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Mendelian inheritance

The founder of the modern science of genetics was Johann Gregor Mendel. Mendel's pea plant experiments established many of the rules of heredity, now referred to as the laws of Mendelian inheritance. Below Mendel's Laws are summarized.

Law of Segregation (the "First Law") states that the two alleles for a heritable character segregate (separate from each other) during gamete formation and end up in different gametes.

Law of Independent Assortment (the "Second Law"), also known as "Inheritance Law", states that separate genes for separate traits are passed independently of one another from parents to offspring.

Law of Dominance (the "Third Law") states that recessive alleles will always be masked by dominant alleles. Therefore, a cross between a homozygous dominant and a homozygous recessive will always express the dominant phenotype, while still having a heterozygous genotype.

A Mendelian trait is one that is controlled by a single locus in an inheritance pattern. In such cases, a mutation in a single gene can cause a disease that is inherited according to Mendel's laws. These diseases are called monogenic diseases.

Mendelian inheritance is the basis of classical genetics. Although our knowledge about classical genetics has significantly expanded lately, the understanding of the heredity of the human diseases / traits can still be related to Mendelian inheritance. Those patterns of inheritance are considered Mendelian in a simplified way, which fulfill two criteria: on the one hand Mendel's principles can be applied, on the other hand the environment has no influence on them. The classical classification of the hereditary patterns is the following: autosomal dominant and recessive, codominant, X-linked dominant and recessive, and Y-linked.

The genetics of human traits is difficult to study, as it is not possible to make backcrosses, and the time lag between the generations is much longer than in the case of classical models, such as bacteria, yeast cells, drosophila, mice and rats. Additionally, the size of the families is significantly smaller than in classical models.

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Interpretation of some basic genetic terms

Gene: a DNA sequence coding for one or more functional product(s). These can be proteins via mRNA or can be any other kind of RNA, like t tRNA, rRNA, snRNA, miRNA, siRNA, etc. In the so-called RNA-viruses (e.g. influenza, HIV1) genes are coded only in the form of RNA.

Allele: it is an alternative form of a gene (one member of a pair) that is located at a specific position (locus) on a specific chromosome. A diploid cell contains two alleles at a time. Their relationship determines whether the inheritance of a gene-coded trait is dominant or recessive.

Allelic heterogeneity: different mutant alleles of the same gene result in similar symptoms /diseases. (e. g. mutations of FGFR3 gene)

Dominance / recessivity: the expression "dominance / recessivity" refers to phenotype, not to genotype. A trait is said to be dominant when it is visible even in heterozygous form. In case it is not, it is said to be recessive. These expressions show the relationship between the two alleles of the same gene. If the expression of one of the alleles represses the expression (the phenotypic form) of the other one, the inheritance pattern is dominant.

Modifier genes": genes that influence the expression of another gene. These are interactions between two or more genes of different loci.

Co-dominance: both alleles are manifested phenotypically in heterozygotes. AB0 blood group system is the classical example. Earlier incomplete dominance was also called codominance. Incomplete dominance occurs when the phenotype of the heterozygous phenotype is distinct from and often intermediate to the phenotypes of the homozygous phenotypes. E.g. LDLR mutations in familial hypercholesterolemia

1-Dominant-recessive inheritance

In dominantly inherited diseases only one faulty gene is enough for the manifestation of the disease. Such disease is e.g. familial hypercholesterolemia or Huntington disease. In cases of recessive diseases the faulty gene product is compensated by the normal variant. In this case two mutated homologous genes are required for the manifestation of the disease. Such diseases are e.g. cystic fibrosis or albinism. The codominant inheritance is a variation of the dominant-recessive inheritance. In case of codominant inheritance

two different alleles of a gene can be expressed, and each version makes a slightly different protein. Both alleles influence the genetic trait or determine the characteristics of the genetic condition. E.g. blood type AB is inherited in a codominant pattern. Here the A and B blood group is dominant over O blood group and show codominant inheritance to each other. It means that if a person has one gene for A blood group, one for 0 blood group then his/her blood group will be A, in the case of one A and one B, the blood group will be AB .

2-Polygenic inheritance In most cases, however, a trait or feature is determined more than one allele pair. Often the genes are large in quantity but small in effect. Examples of human polygenic inheritance are height, skin color, eye color, weight and diseases like diabetes mellitus, high blood pressure, asthma, allergy or atherosclerosis .

3-Genetic pleiotropy

It can also occur that an allele pair is responsible for more than one trait. Here, the product of the gene participates in several metabolic pathways, which have effects on different organs or tissues. In this case mutations in this gene can have different consequences. It is called genetic pleiotropy. A classic example of pleiotropy is the human disease phenylketonuria (PKU). This disease can cause mental retardation and reduced hair and skin pigmentation, and can be caused by any of a large number of mutations in a single gene that codes for the enzyme phenylalanine hydroxylase, which converts the amino acid phenylalanine to tyrosine, another amino acid .

4- Sex-linked inheritance

Humans have altogether 46 chromosomes, which consist of 22 pairs of autosomes in both females and males and two sex chromosomes. There are two copies of the X-chromosome in females (homogametic), but males have a single X-chromosome and a Y-chromosome (heterogametic). Genes on the X or Y chromosome are called sex-linked. Since humans have many more genes on the X than the Y, there are many more X-linked traits than Y-linked traits. The gender of the offspring is determined by the sperm. **Cytogenetics** is a field of genetics dealing with species or cell specific number of chromosomes, and their structure and characteristic segments, their functional roles, and all the differences - namely the chromosomal mutations - related to them. With

cytogenetic methods (e.g. with chromosome staining) the chromosome X and Y can be easily differentiated. Chromosome X is significantly larger than the Y.

Both chromosomes contain homologous and non-homologous regions. The non-homologous regions contain genes which do not have pairs in the other chromosome. In males these genes are in hemizygotic state. Females possessing one X-linked recessive mutation are considered carriers and will generally not manifest clinical symptoms of the disorder. All males possessing an X-linked recessive mutation will be affected, since males have only a single X-chromosome and therefore have only one copy of X-linked genes. All offspring of a carrier female have a 50% chance of inheriting the mutation if the father does not carry the recessive allele.

The Patterns of Genetic Inheritance

1- Mendelian

- Autosomal Dominant ex (Huntington's disease)
- Autosomal Recessive ex :-(Phenylketonuria PKU, congenital adrenal hyperplasia, Cystic fibrosis, Haemoglobinopathies and Xeroderma pigmentosum)
- X-linked Recessive
- X-linked Dominant
- Y-linked

2- Non-Mendelian

- Imprinting
- Mitochondrial
- Multifactorial
- Sporadic
- Contiguous gene syndromes