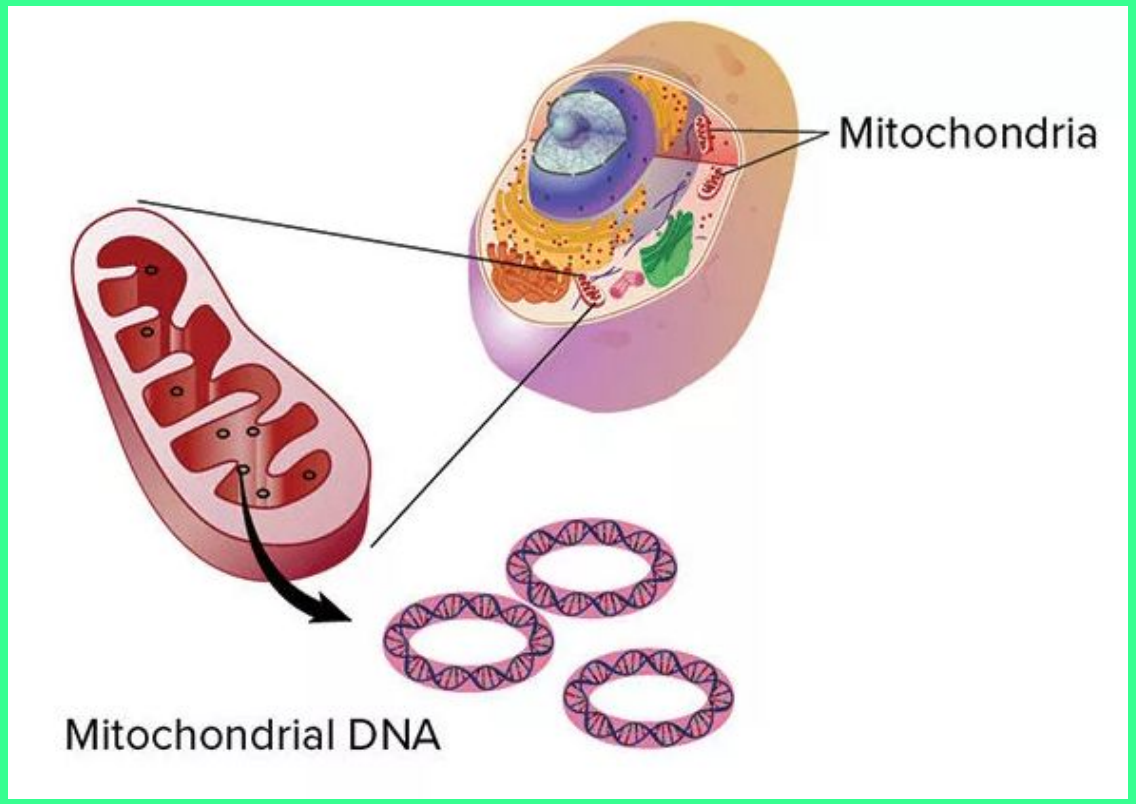
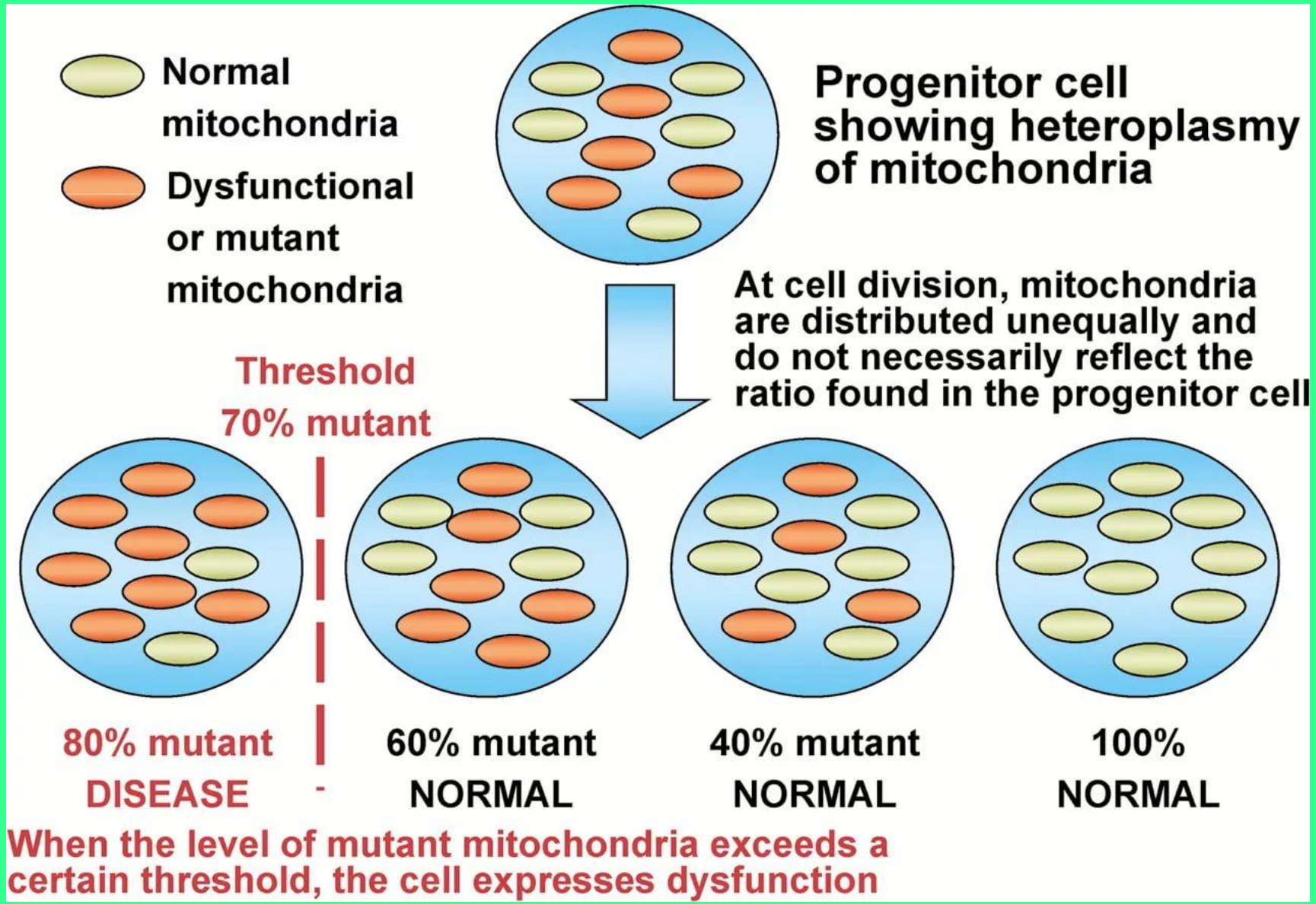
Cytoplasmic or extranuclear inheritance

Cytoplasmic heredity is associated with the cytoplasmic structures of cells containing DNA molecules, such as mitochondria. Human mitochondrial DNA includes 37 genes.

If mutation occurs there is phenotype changing highly expected.
These mutations are transmitted along the maternal line, since the zygote receives the entire cytoplasm from the maternal ovule.



Mitochondrial distribution during cell division



Box 1 | **Common features of mitochondrial DNA-associated diseases**

Adult

- Neurological: migraine | strokes | epilepsy | dementia | myopathy | peripheral neuropathy | DIPLOPIA | ATAXIA | speech disturbances | sensorineural deafness
- Gastrointestinal: constipation | irritable bowel | DYSPHAGIA
- Cardiac: heart failure | heart block | cardiomyopathy
- Respiratory: respiratory failure | nocturnal hypoventilation | recurrent aspiration | pneumonia
- Endocrinal: diabetes | thyroid disease | parathyroid disease | ovarian failure
- Ophthalmological: optic atrophy | cataract | ophthalmoplegia | PTOSIS

Paediatric

- Neurological: epilepsy | myopathy | psychomotor retardation | ataxia | spasticity | DYSTONIA | sensorineural deafness
- Gastrointestinal: vomiting | failure to thrive | dysphagia
- Cardiac: biventricular hypertrophic cardiomyopathy | rhythm abnormalities
- Respiratory: central hypoventilation | apnoea
- Haematological: anaemia | PANCYTOPAENIA
- Renal: renal tubular defects
- Liver: hepatic failure
- Endocrinal: diabetes | adrenal failure
- Ophthalmological: optic atrophy

(R.W. Taylor, D.M. Turnbull, 2005)

Table 2 | **Clinical disorders that are caused by mutations in mitochondrial DNA**

Mitochondrial DNA disorder	Clinical phenotype	mtDNA genotype	Gene	Status	Inheritance	Reference
Kearns–Sayre syndrome	Progressive myopathy, ophthalmoplegia, cardiomyopathy	A single, large-scale deletion	Several deleted genes	Heteroplasmic	Usually sporadic	61,158
CPEO	Ophthalmoplegia	A single, large-scale deletion	Several deleted genes	Heteroplasmic	Usually sporadic	61, 64
Pearson syndrome	Pancytopoenia, lactic acidosis	A single, large-scale deletion	Several deleted genes	Heteroplasmic	Usually sporadic	65
MELAS	Myopathy, encephalopathy lactic acidosis, stroke-like episodes	3243A>G; 3271T>C Individual mutations	*TRNL1* *ND1 and ND5*	Heteroplasmic Heteroplasmic	Maternal Maternal	159 160, 161
MERRF	Myoclonic epilepsy, myopathy	8344A>G; 8356T>C	*TRNK*	Heteroplasmic	Maternal	162
NARP	Neuropathy, ataxia, retinitis pigmentosa	8993T>G	*ATP6*	Heteroplasmic	Maternal	163
MILS	Progressive brain-stem disorder	8993T>C	*ATP6*	Heteroplasmic	Maternal	67
MIDD	Diabetes, deafness	3243A>G	*TRNL1*	Heteroplasmic	Maternal	164
LHON	Optic neuropathy	3460G>A 11778G>A 14484T>C	*ND1* *ND4* *ND6*	Hetero- or homoplasmic Hetero- or homoplasmic Hetero- or homoplasmic	Maternal Maternal Maternal	165 62 166
Myopathy and diabetes	Myopathy, weakness, diabetes	14709T>C	*TRNE*	Hetero- or homoplasmic	Maternal	167,168
Sensorineural hearing loss	Deafness	1555A>G Individual mutations	*RNR1* *TRNS1*	Homoplasmic Hetero- or homoplasmic	Maternal Maternal	55 169,170
Exercise intolerance	Fatigue, muscle weakness	Individual mutations	*CYB*	Heteroplasmic	Sporadic	68
Fatal, infantile encephalopathy; Leigh/Leigh-like syndrome	Encephalopathy, lactic acidosis	10158T>C; 10191T>C	*ND3*	Heteroplasmic	Sporadic	66

ATP6, ATPase 6; CPEO, chronic progressive external ophthalmoplegia; *CYB*, cytochrome *b*; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy and ragged-red fibres; MIDD, maternally-inherited diabetes and deafness; MILS, maternally-inherited Leigh syndrome; *ND1,3–6*, NADH dehydrogenase subunits 1,3–6; NARP, neurogenic weakness, ataxia and retinitis pigmentosa; *RNR1*, 12*S* ribosomal RNA; *TRNE, TRNK, TRNL1, TRNS1*, mitochondrial tRNAs.

Example of mitochondrial inheritance effects

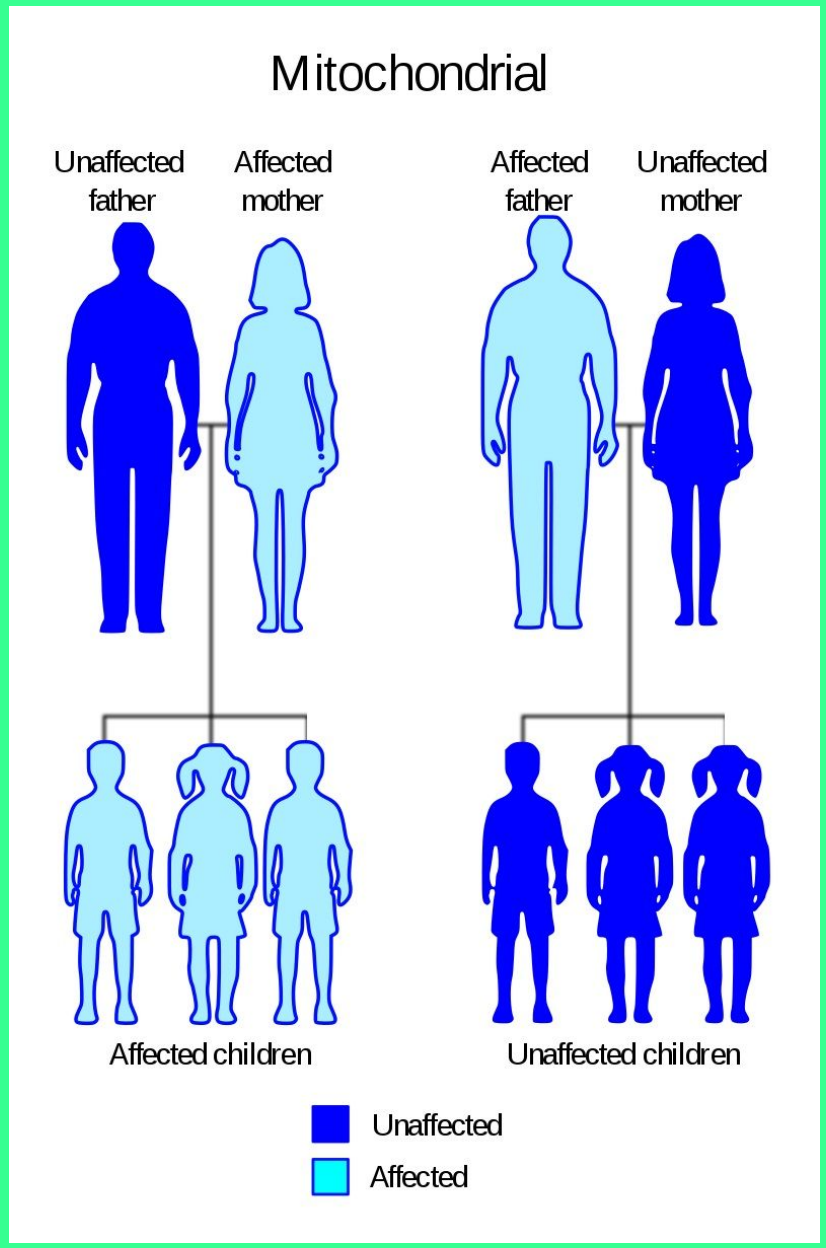
The large myelin-associated glycoprotein (**L-MAG**), which connected with the cytoplasmic domain of the genome, is thought to play a critical role in the interaction of myelinating glial cells with the axon.

That defect leads to various subtle abnormalities in the central nervous system and degenerates with age in the peripheral nervous system .

(N.Fujita, et all, 1998)

Examples of mitochondrial effects in humans

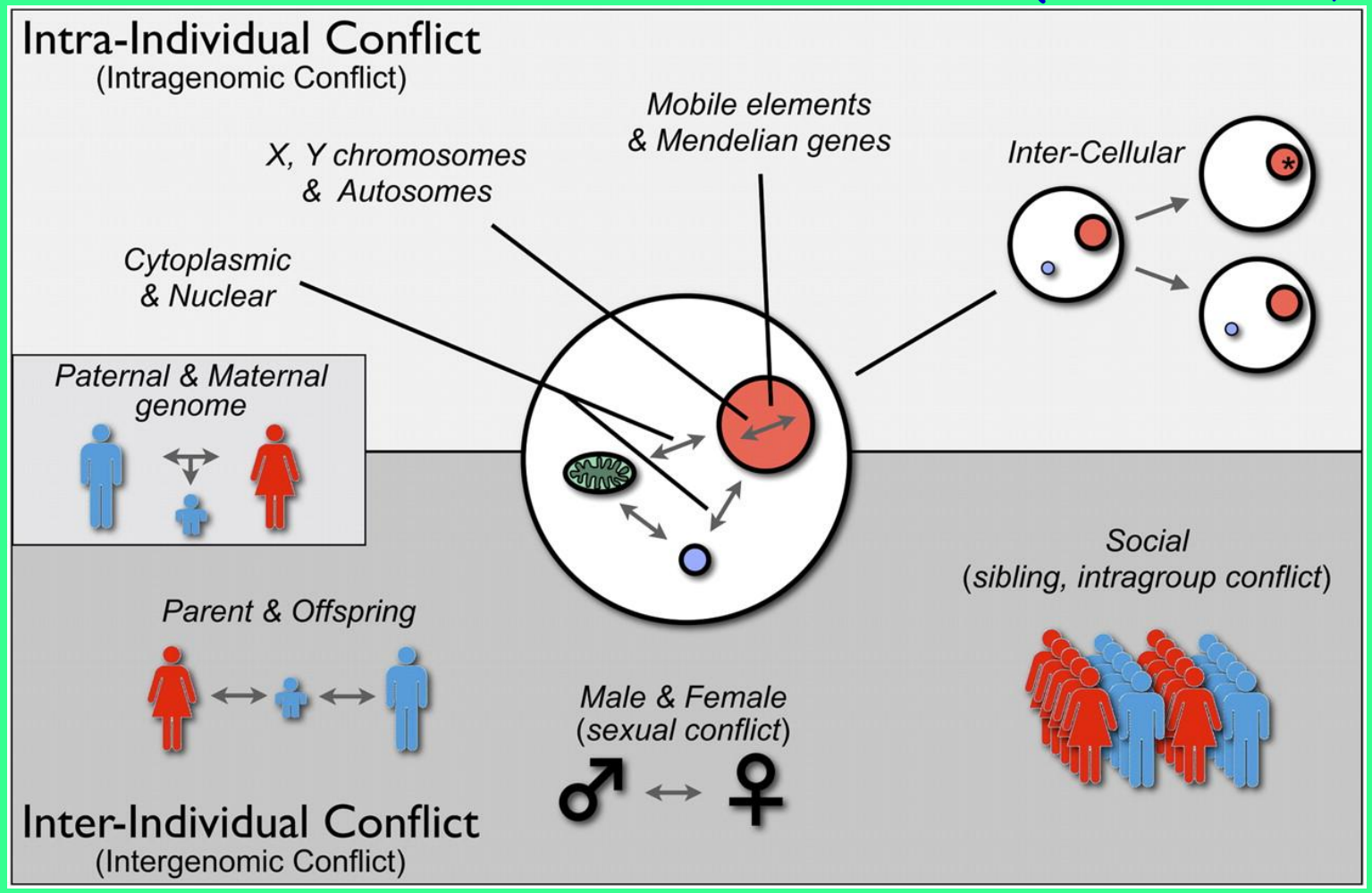
MERRF syndrome - myoclonic epilepsy and ragged redfibers.
The disease is a multisystem disorder indicating dysfunction of the mitochondrial respiratory chain, that is due in about 80% of cases to a A > G mutation at nucleotide 8344.
Patients with the syndrome will primarily display myoclonus (brief convulsions of the body), seizures, cerebellar ataxia and myopathy.
Secondary features include dementia, optic atrophy, bilateral deafness, peripheral neuropathy, spasticity, or lipomatosis.
Due to the multiple symptoms presented by the individual, the severity of the syndrome is very difficult to evaluate.
Mitochondrial disorders, including MERRF, may present at any age.



There are processes, which can influent on the clarity of inheritance pattern identification. Ones of them are genetic conflicts lead to forming mixed phenotypes.

Types of genetic conflicts

(J.H. Werren, 2011)



Genetic conflicts can be categorized as **intraindividual** (or intragenomic) and **interindividual** (or intergenomic).

Intraindividual conflicts occur among genetic elements with different inheritance patterns (e.g., cytoplasmic genes; nuclear genes; X, Y, and autosomally located genes etc).

Such conflict also arises among cells within an organism that are genetically different because of *de novo* mutations or transpositions or heteroplasmy attributable to unequal segregation (blue circle).

Genetic conflicts also occur between individuals, including parent-offspring, sexual, or social conflict.

Paternal-maternal genome interactions within offspring have features of both intraindividual and interindividual conflict.

As was shown above, identification of the types of inheritance may be accompanied by certain difficulties caused by complex relationships between components of the genome.
In this case, it is recommended to use molecular analysis.

Practical facets of the pedigree method

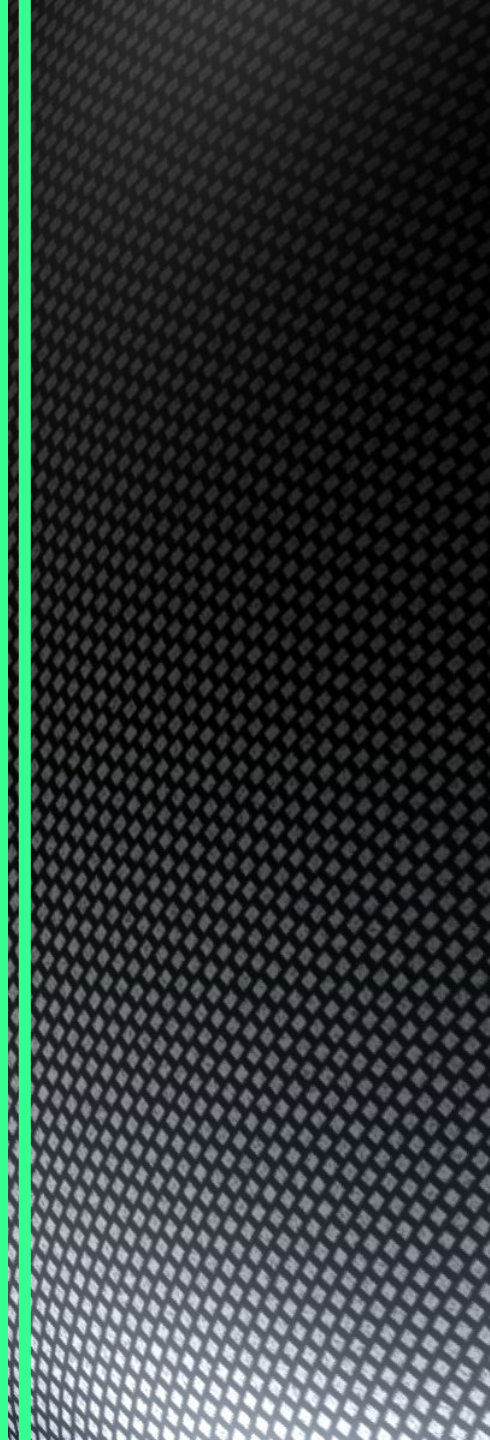
The genealogical method is a well-established procedure in behavioural genetics.
The worth fact is that human is the most studied organism.
Lots of records accompany the majority of people since the writing invention.

Nowadays there is not necessity to observe all the patients personally if needed data to compose a pedigree are available.
Church and medical reports, gravestone inscriptions and family memories give various information to researchers.
Modern ways of communication allow to receive information from remote respondents to complete a scheme.

Methods in behavioral genetics

Twin Studies:

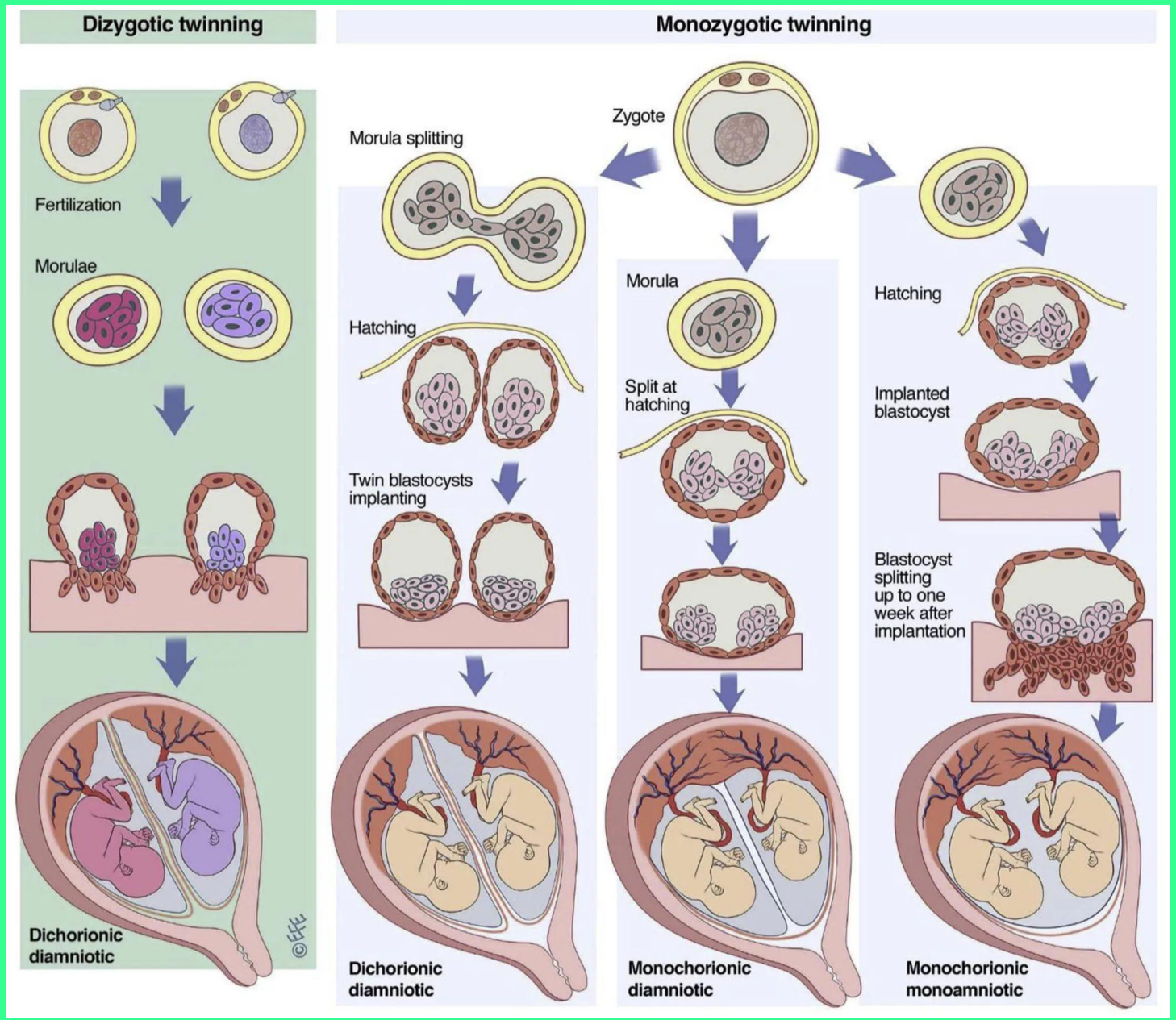
the history and the practical facets



Victorian scientist Francis Galton, a half-cousin of Charles Darwin, was one of the first people to recognize the value of twins for studying the heritability of traits.
In an 1875 paper titled "The History of Twins," Galton used twins to estimate the relative effects of **nature versus nurture** (a term that Galton himself coined).

Genetic diversity between people can manifest itself in phenotypic, psychological, and psycho-physiological differences.
Therefore, in order to study the influence of a genotype, it is possible to study those features that are available for external observation and which can be measured.
In addition, genetic distinctions are easier to detect by comparing people with varying degrees of genetic similarity, that is, close and distant relatives.

How do twins appear



Monozygotic (**MZ**) twins come from the same fertilised egg and are genetically identical, that is, they have 100% of their genes in common.
Non-identical or dizygotic (**DZ**) or fraternal twins, like other siblings, share, on average, 50% of their genes.
A greater similarity or correlation between MZ twins than DZ twins indicates a genetic influence.
Studies of twins allow researchers to examine what proportion of the total phenotypic variance is explained by genetic factors, shared environmental factors and non-shared environmental ones.

Concordance usually means the presence of the same trait in both members of a pair of twins.
For example, twins are concordant when both have or both lack a given trait.
The ideal example of concordance is that of identical twins.

Similarities and differences between twins

Trait	Identical Twins	Fraternal Twins
Develop from	The splitting of the same fertilized egg into two	Two different eggs fertilized by two different sperm cells
Genetic code	Nearly identical	Like any other sibling
Gender	Always the same	Usually different
Probability	Frequency is about 3:1,000. Only one-third of all twins in the world	Frequency is about 6:1,000 in Japan, up to over 20:1,000 in West Africa. Two-thirds of all twins in the world
Blood type	Always the same	May be different
Causes	Not known	Hereditary predisposition, certain fertility drugs
Appearance	Extremely similar, although may not be exactly identical due to environmental factors	As similar as any other sibling
In utero	May be contained in one sac in utero.	Develop separate sacs in utero.
Fingerprints	Different	Different

What the difference between twins?

Twin studies are represented by several varieties.

The classical twin method

In these experiments, the grade of manifestation of the test trait is compared in pairs of twins MZ and DZ, and the concordance is estimated.

The method of control twins

This method is used to study the effect of specific environmental effects on the variability of symptoms in samples from the MZ twins.
From the MZ pairs, should be made two equalized samples, one of which is the control group, and the second is the experimental one is undergoing an influence.
Since the participants are genetically identical, this method can be considered as a model for studying the influence of environmental factors on the same person.

The long-term observation

The observation of the same twins is carried out for a long time.
It is widely used to study the of influence of environmental and genetic factors during their development.

The method of twin families

This is a study of family members of adult twin couples. Under the genetic constitution, children of the MZ twins may be considered as an offspring of the same person.
The method is applicable to the study of the hereditary causes of a number of diseases.

The method of twin pairs

This study is an observation of specific twins' effects and features of inside-pair relations.
It could be used as an auxiliary method for verifying the validity of the hypothesis about the equality of environmental conditions for both MZ and DZ twin pairs.

The method of single twins

Comparison of features of development of single-born and children were born in multiple birth whose twin died just after.

The method of twins-non-twins comparison

An auxiliary method to evaluate the substantiality of the difference between twins and non-twins.
If the distinction is not significant, therefore the twins and other people could be assigned to the same general sample and, as the result, twin studies can be distributed to the entire population.

The method of separated twins

In this method, a pair-wise comparison of twins separated at an early age is performed.
If the MZ twins were separated in a similar way and grew up in different conditions, then all their similarities should be determined by their genetic identity, and the differences - by the influence of environmental factors.

The method of partially separated twins

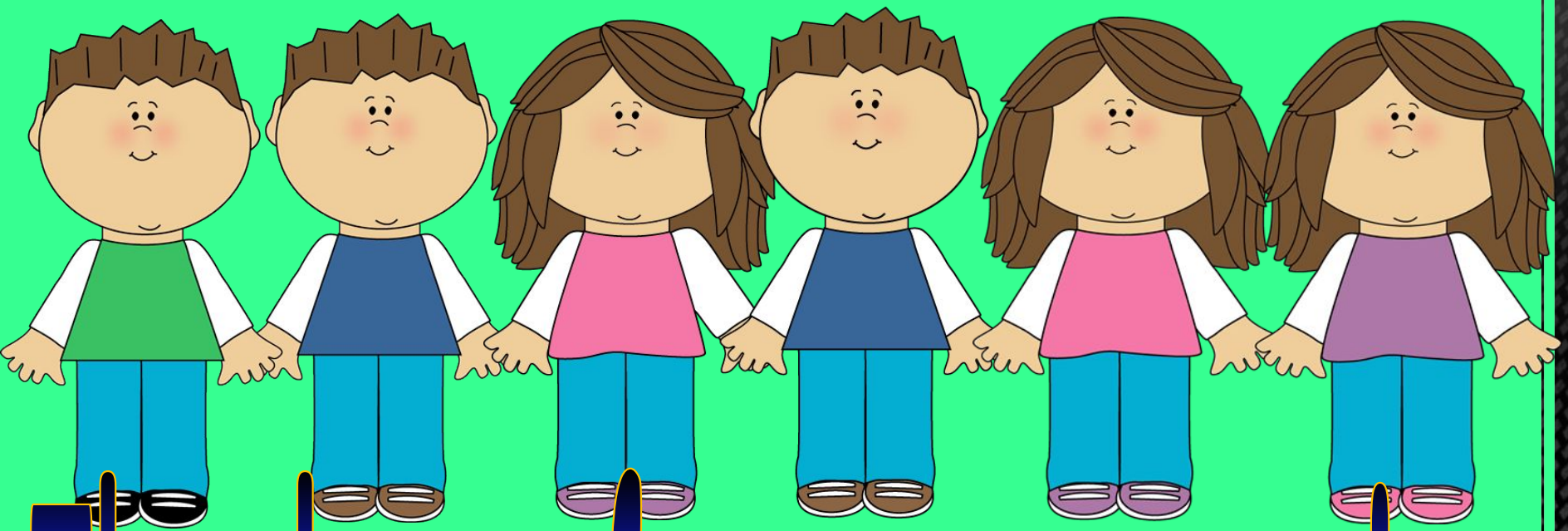
This method is the comparison the inside-pair twins similarity and allows to test the validity of the idea of the equality of environment of MZ and DZ twins is valid.

If MZ twins living separately become less similar to each other according to a certain psychological characteristic, and DZ twins living apart, do not differ in the pairwise twins similarity to DZ twins living together, therefore it could be concluded that the conditions of MZ and DZ are unequal, and supposal about the heritability of the studied characteristics is overestimated.

Practical facets of twin studies

The twin method is based on a assumption that the environment for partners in the MZ and DZ pairs is similar.
If the variability of the trait entirely depends on the genotype, the correlation index in MZ will be close to 1, and in the DZ it will approach 0.5 (since they have 50% common genes).
If the diversity of the trait depends on the environment, then both the MZ and the DZ should have an equally high inside-pair correlation equal to 1.

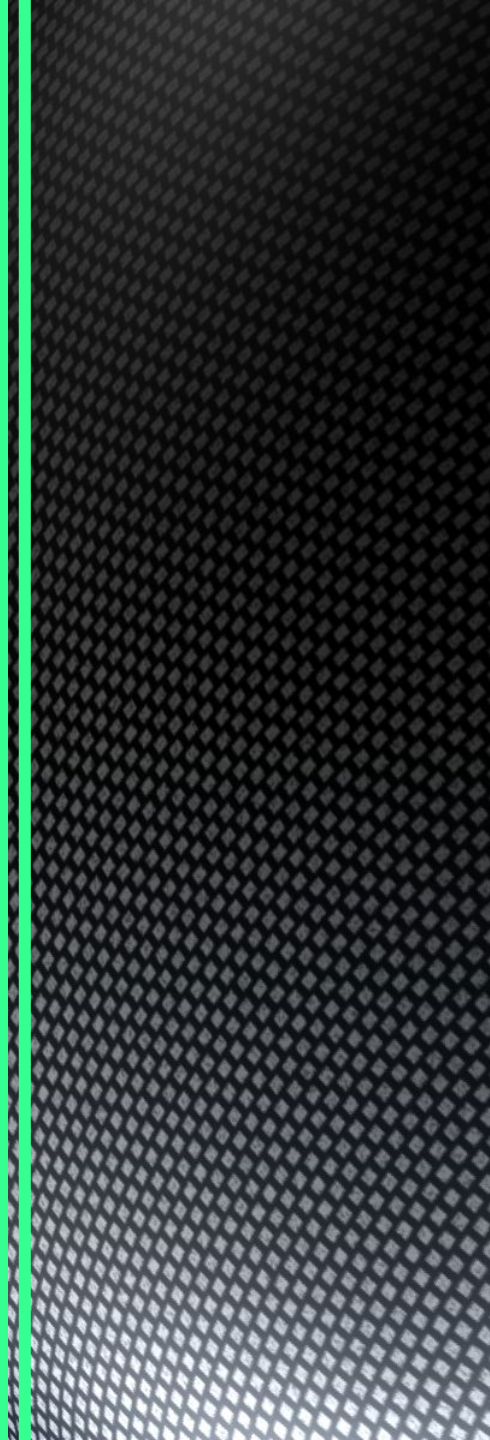
Correlations between members of MZ and DZ couples can be determined by genotype and common environment.
Development conditions can likewise reduce the similarities of the MZ and DZ twins. This is due to the period of prenatal development and childbirth and postnatal development of twins.
The identical environment will provide information on the role of the genotype and the environment in changing the traits studied.
In the different conditions the estimations of the compared phenotypic deviations are distorted.



Thank you for your attention

Methods in behavioral genetics

Family Studies:
the history and the practical facets



The method is based on the comparison of similarities between members of the same family and the compared ones may belong to the same generation (siblings who have get the half of common genes, half-siblings, and cousins).

Relatives are belonging to different generations can also be undergo comparison (parents - children, grandparents - grandchildren, aunts and uncles - nieces and nephews).

The interpretation of the results is similar to the twin method.

Thank you!