. **STRUCTURAL**

They consist in the change of the structure of chromosomes during meiosis and can cause the addition or loss of chromosomal material that is broken and rearranged.

Often these breaks or rearrangements are repaired in a natural way, but when this is not the case, anomalies appear, which can be classified into two groups:

- Balanced: with no apparent loss or gain of genetic material
- Unbalanced: with loss or gain of genetic material

a. **deletion** (a deletion removes a chromosomal segment),
b. **duplication** (a duplication repeats a segment),
c. **inversion** (an inversion reverses a segment within a chromosome)
   - Pericentric inversion: when the centromere is included in the inverted section, i.e. the two breaking points are respectively on the arm p and q.
   - Paracentric inversion: they show breaking points on the same arm (or p, or q) and therefore do not include the centromere.
d. **translocation** (a traslocation moves a segment from one chromosome to another, non homologous one) are types of demage that can occur to chromosomes during meiosis.

In Translocation a portion of one chromosome is transferred to another chromosome. There are two main types of translocations:

- Reciprocal translocation: segments from two different chromosomes have been exchanged.
- Robertsonian translocation: an entire chromosome has attached to another at the centromere – in humans these only occour with chromosomes 13, 14, 15, 21 and 22.

Depending on the chromosomal tract involved, the resulting clinical conditions are very different from each other.
The most common causes of disease are, for example:

Williams syndrome is caused by the micro-deletion of the q11.23 region of chromosome 7
Williams syndrome is a rare genetic disease that occurs from birth or early childhood with several features such as congenital heart disease, blood vessel defects, a particular aspect of the face (small head, wide forehead, thick lips, "full" aspect of the cheeks and of the tissues around the eyes). Affected children show psychomotor retardation, difficulty in coordinating movements and have an extreme variability in the degree of mental development, with more or less severe delay. They have good language skills, often suffer from visual and dental disorders, can develop kidney disorders and a certain tendency to hypertension.

Cri-du-chat syndrome is caused by the partial deletion of the short arm of chromosome 5
The cri du chat syndrome is a genetic syndrome characterized by psychomotor retardation, microcephaly, facial abnormalities (wide nasal saddle, epicanthus, small jaw) and the emission of a very typical cry (acute and monotonous, similar to the meow of a cat) by patients during early childhood. This type of crying is mainly caused by structural abnormalities of the larynx and central nervous system.

RECIPROCAL TRANSLOCATIONS may create deleterious effects.
A common human translocation (8;14) involving My cis critical to the development of Burkitt lymphoma. Malfunctions in Myc have also been found in carcinoma of the cervix, colon, breast, lung and stomach.
In the human genome, Mycis located on chromosome 8 and is believed to regulate expression of 15% of all genes.

ROBERTSONIAN TRANSLOCATION frequently observed anomaly (1:100 new-borns) is the Robertsonian translocation, which occurs between two acrocentric chromosomes of groups G and D. it is also referred to as the centric fusion of two acrocentric chromosomes.

Carriers of such Robertsonian translocations are phenotypically inconspicuous. Also, here, though, problems arise when it comes to gamete formation because, normally, the diploid chromosome set is halved thereby.

NON-DISJUNCTION

Both **mitosis** and **meiosis** consist of an anaphase stage (two in meiosis) during which the chromosome separate to opposite poles of the cell.
This separation processes is known as disjunction

Nondisjunction is the process by which the chromosomes fail to separate correctly causing an incorrect number of chromosomes variation to the number (46 chromosomes) leads to a condition called **aneuploidy**

Primary nondisjunction occurs during meiosis I when both members of a homologous pair go into the same daughter cell. No normal gametes produced.

During **anaphase II** chromatids fail to separate as in mitosis. Only **50% of gametes are abnormal**
If non-disjunction occurs in a secondary spermatocyte undergoing meiosis II, then only two of the four sperm will be abnormal.

EXAMPLES OF NON-DISJUNCTION ANEUPLOIDIES

AUTOSOMAL TRIPLOIDIES SUCH AS:

- Down's syndrome
- Edwards syndrome
- Patau's syndrome

SEX TRIPLOIDIES SUCH AS:

- Klinefelter's syndrome
- Triple x syndrome
- XYY condition

MONOSOMIES SUCH AS:

- Turner's syndrome

AUTOSOMAL TRIPLOIDIES

1. DOWN'S SYNDROME

Down syndrome or **Down's syndrome**, also known as **trisomy 21**, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. The main causes are meiotic nondisjunction (95% trisomy 21).

It is usually associated with physical growth delays, mild to moderate intellectual disability, and characteristic facial features.[1] The average IQ of a young adult with Down syndrome is 50, equivalent to the mental ability of an 8- or 9-year-old child, but this can vary widely.

The parents of the affected individual are usually genetically normal.
The probability increases from less than 0.1% in 20-year-old mothers to 3% in those of age 45.

2. EDWARDS SYNDROME
47, XY+18, 47, XX+18

Edwards syndrome, also known as **trisomy 18**, is a genetic disorder caused by the presence of a third copy of all or part of chromosome 18.
Many parts of the body are affected. Babies are often born small and have heart defects. Other features include a small head, small jaw, clenched fists with overlapping fingers, and severe intellectual disability.
Most cases of Edwards syndrome occur due to problems during the formation of the reproductive cells or during early development. The rate of disease increases with the mother's age

Edwards syndrome occurs in around 1 in 5,000 live births.

3. PATAU SYNDROME

Patau syndrome is a syndrome caused by a chromosomal abnormality, in which some or all of the cells of the body contain extra genetic material from chromosome 13. The extra genetic material disrupts normal development, causing multiple and complex organ defects.

Patau syndrome affects somewhere between 1 in 10,000 and 1 in 21,700 live births.
More than 80% of children with Patau syndrome **die within the first year of life.**

Of those fetuses that do survive to gestation and birth, common abnormalities may include:

- Nervous system
  - Intellectual disability and motor disorder
  - Microcephaly
- Musculoskeletal and cutaneous
  - Polydactyly (extra digits)
  - Cyclopia
  - Prominent heel
  - Abnormal palm pattern
  - Overlapping of fingers over thumb
  - Cutis aplasia (missing portion of the skin/hair)
  - Cleft lip and palate
- Urogenital
  - Abnormal genitalia
- Other
  - Heart defects (ventricular septal defect) (Patent Ductus Arteriosus)
  - Dextrocardia
  - Single umbilical artery

SEX ANOMALIES

Sex triploidies such as **Klinefelter's syndrome, Triple X syndrome, XYY condition**

1. KLINEFELTER'S SYNDROME

Not to be confused with XYY syndrome.

Klinefelter syndrome (**KS**), also known as **47,XXY** is the set of symptoms that result from two or more X chromosomes in males. The primary features are infertility and small poorly functioning testicles. Often, symptoms are subtle and subjects do not realize they are affected. Sometimes, symptoms are more evident and may include weaker muscles, greater height, poor coordination, less body hair, breast growth, and less interest in sex. Often it is only at puberty that these symptoms are noticed. Intelligence is usually normal; however, reading difficulties and problems with speech are more common. Symptoms are typically more severe if three or more X chromosomes are present (48,XXXY syndrome or 49,XXXXY syndrome).

2. TRIPLE X SYNDROME

Triple X syndrome, also known as **trisomy X** and **47, XXX**, is characterized by the presence of an extra X chromosome in each cell of a female. Those affected are often taller than average. Usually there are no other physical differences and normal fertility. Occasionally there are learning difficulties, decreased muscle tone, seizures, or kidney problems.

3. XYY CONDITION

XYY syndrome or Jacob syndrome is a genetic condition in which a male has an extra Y chromosome.

The extra Y chromosome in 47, XYY males can be generated by at least two mechanisms:

- **paternal non-disjunction at meiosis II** after normal chiasmate meiosis I (**84%)**
- **postzygoticmitoticerror(16%)**.

There are usually few symptoms. These may include being taller than average, acne, and an increased risk of learning problems. The person is generally otherwise normal, including normal fertility.

Males with an extra Y chromosome are **mostly fertile**. However, as in the general male population, semen parameters may vary from **normozoospermia** to **severe oligozoospermia**

4. TURNER SYNDROME

Turner syndrome (**TS**), also known **45,X**, or **45,X0**, is a genetic condition in which a female is partly or completely missing an X chromosome. Signs and symptoms vary among those affected. Often, a short and webbed neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth. Typically, they develop menstrual periods and breasts only with hormone treatment, and are unable to have children without reproductive technology. Heart defects, diabetes, and low thyroid hormone occur more frequently. Most people with TS have normal intelligence. Many have troubles with spatial visualization that may be needed for mathematics. Vision and hearing problems occur more often.

ALLELES
Maternal and paternal homologs carry the same genes, but genes occur in variant versions called alleles. One allele is **dominant,** the other **recessive or hidden.**

An individual that possesses **two identical alleles** is said to be **homozygous** for this trait.
An individual that receives **two dissimilar alleles** is **heterozygous** for that trait.
The appearance is the **phenotype,** the genetic type is the **genotype (PP** – homozygous for the dominant allele, **Pp** – heterozygous, **pp** – homozygous for the recessive allele**)**.

GREGOR MENDEL

Johann Gregor Mendel (1822–1884), often called the "father of genetics," was a teacher, lifelong learner, scientist, and man of faith.

In 1856, Mendel began a decade-long research project to investigate patterns of inheritance.
He began his research using peas as his primary model system
A **model system** is an organism that makes it easy for a researcher to investigate a particular scientific question, such as how traits are inherited.

Mendel chose to study **pea plants (**because they are easy to cultivate in large numbers and could be raised in a small space, as an abbey garden).

Mendel studied the inheritance of seven different features in peas, including **height**, **flower colour**, **flower position**, **pod shapes**, **pod colour**, **seed colour**, and **seed shape**. To do so, he first established pea lines with two different forms of a feature, such as tall vs. short. He grew these lines for generations until they were pure-breeding (always produced offspring identical to the parent), then bred them to each other and observed how the traits were inherited.

FIRST GENERATION
Mendel took the unique approach of studying **each trait one at a time.**
He would cross-pollinate **two of this true-breeding contrasting** varieties.
Mendel crossed plants producing **yellow peas** with plants producing **green peas** and discovered that the resulting **hybrid offspring**, called **first filial or F1, generation all had yellow peas (only reassembles one of the two parents).**

SECOND GENERATION
Mendel took his breeding experiments to the next step: **he crossed the F1 plants with one another** (**or allowed them to self-fertilize**) and examined the results.
He found in F2 that «the disappearing trait» returned, although **three quarters of the offspring had yellow peas and one quarter had green peas (3:1 ratio).**

With his experiments he found very similar patterns of inheritance for all seven features he studied:

- One form of a feature, such as yellow, always concealed (hide) the other form, such as green, in the first generation after the cross. Mendel called the visible form the **dominant trait** and the hidden form the **recessive trait**.
- In the second generation, after plants were allowed to self-fertilize (pollinate themselves), the hidden form of the trait reappeared in a minority of the plants. Specifically, there were always about 3 plants that showed the dominant trait (e.g., yellow) for every 1 plant that showed the recessive trait (e.g., green), making a 3:1 ratio.
- Mendel also found that the features were inherited independently: one feature, such as plant height, did not influence inheritance of other features, such as flower colour or seed shape.

THREE LAWS – MENDEL'S LAWS

1. **Law of dominance**
   This is also called Mendel's first law of inheritance. According to the law of dominance, hybrid offspring (prole) will only inherit the dominant trait in the phenotype. The alleles that are suppressed are called as the recessive traits while the alleles that determine the trait are known as the dormant traits.

2. **Law of independent assortment**

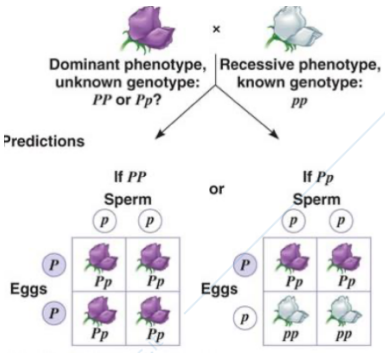
Also known as Mendel's second law of inheritance. Genes for different traits are inherited independently of each other. Example – seed colour and flower colour are inherited sparely. Law is only true if the genes are far apart the genome.

3. **Law of segregation**

This is also known as Mendel's third law of inheritance. The law of segregation states that during the production of gametes, two copies of each hereditary factor segregate so that offspring acquire one factor from each parent. In other words, allele (alternative form of the gene) pairs segregate during the formation of gamete and re-unite randomly during fertilization.

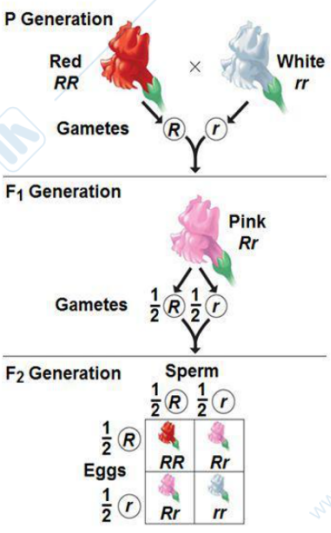
TEST CROSS

Used to find the true genotype of a plant or animal that is dominant. They could be homozygous dominant (RR) or heterozygous dominant (Rr) we don't know until we perform the cross.



VARIATIONS ON MENDEL'S LAWS

- **Incomplete dominance:** F1 has an appearance in between the two parental phenotypes
- **Codominance:** both alleles are fully expressed in heterozygous individuals
- **Pleiotropy:** single gene influences more than one character
- **Polygenic Inhertitance:** additive effects of two or more genes on a single phenotype
- **Environmental Factors:** non-genetic, non-hereditary factors that contribute to phenotype



MEDELIAN GENETC DISEASE

Disease in which the phenotypes are largely determined by the action, lack of action, of mutations at individual loci.
Rare 1% of all live born individuals

4 types of inheritance:

1. Autosomal dominant: involves a dominant allele on a non sex chromosome
2. Autosomal recessive: involves a recessive allele on a non sex chromosome
3. X linked dominant or recessive (involves a recessive allele on the X chromosome)
4. Y linked: involves an allele on the Y chromosome

Most of mendelian disorders are autosomal (12.000), followed by X chromosome linked (760).
The remaining few are Y chromosome linked and mitochondrial disorders

GENETIC COUNSELING

Pedigrees: a pedigree is a biological family tree that shows the interrelationship between parents and children across generations.
Helps illustrate a pattern of inheritance for a single trait through that family.

In a diagnosis approaches of genetic diseases, the **sample used** can be blood, **amniotic fluid**, skin, hair, different kind of cells.
The **approaches** can be chromosome analysis, biochemical test, enzyme analysis, gene analysis, **pedigree analysis**, dermatoglyphics.

The treatment of genetic diseases: most genetic diseases couldn't be cured. Better care from family, better welfare of the society, function training, gene therapy has shown us a bright future.

MENDELIAN GENETICS AND HUMANS

TABLE 11.3 SOME IMPORTANT GENETIC DISORDERS

Disorder	Symptom	Defect	Dominant/Recessive	Frequency Among Human Births
Cystic fibrosis	Mucus clogs lungs, liver, and pancreas	Failure of chloride ion transport mechanism	Recessive	1/2,500 (Caucasians)
Sickle-cell anemia	Poor blood circulation	Abnormal hemoglobin molecules	Recessive	1/625 (African Americans)
Tay-Sachs disease	Deterioration of central nervous system in infancy	Defective enzyme (hexosaminidase A)	Recessive	1/3,500 (Ashkenazi Jews)
Phenylketonuria	Brain fails to develop in infancy	Defective enzyme (phenylalanine hydroxylase)	Recessive	1/12,000
Hemophilia	Blood fails to clot	Defective blood-clotting factor VIII	Sex-linked recessive	1/10,000 (Caucasian males)
Huntington's disease	Brain tissue gradually deteriorates in middle age	Production of an inhibitor of brain cell metabolism	Dominant	1/24,000
Muscular dystrophy (Duchenne)	Muscles waste away	Degradation of myelin coating of nerves stimulating muscles	Sex-linked recessive	1/3,700 (males)
Congenital hypothyroidism	Increased birth weight, puffy face, constipation, lethargy	Failure of proper thyroid development	Recessive	1/1,000 (Hispanics) 1/700 (Native Americans)
Hypercholesterolemia	Excessive cholesterol levels in blood, leading to heart disease	Abnormal form of cholesterol cell surface receptor	Dominant	1/500

AUTOSOMAL RECESSIVE DISEASE

An autosomal recessive trait (disease) is expressed only when the **mutant gene is present in a double dose (homozygous state)**.
Both parents are heterozygous and possess one copy of the mutant gene and one copy of the normal or functional gene.

Autosomal recessive traits are characterized as follows:

- (1) there is rarely a positive family history outside the affected sibship;
- (2) males and females are equally likely to be affected;
- (3) heterozygous parents have a 25% chance of producing an offspring affected with the disease. (su 4 figli: 1 completamente sano, 2 portatori sani, 1 malato)

CYSTIC FIBROSIS

This autosomal recessive condition is the **most common recessive condition** affecting **whites**, with a carrier frequency of **one in 29**.

Cystic fibrosis is caused by a mutation in the **CFTR gene, a chloride ion channel in epithelial cells**.
Mutations in this gene cause severe **lung disease and pancreatic insufficiency** in the classic form but may result in milder phenotypes, including only congenital bilateral absence of the vas deferens in some affected males.
The most common mutation is **delta-F508**, the deletion of **a phenylalanine residue at position 508**, which accounts for 70% of the mutations in the white population.
To date, however, there are more than **1000 known mutations** throughout the gene that can cause disease.

HEMOGLOBINOPATHIES

In the **hemoglobinopathies**, the specific disorder may be considered **recessive**

THALASSEMIA

Autosomal recessive disorder of haemoglobin that results in haemolytic anaemia.
Frequently encountered in people of Mediterranean or south Asian ancestry.
There are multiple forms of thalassemia's imbalance of alpha and beta chains results in rapid erythrocyte destruction and turnover with a chronic haemolyoc anaemia.
Silent carriers and persona with alpha thalassemia trait or beta thalassemia trait (also called carriers) usually have no symptoms. Those with alpha or beta thalassemia trait often have mild anaemia that may be found by a blood test.

PHENYLKETONURIA (PKU)

Phenylketonuria (**PKU**) is an inborn error of metabolism that results in decreased metabolism of the amino acid phenylalanine.
Untreated, PKU can lead to intellectual disability, seizures, behavioural problems, and mental disorders. It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight.

TAY SACHS DISEASE

Tay–Sachs disease is a genetic disorder that results in the destruction of nerve cells in the brain and spinal cord. The most common form is infantile Tay–Sachs disease which becomes apparent around three to six months of age, with the baby losing the ability to turn over, sit, or crawl.

AUTOSOMAL DOMINANT DISEASES

Autosomal dominant traits manifest in the heterozygous state (single-gene dose) and are characterized by the following:

(1) they can be **transmitted from generation to generation**. Only one allele is required to contain a mutation;
(2) the probability that a person carrying the gene will pass it on to offspring is **50%.** A parent has a 50% chance of passing the mutation to each offspring;
(3) **males and females are equally likely to be affected**.

Examples:

- Marfan syndrome
- neurofibromatosis
- Huntington's disease

HUNTINGTON'S DISEASE

HD is also caused by a **mutation involving a trinucleotide repeat sequence**.
The full mutation range is between **38 and 100 copies**.
There is **an intermediate range of 32–38** repeats, and there are examples of both affected and unaffected persons with this number of repeats.

Although predictive testing can offer freedom from the psychological burdens associated with being at risk if the person does not carry the mutation, the impact on persons found to have the gene can be devastating.

Those found to carry the gene face the inevitability of a disease for which there is currently no treatment.

MARFAN SYNDROME

Marfan syndrome is an autosomal dominant disorder that affects the body's **connective tissue** (prolasso del tessuto connettivo). It is caused by a mutation in the gene of the protein fibrillin-1
This mutation results in an increase of transforming growth factor beta (TGF-β).
Because connective tissue is found throughout the body, **features of the disorder are most often found in the heart, blood vessels, bones, joints, and eyes.**

FAMILIAL HYPERCHPLESTEROLEMIA FH

Monogenic disorder, autosomal dominant, rare.
LDL receptor gene mutations
Very high plasma cholesterol e LDL-C levels
Lipid deposits at eyelids, tendon, hand, cornea
Heterozygotes: also symptomatic, develop CHD at the age of 20s-50s

Increased risk of coronary heart disease
Prevalence estimates at 1/1500 in the UK (approx. 100000 people in the UK have FH, approx. 85% of these remain undiagnosed).

X – LINKED INHERITANCE

The following are characteristics of X- linked inheritance:
(1) there is **no male-to-male transmission;**
(2) all daughters of an affected male receive the mutant gene and are therefore **carriers**;
(3) one-half the sons and daughters of a heterozygous female receive the mutant gene.

The distinction between X-linked dominant and X-linked recessive is unclear, but in general, X-linked recessive refers to **a trait that is not clinically expressed in the heterozygous female**, and **X-linked dominant to a trait that is expressed in the heterozygous female**.

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder affecting one in 3,500 males. The disease is caused by **a mutation in the dystrophin gene.**

HAEMOPHILIA

Rare bleeding disorders due to inherited deficiencies in coagulation factors
Types:

1. Haemophilia A (classic) Factor VIII deficiency
2. Haemophilia B (Christmas disease) factor IX deficiency
3. Von Willebrand's disease bleeding disorder with low levels of Factor VIII but also an abnormality of platelet adhesiveness.

FRAGILE X SYNDROME

Is the most common inherited form of mental retardation, affecting approximately one in 4,000 men and one in 8,000 women
Has a wide range of clinical presentations, including moderate disabilities in females, autism, and other psychiatric disorders
This variable clinical phenotype reflects the novel mutation in the gene known as **fragile X mental retardation 1 (FMR1).**

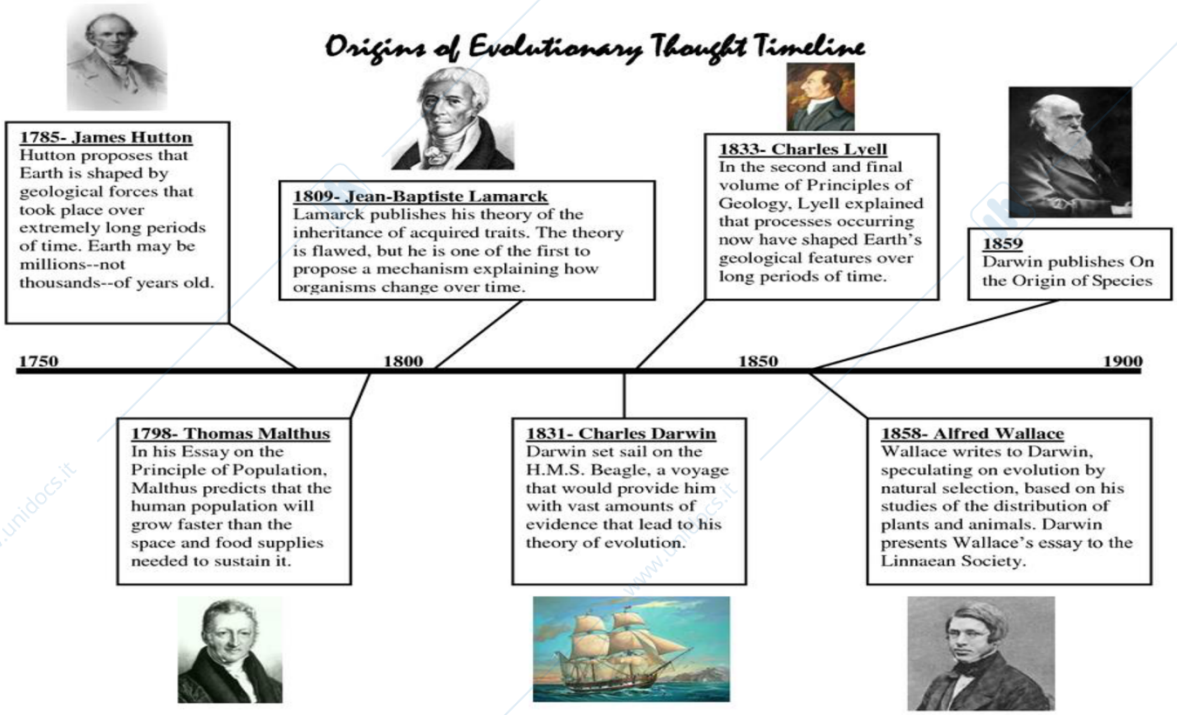
Physical male characteristics: Large, protruding ears, Long, narrow face, Prominent chin, Prominent forehead, Double jointed fingers, Flat feet.

Y LINKED INHERITANCE (HOLANDRIC TRAITS)

chromosome is inherited from father to son **Y linkage**, also known as **holandric inheritance**
Describes traits that are produced by genes located on the Y chromosome. It is a form of sex linkage.

We will now look at how various kinds of traits (traits = tratto) are inherited from a pedigree point of view.
Traits on the Y chromosome are only found in males, never in females.
Dominance is irrelevant: there is only 1 copy of each Y-linked gene (hemizygous).

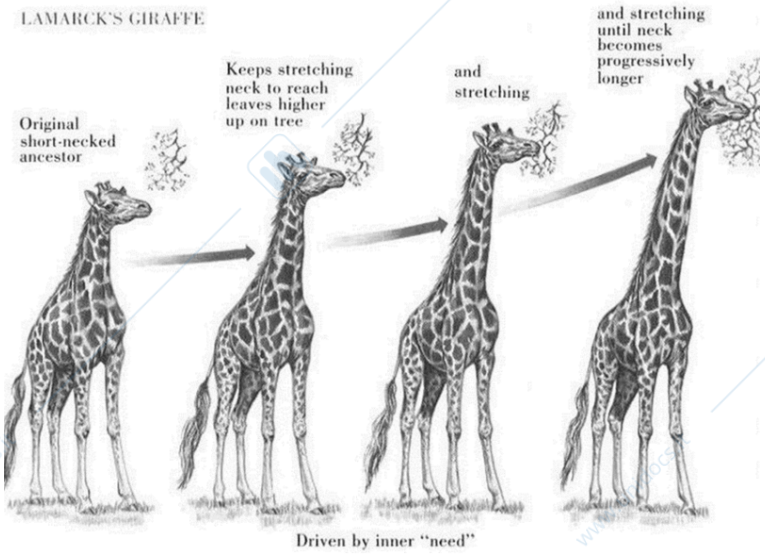
THEORIES OF EVOLUTION



JEAN BAPTISTE LAMARCK

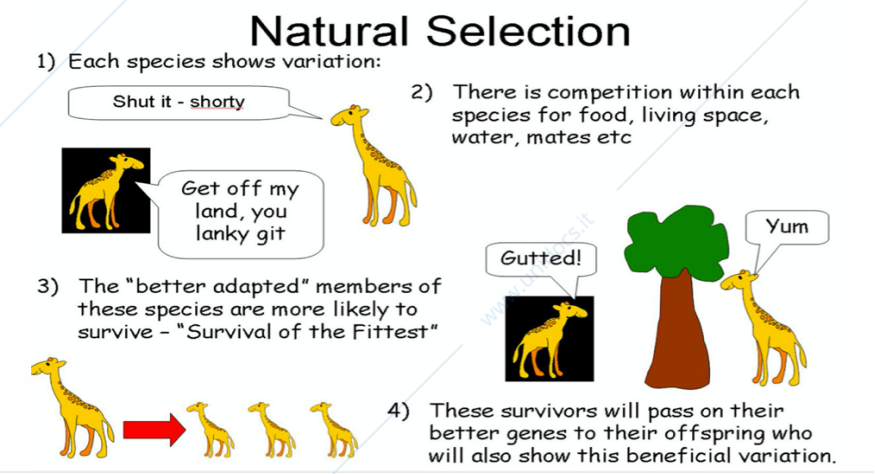
Jean Baptiste Lamarck – 1809 French Biologist: proposed that life evolves or changes.
Explained evolution as a process of adaptation.
Law of use and disuse. New organs arise according to the needs of an organism, and their size is determined by the degree to which they are used.
Inheritance of acquired characteristics. Useful characteristics acquired by an individual during its lifetime can be passed on to its offspring. No evidence to support this theory.

Lamarck believed that giraffes stretched their necks to reach food. Their offspring and later generations inherited the resulting long necks.



CHARLES DARWIN
Born in England, February 12, 1809.
Ships naturalist on a trip around the world aboard the HMS Beagle.
During his travels, Darwin made numerous observations and evidence that lead him to propose a revolutionary hypothesis about the way life changes over time

Darwin and his theory of evolution by natural selection: evolution – changes in populations over time. Charles Darwin was the first to propose a feasible mechanism for evolution. It is called natural selection.



The theory of evolution by Natural Selection
There are 5 key observation:

1. in each generation, populations produce more offspring than there are adults
2. population do not continue to grow in size
3. food and many other resources are limited
4. individuals within all population vary
5. many variations are heritable (some individuals will inherit characteristics that give them a better chance of surviving and reproducing).

Over time the population changes as advantageous heritable characteristics become more common generation after generation.

Summary of Darwin's Theory

5. Individuals best suited to their environment survive and reproduce most successfully. The characteristics that make them best suited to their environment are passed on to offspring. Individuals whose characteristics are not as well suited to their environment die or leave fewer offspring.
6. Species change over time. Over long periods, natural selection causes changes in the characteristics of a species, such as in size and form. New species arise, and other species disappear.
7. Species alive today have descended with modification from species that lived in the past.
8. All organisms on Earth are united into a single tree of life by common descent.

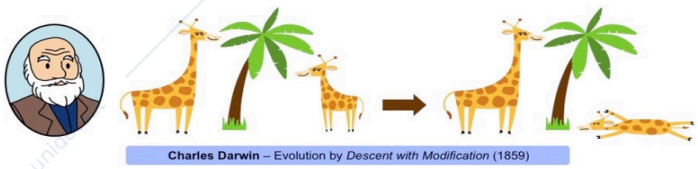
Summary of Darwin's Theory

Individual organisms in nature differ from one another. Some of this variation is inherited

Organisms in nature produce more offspring than can survive, and many of those that survive do not reproduce.

Because more organisms are produced than can survive, members of each species must compete for resources.

Because each organism is unique, each has different advantages and disadvantages in the struggle for existence.



Charles Darwin – Evolution by *Descent with Modification* (1859)

Long-necked giraffes are randomly born and have more offspring due to their competitive advantage

The 5 areas of scientific study provide evidence for evolution.

1. Fossil record
2. Comparative anatomy
3. Comparative embryology
4. Molecular biology
5. Biogeography

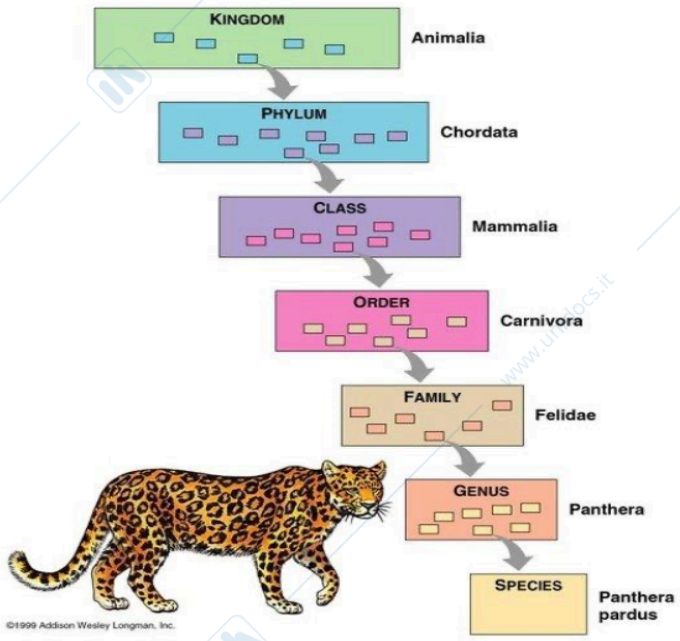
DEFINITIONS OF SPECIES

Biological species concept – species defined as populations of individuals that can produce viable offspring.
Probably the most well-known definition of a species.
Hybridisation (female horse male donkey = mule (hybrid), (rarely, male horse and female donkey = hinny (hybrid).

Morphological species concept – classified as the same species if organisms find into the same morphological criteria.
Classical definition going back to the days on Carl Linnaeus – the father of taxonomy.

CAROLUS VON LINNAEUS (1707-1778) Swedish scientist who laid the foundation for modern taxonomy

STANDARD SYSTEM OF NAMING SPECIES



THE SPECIES

Speciation is the evolutionary process by which populations evolve to become distinct species. There are four geographic modes of speciation in nature, based on the extent to which speciating populations are isolated from one another: allopatric, peripatric, parapatric, and sympatric. Speciation may also be induced artificially, through animal husbandry, agriculture, or laboratory experiments.

Speciation: reproductive isolation, mutation, recombination, natural selection, genetic drift (deriva genetica), hybridisation, polyploidy, geographical isolation, reproductive isolation.